Paper No. 1
Filed: February 21, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00024
U.S. Patent No. 12,060,590

PETITION FOR POST GRANT REVIEW

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I. Introduction

Petitioner Merck Sharp & Dohme LLC ("Merck") requests post grant review of claims 1-35 of U.S. Patent No. 12,060,590 ("'590 Patent").

The '590 Patent claims are unpatentable for three independent reasons.

The first two are linked to the extreme breadth of the claims, which aim to capture any enzymatically active modified human hyaluronidase ("PH20") polypeptide within genera having between 10^{59} and 10^{112} distinct species. That results from the claim language, which specifies each PH20 polypeptide (i) ***must have one*** amino acid substitution at position 307, and (ii) ***may have*** between 20 and 41 additional substitutions at ***any*** of 430+ positions, and to ***any*** of 19 other amino acids. The scale of these genera is unfathomable. A collection of one molecule of each polypeptide in the smallest genus exceeds the weight of the Earth, and practicing the full scope of the narrowest claimed genus would require many lifetimes of "making and testing" using the patent's methodology.

These immensely broad claims, measured against the common disclosure of the '590 Patent and its ultimate parent '731 Application,[1] utterly fail the written description and enablement requirements of § 112(a). That renders every claim of the '590 Patent unpatentable. It also precludes the claims from a valid § 120

[1] 13/694,731 ('731 Application) (EX1026).

benefit claim to the ’731 Application, the only non-provisional application filed before March 16, 2013, thus making the ’590 Patent PGR eligible.

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by the enzymatically active, multiply-modified PH20 polypeptides within each claimed genus. The disclosed examples also are not representative of these structurally diverse genera: each has only ***one*** amino acid substitution in ***one*** PH20 sequence (1-447), while the claims encompass PH20 proteins with myriad ***undescribed*** combinations of 5, 10, 15, or 20+ substitutions anywhere within PH20 sequences of varying length. The claims even capture mutated PH20 polypeptides the disclosure says to avoid (*e.g.*, $PH20_{1\text{-}447}$ mutants rendered inactive by a single substitution, inactive truncated forms). The disclosure is nothing more than a research plan, lacking any blaze marks, and does not describe the claimed genera.

Regarding enablement, the common disclosure has equally fatal problems: it identifies ***no*** enzymatically active modified PH20 with 2 or more substitutions, much less affirmatively guides the selection of ***which*** combinations of substitutions yield such enzymes. The only process it discloses for making such multiply-substituted PH20 mutants is prophetic and uses the “trial-and-error discovery” methodology the Supreme Court has found incapable of enabling a

much smaller genus of polypeptides.[2] And practicing the full scope of the claims requires scientists to repeat this "make-and-test" methodology innumerable times until they had made and tested between 10^{59} and 10^{112} unique proteins. That is far more than undue experimentation—it is impossible.

Finally, claims 1-2 and 5-35 are unpatentable because each captures obvious $PH20_{1-447}$ mutants that change a ***single*** residue in a non-essential region of PH20 from leucine at position 307 to tryptophan ("L307W"), threonine ("L307T"), or serine ("L307S"). But Patentee's '429 Patent (EX1005) directs artisans to make such single amino acid substitutions in non-essential regions of $PH20_{1-447}$ (and expressly claimed them). Skilled artisans implementing that guidance in 2011 would have found Chao (EX1006)—a 2007 paper ignored in the common disclosure and never cited to the Office. Skilled artisans, using their knowledge and the collective teachings of Chao and the '429 Patent, would have (i) readily identified position 307 as being in a non-essential region of PH20, and (ii) found it obvious to change leucine to tryptophan, threonine, or serine at position 307. They also would have reasonably expected both mutants to retain enzymatic activity because that is what Patentee said in its '429 Patent ("Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions

[2] *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023).

of a polypeptide do not substantially alter biological activity").[3] Because the claims capture these obvious species, they are unpatentable, along with the dependent claims.

The '590 Patent claims are unpatentable. The Board should institute trial.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the '590 Patent's issuance. Petitioner certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '590 Patent.

The '590 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

A patent is PGR eligible if it issued from an application filed after March 16, 2013 "if the patent contains … at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought." *See Inguran, LLC v. Premium Genetics (UK) Ltd.*, Case PGR2015-00017, Paper 8 at 16-17 (P.T.A.B. Dec. 22, 2015); *US*

[3] EX1005, 16:17-22.

Endodontics, LLC v. Gold Standard Instruments, LLC, PGR2015-00019, Paper 17 at 8 (P.T.A.B. Jan. 29, 2016); *Collegium Pharm., Inc. v. Purdue Pharma L.P.*, 2021 WL 6340198, at *14-18 (P.T.A.B. Nov. 19, 2021) (same) *aff'd Purdue Pharma L.P. v. Collegium Pharm., Inc.*, 86 F.4th 1338, 1346 (Fed. Cir. 2023); *Intex Recreation Corp. v. Team Worldwide Corp.*, 2020 WL 2071543, at *26 (P.T.A.B. Apr. 29, 2020) (same).

Only one of the applications to which the '590 Patent claims benefit under 35 U.S.C. § 120 and/or § 121—U.S. Application No. 13/694,731 (the '731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011) and WO 01/3087 ("WO087"). The '731 Application, however, alters several passages of the provisional disclosures, adds new examples and tested mutants, and makes other changes.[4]

The '731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '590 Patent (§§ V.A, V.B). The same is true for the '590 Patent, whose

[4] EX1026, 153:15-163:26, 324-34, 19:25-26, 28; EX1051; EX1052.

disclosure relative to the claims is generally the same as the '731 Application.[5] The '590 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the '731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

Merck Sharp & Dohme LLC is the real party-in-interest for this Petition.

2. Related Proceedings

PGR2025-00003, PGR2025-00004, PGR2025-00006, PGR2025-00009, PGR2025-00017, and PGR2025-00030 are related proceedings.

3. Counsel and Service Information

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[5] The "common disclosure" refers to the shared disclosure of the '590 Patent and the '731 Application (EX1026). Citations are to the '590 Patent; EX1015 correlates citations to the '731 Application. The '590 Patent alters the list of positions to avoid changing in enzymatically active PH20 proteins in the '731 Application: it removes positions 282, 298, and 431. EX1045, 78; EX1068, ¶ 6.

Petitioner consents to service via e-mail at the email addresses listed above.

III. Grounds

The grounds advanced in this Petition are:

(a) Claims 1-35 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.

(b) Claims 1-35 are unpatentable under 35 U.S.C. § 112 as not being enabled.

(c) Claims 1-2 and 5-35 are unpatentable as obvious under 35 U.S.C. § 103 based on the '429 Patent (EX1005), Chao (EX1006), and knowledge held by a person of ordinary skill in the art.

Petitioner's grounds are supported by the evidence submitted with this Petition, including testimony from Dr. Michael Hecht (EX1003) and Dr. Sheldon Park (EX1004).

In this Petition, "PH20" refers to the human PH20 hyaluronidase protein. The full-length PH20 protein (SEQ ID NO: 6) includes a 35 amino acid signal sequence, which is absent in mature forms of PH20, yielding positional numbers that differ from SEQ ID NO: 6 by 35 residues.[6] The annotation "$PH20_{1-n}$" refers to

[6] EX1003, ¶ 15.

a sequence of 1-n residues in PH20 (*e.g.*, $PH20_{1-447}$ is SEQ ID NO: 3), and "AxxxB" is used to identify the position of a substitution (*e.g.*, "L307W").

IV. Background on the '590 Patent

A. Field of the Patent

The '590 Patent concerns the human PH20 hyaluronidase enzyme, and structurally altered forms of that protein that retain enzymatic activity.[7]

1. Protein Structures

Proteins are comprised of sequences of amino acids. A protein's activity, however, derives from its unique, three-dimensional shape—its structure.[8] That is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary structures and structural motifs, which are packed into compact domains that define the protein's overall structure (tertiary structure).[9]

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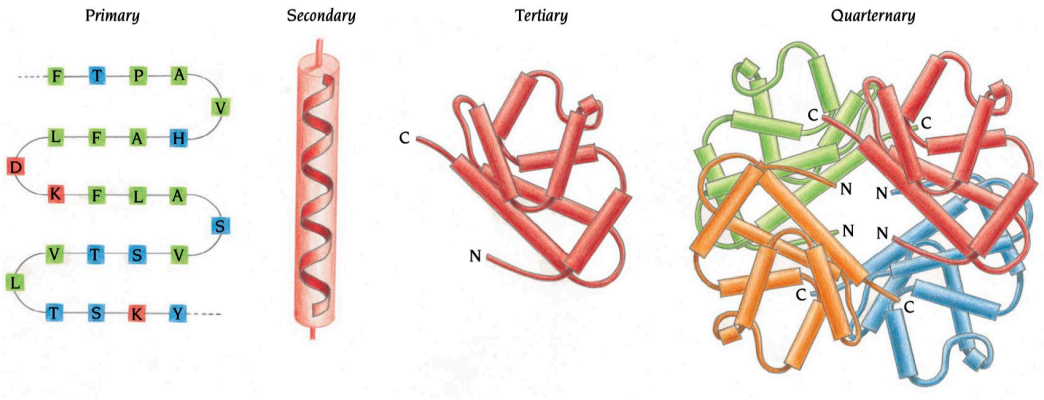
[7] EX1001, 4:16-20.

[8] EX1003, ¶ 36.

[9] EX1014, 3-4, 24-32, Figure 1.1; EX1039, 136-37 (Figure 3-11); EX1003, ¶¶ 36-40.



Secondary structures, such as α-helices or β-strands, are formed and stabilized by different but characteristic patterns of amino acids (below).[10]

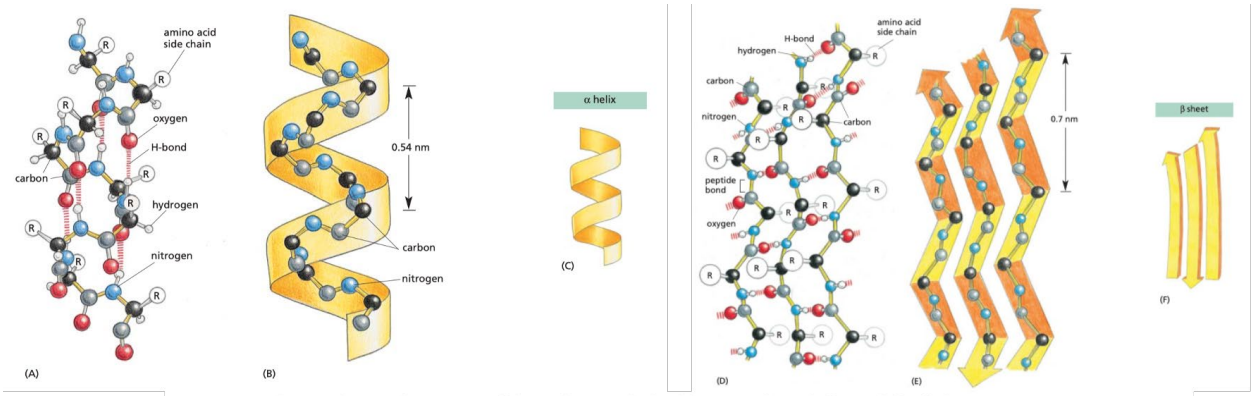


Figure 3–7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N–H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N–H groups point up in this diagram and that all of the C=O groups point down (toward the C-terminus); this gives a polarity to the helix, with the C-terminus having a partial negative and the N-terminus a partial positive charge. (D, E, and F) The β sheet. In this example, adjacent peptide chains run in opposite (antiparallel) directions. Hydrogen-bonding between peptide bonds in different strands holds the individual polypeptide chains (strands) together in a β sheet, and the amino acid side chains in each strand alternately project above and below the plane of the sheet. (A) and (D) show all the atoms in the polypeptide backbone, but the amino acid side chains are truncated and denoted by R. In contrast, (B) and (E) show the backbone atoms only, while (C) and (F) display the shorthand symbols that are used to represent the α helix and the β sheet in ribbon drawings of proteins (see Panel 3–2B).

[10] EX1039, 134; EX1014, 14-22, Figures 2.2, 2.5, Table 2.1; EX1047, 2031-32; EX1003, ¶¶ 40-43.

Intervening sequences between those characteristic sequences are important too; they direct and facilitate positioning and arrangement of the various secondary structures into structural motifs and the protein's tertiary structure.[11]

Changes to a protein's amino acid sequence can affect the folding, formation and stability of these various structures that define the protein's overall shape. For example, changing even a single residue known to be critical to the protein's structure or activity can render a protein inactive.[12]

Making many concurrent changes to a protein's sequence can cause myriad effects on the protein's structure, especially when they are in or affect the same region(s) of the protein.[13] For example, it can disrupt the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of secondary structures, and disrupt folding and positioning of the secondary structures and structural motifs into the protein's tertiary structure.[14] Multiple changes in different regions of the amino acid sequence also cause unfavorable

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11 EX1003, ¶¶ 44-46; EX1014, 21-22.

12 EX1003, ¶¶ 54, 150; EX1004, ¶¶ 20, 25.

13 EX1003, ¶ 158.

14 EX1003, ¶¶ 55-56, 142; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

spatial interactions that destabilize or impair folding.[15] Consequently, in 2011, predicting the effects of the myriad interactions that may be disrupted by multiple concurrent substitutions was beyond the capacity of skilled artisans and available computational tools.[16]

2. Hyaluronidase Enzymes

PH20 is one of five structurally similar hyaluronidases in humans and is homologous—evolutionarily related to—hyaluronidases in many species.[17] It breaks down hyaluronan ("HA") by selectively hydrolyzing glycosidic linkages.[18] PH20 exists naturally as a GPI anchored protein; deletion of its GPI-anchoring sequence yields a soluble, neutral active enzyme.[19]

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15 EX1003, ¶¶ 57-59.

16 EX1003, ¶¶ 50, 158, 190, 229; EX1004, ¶¶ 167-169.

17 EX1007, 10:18-30; EX1006, 6911, 6916 (Figure 3); EX1003, ¶¶ 33, 77.

18 EX1003, ¶ 77; EX1008, 819.

19 EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 89, 196; EX1029, 546, Figure 1.

Before 2011, many essential residues in PH20 were known. Several are in the shared catalytic site of the protein;[20] mutating certain residues in or near that site can abolish enzymatic activity.[21] Conserved cysteine residues that stabilize the protein structure are another example,[22] as are certain conserved asparagine residues involved in glycosylation.[23]

In 2007, Chao reported an experimentally determined structure of the human HYAL1 hyaluronidase, and used an alignment of the five human hyaluronidases to illustrate shared secondary structures and conserved residues in these proteins.[24] Among its findings was that human hyaluronidases contain a unique structure—the Hyal-EGF domain.[25] Using its sequence analysis, an earlier structure of bee

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[20] EX1006, 6914-16, Figure 3; EX1007, 35:28-36:10; EX1011, 810-14; EX1008, 824-25; EX1009, 6912-17.

[21] EX1011, 812-14; EX1010, 9435-39, Table 1.

[22] EX1006, 6914-16, Figure 3; EX1011, 810-11; EX1005, 88:21-22.

[23] EX1005, 7:9-27; EX1007, 36:12-20; EX1010, 9433, 9435-40.

[24] EX1006, 6914-18.

[25] EX1006, 6916-18; EX1010, 9439-40; EX1003, ¶¶ 84-86; EX1004, ¶¶ 97-99.

venom hyaluronidase and a computer model of the protein structures, Chao identified residues in the catalytic site that interact with HA.[26]

3. Protein Engineering

In 2011, skilled artisans used two general approaches to engineer changes into proteins.[27] In "rational design," skilled artisans employed computational tools—sequence alignments and protein structure models—to study the protein and then select where and what changes to introduce.[28] For example, a "multiple-sequence alignment" ("MSA")[29] produced by aligning known sequences of homologous, naturally occurring proteins identifies positions with no or little amino acid variation ("conserved" / "essential" residues) and positions where different amino acids occur ("non-conserved" / "non-essential" residues).[30] A

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[26] EX1006, 6912-13, 6916-18, Figures 2C, 4A; EX1033, 1028-29, 1035; EX1010, 9434, 9436, Figure 1.

[27] EX1003, ¶ 47.

[28] EX1016, 181-82; EX1017, 223, 236; EX1003, ¶¶ 48-50.

[29] EX1017, 224-27; EX1016, 181-86 (Figure 1); EX1003, ¶¶ 48-50; EX1004, ¶¶ 22-23, 29.

[30] EX1003, ¶¶ 213-14; EX1004, ¶¶ 21-22, 25, 30-31; EX1016, 181-84; EX1017, 224-25; EX1014, 351.

structural model using the protein's sequence but based on a known structure of a homologous protein enabled assessment of interactions between amino acids at a particular positions.[31] In 2011, using rational design techniques, a skilled artisan could assess, with varying effort, effects of changing one or a few amino acids, but could not use those techniques to predict the effects of many concurrent changes, given the escalating complexity of numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.[32]

"Directed evolution" techniques arose due to the limits of rational design.[33] They use "trial-and-error" experiments to find mutants with randomly distributed changes that exhibit desired properties, but require creation and screening of large libraries of mutants, each with one amino acid randomly changed at one position in its sequence.[34] Importantly, until a desired mutant is made, found and tested,

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31 EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶ 37; *also id.* 33-36; EX1003, ¶¶ 224, 226.

32 EX1003, ¶¶ 50, 158; EX1004, ¶¶ 167-169.

33 EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

34 EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

whether it exists and its sequence are unknown.[35] Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale of experimentation this approach requires.[36] The '590 Patent embodies this approach.[37]

B. Person of Ordinary Skill in the Art

While the '590 Patent claims priority to provisional applications dating to December 30, 2011 and benefit to the '731 Application (filed December 28, 2012), they are not supported as § 112(a) requires by those earlier-filed applications. *See* §§ II.A, V.A, V.B. Regardless, the prior art of the grounds was published before December 2011, and the obviousness grounds use that date to assess the knowledge and perspectives of the skilled artisan.

In 2011, a person of ordinary skill in the art would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production

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35 EX1003, ¶ 184.

36 EX1003, ¶¶ 52-53.

37 EX1003, ¶¶ 138, 173, 183, 186.

of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).[38]

C. Prosecution History

Only one office action issued during examination of the '590 Patent.

In it, several indefiniteness rejections were imposed (*e.g.*, unclear references to "modifications" and use of "Fe" instead of "Fc", failure of a dependent claim to further limit its parent).[39] Patentee overcame these indefiniteness rejections by amending the claims to address the identified deficiencies.[40]

No issues relevant to the present grounds were raised during examination.

D. The Challenged Claims

The terms used in the claims are either expressly defined in the common disclosure or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition. A clear understanding of the ***breadth*** of the claims, however, is important to assessing the

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[38] EX1003, ¶ 13.

[39] EX1002, 835-37.

[40] EX1002, 894-98, 907-908.

grounds. Specifically, each claim captures a massive genus of structurally distinct mutant PH20 polypeptides that is neither adequately described in nor enabled by the common disclosure of the ’731 Application and the ’590 Patent.

1. The Claims Encompass a Staggering Number of Modified PH20 Polypeptides

The claims capture an incredibly broad and diverse genus of “modified PH20 polypeptides,” which the common disclosure defines as “a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement … in its sequence of amino acids compared to a reference unmodified PH20 polypeptide.”[41]

Claim 1 defines the genus as containing modified PH20 polypeptides that:

- ***must*** contain ***one*** amino acid replacement at position 307 (*i.e.*, from L to any of G, K, N, Q, S, T, V, W, and Y); and
- ***may*** contain ***additional*** modifications, provided each polypeptide retains ***at least 91% sequence identity*** to one of the 37 unmodified sequences (SEQ ID NOs: 3, 7, or 32-66), ranging in length from 430 (SEQ ID NO: 32) to 474 residues (SEQ ID NO: 7).

Certain dependent claims restrict these parameters:

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[41] EX1001, 48:38-43. Dependent claims 24-35 reference genera of PH20 polypeptides defined by claims 1 or 6.

(i) claims 2 and 25-26 limit (*inter alia*) sequence identity to 95%,

(ii) claims 8, 10, 15 and 22 omit SEQ ID NO: 7 as a reference sequence, while claims 11-14 and 25-26 require it to be either SEQ ID NO: 35 or 32,

(iii) claims 6, 13-14, and 25-26 require the position 307 substitutions to be W (L307W),

(iv) claims 7 and 9 require the position 307 substitution be either T or S (L307T or L307S), and

(iv) claims 3-5 and 16 add functional requirements (*e.g.*, increased "stability" or activity, solubility).

Claims 17-21, 23-24 and 27-35 depend from claim 1 but do not narrow the number of PH20 polypeptides captured by each genus of that claim.[42] Claims 17-23 specify additional features of the PH20 polypeptides (*e.g.*, glycosylation) while claims 24 and 27-35 define pharmaceutical compositions and methods of treatment using the modified PH20 polypeptides.

[42] Claim 22 removes reference SEQ ID NO: 7, but otherwise does not alter the genus of claim 1.

The specification explains that "sequence identity can be determined by standard alignment algorithm programs …"[43] and provides an example, explaining a polypeptide that is "'at least 90% identical to' refers to percent identities from 90 to 100% relative to the reference polypeptide" where "no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides."[44]

It further explains that "differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence" and that "[d]ifferences are defined as [] amino acid substitutions, insertions or deletions."[45] Also, "amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids" (*e.g.*, 10-18 of the 19 alternative amino acids).[46] Except for position 307, no language in the claims restricts ***where*** substitutions can occur within the modified PH20 sequence, or ***which*** of 19 other amino acids can be substituted at those positions.

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43 EX1001, 60:16-18.

44 EX1001, 60:51-60.

45 EX1001, 60:61-61:2; *see also id.* at 5:1-2, 47:43-47, 56-58.

46 EX1001, 137:29-36; *see also id.* at 142:49-51.

The sequence identity parameters capture an immense number of modified PH20 polypeptides, each with a unique amino acid sequence.[47] The polypeptides may have up to 21-42 total changes but must have one substitution at position 307. Claims 1-5, 8, 11-12, 16-24, and 27-35 permit nine position 307 alternatives (G, K, N, Q, S, T, V, W, and Y), claims 7 and 9 permit two (T and S) and claims 6, 10, 13-15, and 25-26 permit only one (W). Dr. Park's calculations show each claim's parameters capture an immense number of distinct polypeptides:[48]

[47] EX1003, ¶¶ 120, 122.

[48] EX1004, ¶¶ 175-179, Appendix F.

Claims	*Max Length*	*Max Changes*	*Pos. 307 Choices*	*# of Distinct Polypeptides*
1, 3-5, 16-21, 23, 27-35	474	42	9	5.69×10^{112}
2	474	23	9	4.66×10^{66}
6	474	42	1	6.32×10^{111}
7	474	42	2	1.26×10^{112}
8, 22	465	41	9	1.27×10^{110}
9	465	41	2	2.82×10^{109}
10, 15	465	41	1	1.41×10^{109}
12	430	38	9	6.89×10^{101}
11	433	38	9	9.02×10^{101}
13	433	38	1	1.00×10^{101}
14	430	38	1	7.66×10^{100}
25	430	21	1	4.40×10^{59}
26	433	21	1	5.08×10^{59}

2. The Claims Encompass Particular Singly-Substituted $PH20_{1-447}$ Mutants: L307W, L307T, and L307S $PH20_{1-447}$

Each claim captures one (or more) of three modified $PH20_{1-447}$ polypeptides that result from changing only the leucine at position 307 to tryptophan (W) ("L307W"), serine ("L307S") or threonine ("L307T"). These single-replacement $PH20_{1-447}$ mutant are: (i) 99.7% identical to SEQ ID NO: 3 (1 change / 447

residues), (ii) 96.5% identical to SEQ ID NO: 35 (15 changes / 433 residues), and (iii) 95.9% identical to SEQ ID NO: 32 (18 changes / 430 residues).[49]

3. The Claims Are Restricted to One of Two Alternative Embodiments in the Patents: "Active Mutants"

When a specification discloses alternative embodiments, the claim language may limit the claims to only one.[50] That is the case here: the specification describes two mutually exclusive categories of "modified PH20 polypeptides" (*i.e.*, "active mutants" vs. "inactive mutants") but the claims are limited to one (*i.e.*, "active mutants").

According to the specification:

- "***Active mutants***" are modified PH20 polypeptides that "exhibit at least 40% of the hyaluronidase activity of the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[51]

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49 EX1003, ¶ 136.

50 *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008).

51 EX1001, 75:48-53; *see also id.* at 79:30-34 ("active mutants" "can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide …"); *id.* at 79:27-30.

- "***Inactive mutants***" are modified PH20 polypeptides that "generally exhibit less than 20% … of the hyaluronidase activity of a wildtype or reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7."[52]

It then classifies mutants into tables of "active" and "inactive" mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).[53]

The common disclosure reports no examples of an "active mutant" modified PH20 with two or more replacements.[54] Notably, it reports no examples of an enzymatically active $PH20_{1-447}$ that incorporates: (i) a mutation that preserved activity in Tables 3 and 9 ("active mutants") plus (ii) a second mutation that eliminated activity in Tables 5 and 10 ("inactive mutants").

The specification also portrays "active" and "inactive" mutants as having distinct utilities requiring mutually exclusive properties.

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[52] EX1001, 119:24-33. *See also id*. at 257:20-24 (mutants with <20% activity "were rescreened to confirm that the dead mutants are inactive" in Table 10).

[53] EX1001, 80:61-82:10, 234:25-27, 120:34-57, 257:47-50 ("reconfirmed inactive mutants are set forth in Table 10."); EX1003 ¶¶ 98, 104-105, 107.

[54] *E.g.*, EX1003, ¶¶ 141, 172.

- "Active mutants" are portrayed as being therapeutically useful ***because they possess hyaluronidase activity***. For example, the specification explains that ***due to*** having hyaluronidase activity, "the modified PH20 polypeptides can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents."[55]
- "Inactive mutants" are portrayed as being therapeutically useful ***because they lack hyaluronidase activity***. Their only identified utility is "as antigens in contraception vaccines," which is implausible (*see* § V.C) but ostensibly requires them to lack activity.[56]

The specification does not portray "active mutants" as having contraceptive utility even though they may differ by only one amino acid from an inactive mutant; it proposes using them instead ***in combination*** with contraceptive agents.[57]

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[55] EX1001, 181:22-28; *see also id*. at 4:33-36, 73:34-48, 181:22-194:47; EX1003, ¶ 108.

[56] EX1001, 72:61-63; *see also id.* at 194:49-50, 75:57-59, 194:48-67 (for "contraception" "the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.").

[57] EX1001, 147:49-62; EX1003, ¶ 113; EX1060, 1711.

The claim language reinforces that they are limited to the "active mutant" embodiment.

First, every claim requires modified PH20 polypeptides with one of nine replacements at position 307 that were reported to yield an "active mutant" as a single-replacement $PH20_{1-447}$ polypeptide (*i.e.*, L307G, L307K, L307N, L307Q, L307S, L307T, L307V, L307W, and L307Y). All nine mutants are identified as "Active Mutants" in Tables 3 and 9.[58]

Second, claim 4 restricts the genus of active mutants in claim 1 (*i.e.*, those with hyaluronidase activity) to modified PH20 polypeptides that have at least 100% of the activity of unmodified PH20.[59]

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[58] EX1001, 87 (Table 3), 235 (Table 9), 101:4-16; EX1003, ¶¶ 127-128. Patentee classifies the L307G as an "active mutant" despite it having only 32% of the activity of unmodified $PH20_{1-447}$. EX1001, Table 9, column 235, Table 3, column 87. Only three single-substitutions of $PH20_{1-447}$ are listed as "Inactive Mutants" (L307C, L307I, and L307P), none of which are claimed. EX1001, Table 5, column 127.

[59] Claim 3 requires mutants with increased resistance to or stability in denaturing conditions. The specification portrays increased stability as an additional

Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one amino acid modification," but can also "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity.***"[60] This aligns with the specification's prophetic methodology for discovering PH20 polypeptides with multiple changes, which selects "active mutants" with one substitution, randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity.[61] This also tracks the claims, which require one substitution and permit others.

Patentee may contend the claims should be read as encompassing both alternative embodiments (*i.e.*, "active" and "inactive" mutants). Reading the claims in that manner is incorrect. It also exacerbates the § 112 problems, as every claim still necessarily includes (and thus must describe and enable) the full sub-genus of "active mutants" in claim 1 defined by claim 4.[62]

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attribute of an "active mutant." EX1001, 52:41-47, 134:28-47, 180:10-13, 296:21-297:42.

60 EX1001, 48:38-53; *see also id*. at 47:61-65, 76:6-9, 77:1-8, 81:2-82:10.

61 EX1001, 142:14-26; *see also id*. at 42:48-55.

62 EX1003, ¶ 135.

V. All Challenged Claims Are Unpatentable Under § 112 and None Are Entitled to Benefit to Any Pre-March 13, 2013 Application

Claims 1-35 are unpatentable because each lacks written description in and was not enabled by the common disclosure of the ’590 Patent and the ’731 Application in 2011.

As explained in § IV.D.1, the claim language defines enormous genera: between 10^{59} and 10^{112} distinct polypeptides. Their real-world scope is absurd—to practice the claims’ full scope requires a skilled artisan to make-and-test at least ~10^{59} mutants. Simply producing one molecule of each mutant—required to know if each is active or inactive or exhibits increased stability—which, in the case of the genera’s many multi-substituted mutants, would consume an aggregate mass (~3.93 x 10^{37} kg) that exceeds the mass of the Earth (~6 x 10^{24} kg).[63] Testing every polypeptide within the claims’ scope in search of “active mutants” is impossible—literally.

Relative to that broad scope, the ’590 Patent and the ’731 Application provide only a meager disclosure: ***singly***-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones. It nowhere demonstrates possession of the vast remainder of multiply-modified

[63] EX1003, ¶¶ 123, 189; *see also, e.g.*, EX1039, 136-37 (cell theoretically can make 10^{390} forms of a polypeptide with 300 amino acids).

polypeptides in the claims' scope, nor does it enable a skilled artisan to practice that full-range of mutant polypeptides without undue experimentation.

A. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.[64] "To fulfill the written description requirement, a patent owner 'must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent."[65] If the claims define a genus, the written description must "show that one has truly invented a genus …," "[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus."[66]

"[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the

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64 *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

65 *Idenix Pharm., LLC v. Gilead Scis., Inc.,* 941 F.3d 1149, 1163 (Fed. Cir. 2019).

66 *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1300 (Fed. Cir. 2014).

members of the genus so that one of skill in the art can visualize or recognize the members of the genus."[67] "One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent … [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus."[68]

A disclosure that fails to "provide sufficient blaze marks to direct a POSA to the specific subset" of a genus with the claimed function or characteristic does not satisfy § 112(a).[69] And "merely drawing a fence around the outer limits of a purported genus" is insufficient.[70] Instead, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."[71]

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67 *Idenix*, 941 F.3d at 1164.

68 *AbbVie*, 759 F.3d at 1299-1300.

69 *Idenix*, 941 F.3d at 1164.

70 *Ariad*, 598 F.3d at 1350-54.

71 *Ariad*, 598 F.3d at 1349.

Three cases are especially probative. First, in *AbbVie*, the Federal Circuit found a disclosure of 300 examples of IL-12 antibodies to not be representative of a functionally defined antibody genus:

> Although the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.[72]

It also criticized patentee's attempt to use a prophetic description for the remaining claim scope, portraying it as "only a research plan, leaving it to others to explore the unknown contours of the claimed genus" and a "trial and error approach."[73]

Second, *Idenix* addressed claims to methods of treatment with a broad genera of compounds defined by formulas analogous to the challenged claims here: "eighteen position-by-position formulas describing 'principal embodiments' of compounds that may treat HCV," each with "more than a dozen options" at each position (totaling "more than 7,000 unique configurations").[74] The court criticized the specification's failure to indicate which of the thousands of compounds would be effective, and found that "provid[ing] lists or examples of supposedly effective

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[72] *AbbVie*, 59 F.3d at 1300-1301.

[73] *Id.*

[74] *Idenix*, 941 F.3d at 1158-64.

nucleosides," without "explain[ing] what makes them effective, or why" deprives a skilled artisan "of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result" because they "fail[] to provide sufficient blaze marks to direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV."[75]

Finally, the Board in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found.*, PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) considered claims that used "90% sequence homology" language to capture "a broad genus of amino acid sequence homologues" but (like here) imposed no restrictions on where particular amino acids replacements could be made, thus causing the claim "to cover, at minimum, thousands of amino acid sequences."[76] The Board found fatal the specification's failure to "explain what, if any, structural features exist (*e.g.*, remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification" and noted the homology limitation "serves to merely draw a fence around the outer

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75 *Id.* at 1164.

76 *Boehringer*, at 16. The claims were directed to compositions and methods of using proteins. *Id.* at 6.

limits of a purported genus [which] is not an adequate substitute for describing a variety of materials constituting the genus" for purposes of section 112(a).[77]

The deficiencies of the claims here dwarf those in these three cases. They define much larger, much less predictable and much more diverse genera of modified PH20 polypeptides, and the common disclosure is far more limited. Because the common disclosure neither discloses a representative number of species within each immense claimed genus, nor identifies sufficient structural features common to the members of each claimed genus, it fails to demonstrate possession of the genera defined by the claims of the '590 Patent.

1. Claims 1-2, 6-15, and 25-26 Lack Written Description

a) The Claims Capture Massive and Diverse Genera of Enzymatically Active PH20 Polypeptides

The genera of modified PH20 polypeptides defined by the sequence identity language of claims 1-2, 6-15, and 25-26 are not only immense, but are structurally and functionally diverse. They capture PH20 mutants with 2 substitutions, 3 substitutions, and so on up to a number set by the sequence identity boundary (*i.e.*, 21 for the narrowest claims (*e.g.* claims 25 and 26) to 42 for the broadest (claim 1)). The optional substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the

[77] *Id.* at 35-36.

sequence), to any of 19 other amino acids, and arranged in any manner.[78] They thus capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with up to 42 substitutions that mix polar, charged, aliphatic, and aromatic amino acids together in any manner.[79]

Each claim also encompasses substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 37 alternative sequences that terminate at positions 430 to 474. The claims' sequence identity language also captures PH20 polypeptides that terminate at positions before 430. For example, claims referencing SEQ ID NO:32 that allow between 21 and 42 changes (and can be any mixture of deletions and substitutions will capture a PH20 terminating at position 416 or below. But removing so many residues from the C-terminus of PH20 can render it inactive, and the disclosure does not describe or suggest that the claimed position 307 substitution renders such mutants active.[80] The claims, however, capture such polypeptides.

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78 EX1003, ¶ 119; EX1001, 60:61-61:1, 47:43-47, 47:56-58, 42:3-9.

79 EX1003, ¶¶ 119-20.

80 EX1003, ¶¶ 164-67.

b) The Claims Capture Modified PH20 Polypeptides the Common Disclosure Says to Avoid or Not Make

The claims' unconstrained sequence identity language capture three categories of PH20 mutants a skilled artisan would understand the disclosure to be saying to avoid. Each raises unique questions relative to the remainder of the genus and are thus "sub-genera" of PH20 mutants that are not representative of other "sub-genera" within the claimed genera. But instead of providing guidance that navigates this confusing landscape, the patent simply instructs the skilled artisan "to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein."[81] The common disclosure thus does not describe any of these sub-genera within the claims' scope.

(i) Multiply-Modified PH20 Mutants to Not Make

The common disclosure affirmatively addresses only six, specific modified PH20 polypeptides with more than one identified (*i.e.*, position and amino acid) substitution, but its guidance is to ***not make those polypeptides***:

> [W]here the modified PH20 polypeptide contains only two amino acid replacements, the amino acid replacements are ***not*** P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A or N333A/N358A. In a

[81] EX1001, 78:34-39; EX1003, ¶ 193.

> further example, where the modified PH20 polypeptide contains only three amino acid replacements, the amino acid replacements are ***not*** N47A/N131A/N219A.[82]

No explanation is provided why these particular combinations of replacements should be avoided, and nor any data testing their activity or other characteristics.[83] The substitutions are not included in Tables 5 and 10 (i.e., "inactive mutants") and N219A $PH20_{1-447}$ showed increased activity (129%).[84] Nothing in the claim language excludes these combinations.

(ii) Substitutions to Avoid in Active Mutants

The common disclosure indicates that active mutant modified PH20 polypeptides should not incorporate amino acid substitutions that rendered $PH20_{1-447}$ inactive, stating:

> ***To retain hyaluronidase activity***, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.[85]

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82 EX1001, 77:46-58 (emphases added).

83 EX1003, ¶¶ 146-47; EX1001, 49:30-35.

84 EX1001, 247 (Table 9).

85 EX1001, 80:14-16 (emphases added).

It identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10 that are made at other positions.[86] It does not limit this observation to single-replacement $PH20_{1-447}$ mutants, or suggest that any of these substitutions that render $PH20_{1-447}$ inactive should be included in enzymatically active, multiply-modified PH20 polypeptides (much less identify specific combinations including them).[87] Instead, by stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that the ***claimed*** enzymatically active multiply-modified PH20 polypeptides do not and should not contain them.[88] The sequence identity claim parameters, however, capture such mutants.

(iii) PH20 with Significant C-terminal Truncations Can Lose Activity

The common disclosure does not describe and provides no guidance concerning "active mutant" PH20 polypeptides having fewer than 447 residues,

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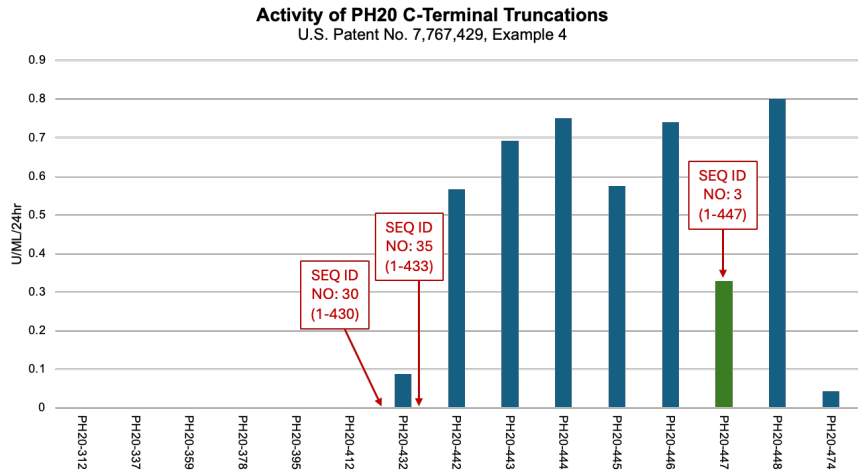
86 EX1001, 80:16-56 ("For example, generally modifications are not made at a position corresponding to position …").

87 EX1003, ¶¶ 151, 161-62, 169.

88 EX1003, ¶¶ 148-51, 162; EX1001, 80:14-56, 70:47-57.

particularly multiply-modified PH20 mutants terminating significantly before that position.[89]

But the common disclosure and the prior art report that wild-type PH20 polypeptides terminating at or below position 442 have ***significantly reduced or no*** hyaluronidase activity. For example, Patentee's '429 Patent reported that PH20 mutants terminating below position 432 residues lacked hyaluronidase activity, while those terminating between positions 432 and 448 had widely varying activities (below):[90]



Position (w/leader)	Mutant	U/ML/24hr	Normalized to PH20(1-447)
347	PH20-312	0	0.00
372	PH20-337	0	0.00
394	PH20-359	0	0.00
413	PH20-378	0	0.00
430	PH20-395	0	0.00
447	PH20-412	0	0.00
467	**PH20-432**	**0.089**	**27.05**
477	PH20-442	0.567	172.34
478	PH20-443	0.692	210.33
479	PH20-444	0.75	227.96
480	PH20-445	0.575	174.77
481	PH20-446	0.74	224.92
482	**PH20-447**	**0.329**	**100.00**
483	PH20-448	0.8	243.16
509	PH20-474	0.044	13.37

89 EX1003, ¶¶ 94, 97, 167-69; EX1001, 74:10-16.

90 EX1005, 87:52-88:24 ($PH20_{1-442}$ activity "decreased to approximately 10%"); EX1013, Figure 2, 430-32 ("[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA"); EX1003, ¶ 91.

The '429 Patent also reported that "a very narrow range spanning … [437-447] … defined the minimally active domain" of human PH20, and elsewhere observed this "minimally active" human PH20 domain contains at least residues 1-429.[91] The common disclosure reiterates these findings, stating that PH20 polypeptides must extend to at least position 429 to exhibit hyaluronidase activity:

> A mature PH20 polypeptide … containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue ***464*** of SEQ ID NO: 6 [position ***429*** without signal] … ***is the minimal sequence required for hyaluronidase activity***.[92]

In 2007, Chao reported that the C-terminal region of human hyaluronidases contains a unique domain ("Hyal-EGF") linked to a characteristic pattern of sequences.[93] In PH20, the Hyal-EGF domain runs from positions 337-409.[94] In

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91 EX1005, 6:65-7:7 ("… sHASEGP from amino acids 36 to Cys 464 [429] … comprise the minimally active human sHASEGP hyaluronidase domain"); EX1003, ¶ 90.

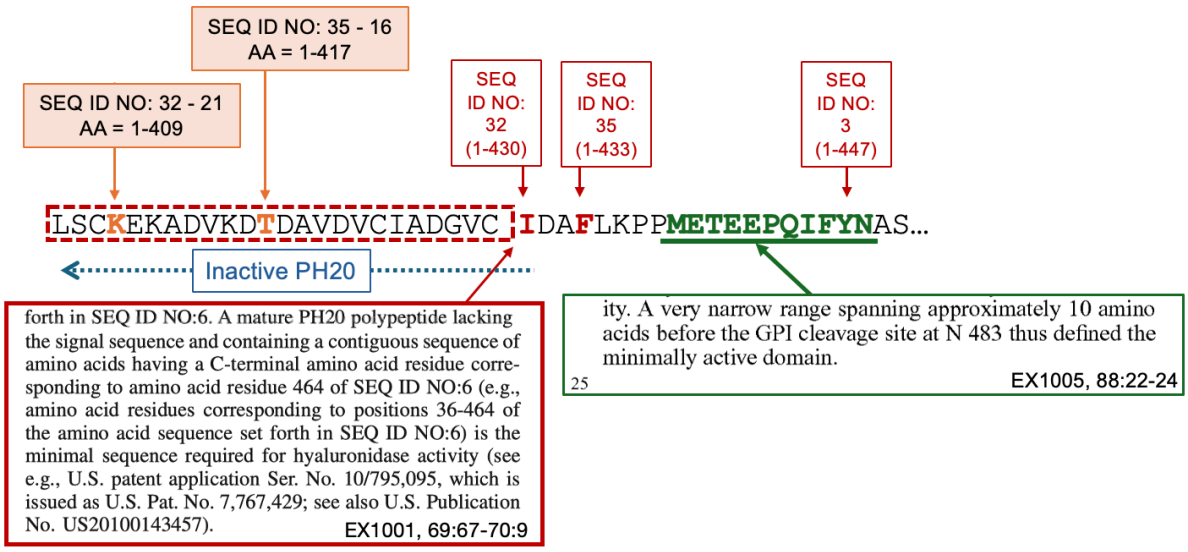
92 EX1001, 69:67-70:9 (emphases added); *also* EX1003, ¶ 91.

93 EX1006, 6912; EX1003, ¶¶ 84-86.

94 EX1004, ¶¶ 97-99; EX1003, ¶ 92.

2009, Zhang showed the Hyal-EGF domain was necessary for hyaluronidase activity.[95]

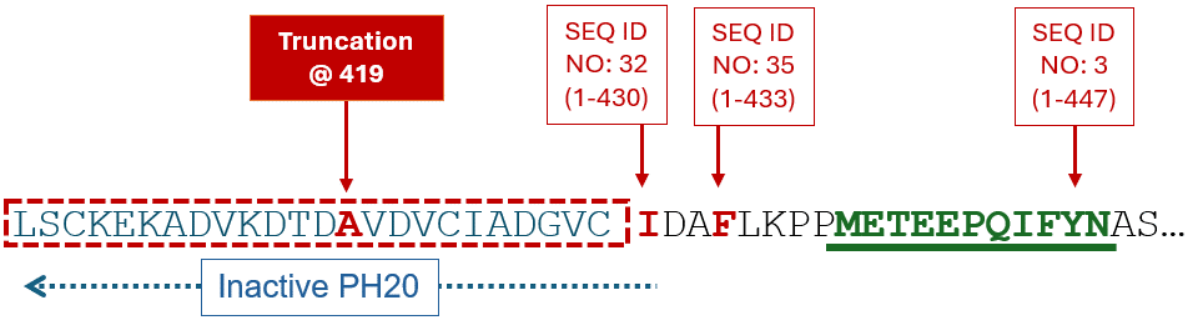
The C-terminus of PH20 is illustrated below, showing (i) the positions where SEQ ID NOS: **3** (447), **32** (430) and **35** (433) terminate, (ii) the "minimally active domain" at 437-447, and (iii) residues below position 429.[96] Positions resulting from deletion of 21 or 16 residues from SEQ ID NOS: 32 and 35 end before position 429.



95 EX1010, 9438; EX1003, ¶ 87.

96 EX1003, ¶ 153.

Consequently, a skilled artisan in 2011 would have believed that PH20 polypeptides that terminate before position 430 would be inactive (*e.g.*, at position 419, below).[97]



The common disclosure provides no examples of (or guidance concerning) PH20 mutants truncated below position 447 with one or more substitutions and that are enzymatically active. It thus ignores the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433.[98] The claims nonetheless capture modified PH20 polypeptides with truncations down to and beyond position 419.[99]

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97 EX1003, ¶¶ 92-93, 165-166.

98 EX1003, ¶¶ 92-93, 95, 97, 168.

99 EX1003, ¶¶ 164-66.

c) Empirical Test Results of Single-Replacement Modified PH20 Polypeptides Do Not Identify Multiply-Modified Enzymatically Active PH20 Polypeptides

The empirical results in the common disclosure provide no predictive guidance to a skilled artisan about the structural features of multiply-modified PH20 polypeptides within the claimed genera that are enzymatically active.

(i) The Data Concerning Single-Replacements Is Not Probative of Multiple-Replacement Mutants

The common disclosure reports results from testing a portion of a randomly generated library of ~6,743 single-replacement $PH20_{1-447}$ polypeptides.[100] These mutants were generated via a mutagenesis process which substituted one of ~15 amino acids into random positions in $PH20_{1-447}$ "such that each member contained a single amino change."[101] Approximately 5,917 were tested, while ~846 were uncharacterized.[102] More than half (~57%) of these mutants were classified as

[100] EX1001, 134:48-59, 202:13-15, 201:8-14.

[101] EX1001, 201:8-202:2.

[102] EX1003, ¶¶ 103-104. Inconsistent numbers of tested mutants and classifications of mutants are reported but not explained: (i) Table 3 lists 2,516 single-replacement $PH20_{1-447}$ mutants as "active mutants," but Table 9 identifies only 2,376 mutants that exhibit >40% hyaluronidase activity; (ii)

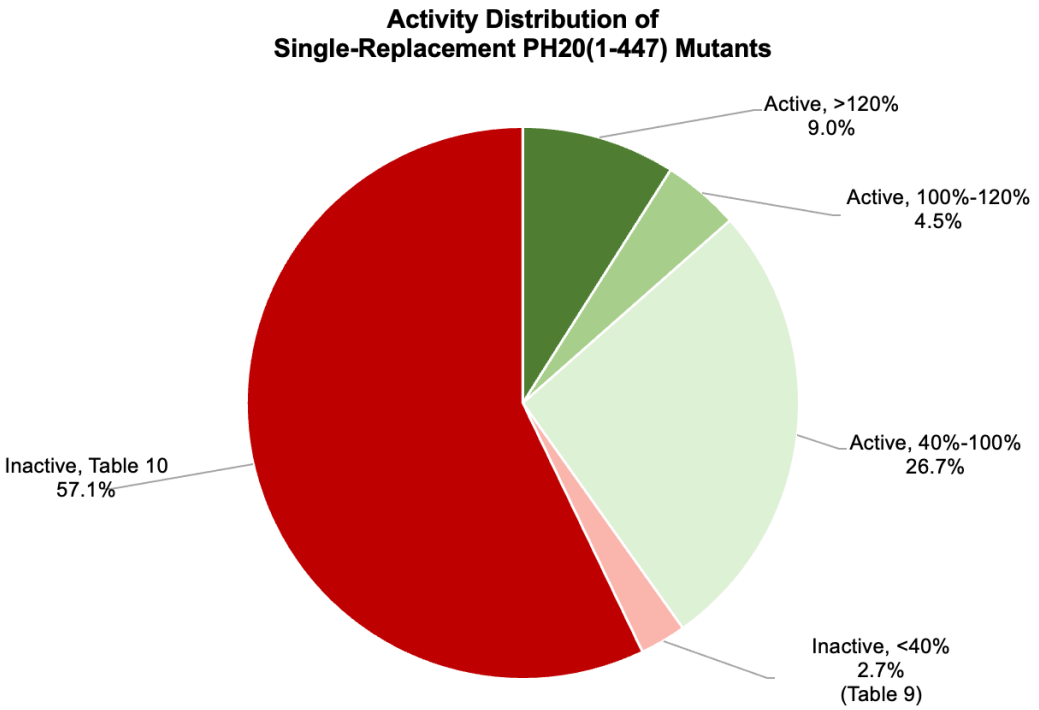
"inactive mutants," while ~30% (1335) were reported to have less activity than unmodified $PH20_{1-447}$ (20%-100%).[103] In other words, ~87% of the single-replacement $PH20_{1-447}$ polypeptides had ***less*** activity than unmodified $PH20_{1-447}$.[104]

Activity vs. Unmodified PH20	**Number**	**% of Tested (5916)**
Active Mutants (Table 9)		
>120%	532	9.0%
100%-120%	267	4.5%
40%-100%	1577	26.7%
Inactive Mutants (Table 9)		
<40%	160	2.7%
Inactive Mutants (Table 10)		
Table 10 'inactive mutants"	3,380	57.1%

Tables 5 and 10 list 3,368 and 3,380 $PH20_{1-447}$ "inactive mutants," respectively.

[103] EX1003, ¶ 105.

[104] *Id.*



The measured activity of single-replacement $PH20_{1-447}$ mutants shows no trends or correlations even for single-replacement $PH20_{1-447}$ polypeptides.[105] Instead, numerous examples show that even introducing different amino acids at the same position in $PH20_{1-447}$ resulted in (i) increased activity, (ii) decreased activity, or (iii) inactive mutants (below).[106]

[105] EX1003, ¶¶ 106, 142-43.

[106] Data from Tables 3, 5, 9, 10.

Position	Inactive	Decreased Activity	Increased Activity
008	P	L, M	I
067	R	L, Y	V
092	H	M, T	C, L, V
165	C	A, R, Y	D, F, N, S, V, W
426	K, S	E, G, N, Q, Y	P

The data on activities of tested single-replacement $PH20_{1-447}$ mutants is not analyzed or explained in the common disclosure—it is simply presented. There is no attempt to extrapolate its results to any combinations of substitutions in PH20 polypeptides, or to assess the impact of a single substitution on the protein's structure.[107] The quality of the data is also questionable: no control values or statistical assessments are provided.[108] All the data shows is that most of the tested single-substitution mutants impaired PH20's activity.[109]

The results from single substitutions provide no insights into PH20 polypeptides with multiple concurrent mutations, which together can cause complex and unpredictable effects on a protein's structure and resulting

[107] EX1003, ¶ 139.

[108] EX1003, ¶ 106.

[109] EX1003, ¶ 138.

function.[110] The patent's empirical test results thus provide no guidance to a skilled artisan about which of the many possible PH20 mutants with different sets of 2-42 substitutions will be enzymatically active.[111]

(ii) Purported Stability Data Is Not Reliable or Probative

The common disclosure reports results in Tables 11 and 12 from two runs of "stability" testing of ~409 single-replacement $PH20_{1-447}$ polypeptides.[112] Table 11 reports the hyaluronidase activity of single-replacement $PH20_{1-447}$ mutants tested at 4° C and 37° C, and in the presence of a "phenolic preservative" (m-cresol),[113] while Table 12 compares relative activities under pairs of these conditions.[114]

The data in Tables 11 and 12 provides no meaningful insights.[115] For example, unsurprisingly, single-replacement $PH20_{1-447}$ polypeptides showed higher activity at 37° C than at 4° C, given that PH20 exists at the former temperature in

[110] EX1003, ¶¶ 139, 142.

[111] EX1003, ¶¶ 140, 143.

[112] EX1001, 263:47-265:29.

[113] EX1001, 265:31-272:14 (Table 11).

[114] EX1001, 272:16-283:20 (Table 12).

[115] EX1003, ¶ 76.

humans.[116] And all that testing with m-cresol showed was that only a few mutants were able to resist its effects, with no explanation why.[117]

With one exception, there is no evidence the measured activity data was attributable to improved stability of PH20.[118] More directly, the common disclosure does not identify which ***combinations*** of substitutions improve stability.[119] It thus provides no probative insight regarding multiply-modified PH20 polypeptides with increased stability.[120]

The data is also largely meaningless, as many of their values fall within the range of activity observed for the positive control.[121] As the charts and table below show, the activity of unmodified $PH20_{1-447}$ varied by 97% and 87% in two rounds of testing.[122]

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116 EX1003, ¶ 73; EX1001, 177:66-178:8.

117 EX1003, ¶ 69.

118 EX1003, ¶ 69.

119 EX1003, ¶¶ 75-76.

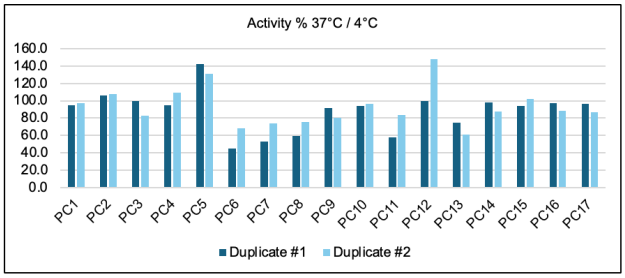
120 *Id*.

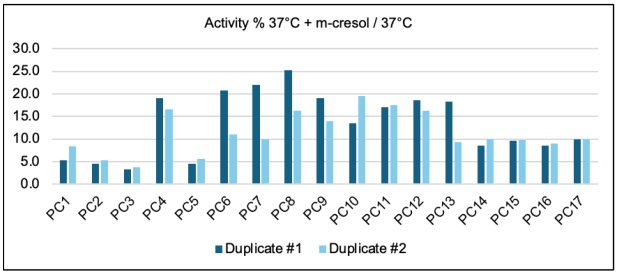
121 EX1003, ¶ 71; EX1001, 281-283 (Table 12).

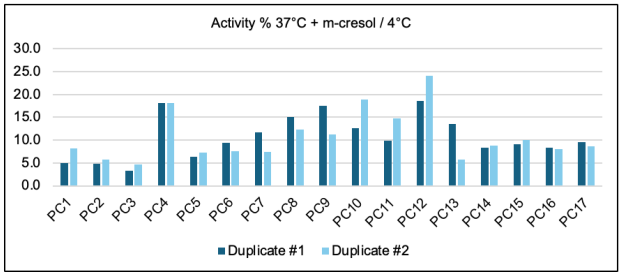
122 EX1003, ¶ 71, Appendix A-7, A-8.

Positive Control ("PC") (OHO)	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C+mcr/4°C
PC1	94.998	5.230	4.970	96.871	8.456	8.190
PC2	105.798	4.480	4.740	108.066	5.246	5.670
PC3	100.000	3.330	3.330	82.778	3.759	4.590
PC4	94.762	19.070	18.070	109.539	16.529	18.110
PC5	142.024	4.480	6.360	130.947	5.595	7.330
PC6	45.115	20.770	9.370	68.017	11.035	7.510
PC7	53.324	21.950	11.710	74.253	9.960	7.400
PC8	59.581	25.240	15.040	75.872	16.231	12.310
PC9	91.844	19.050	17.500	80.371	13.977	11.230
PC10	93.828	13.470	12.630	96.630	19.454	18.800
PC11	57.773	17.040	9.850	83.536	17.573	14.680
PC12	100.000	18.560	18.560	148.226	16.239	24.070
PC13	74.325	18.290	13.600	61.119	9.286	5.680
PC14	98.132	8.480	8.320	87.677	10.006	8.770
PC15	93.817	9.620	9.020	102.223	9.745	9.960
PC16	96.922	8.560	8.300	87.993	9.064	7.980
PC17	96.648	9.910	9.580	86.891	9.938	8.630

KEY
Coloration of Percent (%) Activity Values
n/a
>120
between 100 and 120
between 80 and 100
between 40 and 80
between 20 and 40
between 10 and 20
between 0 and < 10







	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C + m-cresol	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol	% Activity at 37°C+mcr/4°C
High	142.02	25.24	18.56	148.23	19.45	24.07
Low	45.12	3.33	3.33	61.12	3.76	4.59
Range	96.91	21.91	15.23	87.11	15.70	19.48
Average	88.17	13.38	10.64	93.00	11.30	10.64
Mean	94.76	13.47	9.58	87.68	9.96	8.63

As Dr. Hecht observes, this "significant variation raises serious doubts about how probative or instructive the values of individual tested mutants that fall within the range of variability observed for the control can possibly be."[123] The data not only fails to identify specific combinations of substitutions that yield PH20 mutants with increased resistance to or stability in denaturing conditions, it is unreliable.

d) The Common Disclosure's Research Plan Does Not Identify Multiply-Mutated Enzymatically Active PH20 Polypeptides

The common disclosure does not describe any multiply-modified PH20 polypeptides that are "active mutants." Instead, it simply presents ***the idea*** of multiply-modified PH20 polypeptides. First, it observes that "[a] modified PH20 polypeptide can have up to 150 amino acid replacements," "[t]ypically" contains between 1 and 50 amino acid replacements and "can include any one or more other

[123] EX1003, ¶¶ 70-72; *see also* EX1001, 283:27-37 (positive control also varied).

modifications**,** in addition to at least one amino acid replacement as described herein."[124] It also contends a modified PH20 polypeptide with "a sequence of amino acids that exhibits" between 68% and 99% sequence identity with any of unmodified Sequence ID Nos. 74-855 "***can*** exhibit altered, such as improved or increased, properties or activities compared to the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[125]

None of these statements identify ***any*** actual multiply-modified PH20 polypeptides (*i.e.*, particular sets of specific amino acid substitutions), much less provide results from testing any.[126] They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides.

The common disclosure also describes no methods that produce any specific multiply-modified, enzymatically active PH20 polypeptides. What it provides instead is a prophetic research plan requiring "iterative" make-and-test experiments that ***might discover*** multiply-modified enzymatically active PH20 PH20 polypeptides:

> The method provided herein [] is ***iterative***. In one example, after the method is performed, any modified hyaluronan-

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124 EX1001, 48:43-53.

125 EX1001, 100:22-37 (emphasis added).

126 EX1003, ¶ 172.

> degrading enzymes identified as exhibiting stability … ***can be modified or further modified*** to increase or optimize the stability. A secondary library ***can be*** created by introducing additional modifications in a first identified modified hyaluronan-degrading enzyme. … The secondary library ***can be*** tested using the assays and methods described herein.[127]

This prophetic research plan is effectively meaningless—it does not indicate that any active mutant multiply-modified PH20 polypeptides will be found, much less identify ***which*** multiply-modified PH20 polypeptides are active mutants.[128] An alternative focus is then proposed: mutations can be "targeted near" "critical residues" which supposedly "can be identified because, when mutated, a normal activity of the protein is ablated or reduced."[129] But Tables 5 and 10 show that at least one substitution at each of 405 positions between positions 1 and 444 of $PH20_{1-447}$ resulted in an inactive mutant.[130] In other words, the common

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127 EX1001, 142:13-26 (emphases added); *see also id.* at 42:48-55, 135:27-32; EX1003, ¶¶ 173-177.

128 EX1003, ¶¶ 173, 184-85, 190; EX1001, 44:1-3; *see generally id.*, 134:48-135:26, 135:35-137:10, 137:38-142:12.

129 EX1001, 142:27-53; EX1003, ¶¶ 178-79.

130 EX1003, ¶ 180, Appendix A-3.

disclosure's guidance is to target locations "near" ~90% of the amino acids in $PH20_{1-447}$, which is no different than targeting every residue in the protein.[131] It is, like the first proposed "iterative" process, meaningless.

These prophetic research plans, based entirely on unfocused, iterative "make-and-test" experiments, provide no direction to the skilled artisan about which of the trillions and trillions of possible multiply-modified PH20 polypeptides are enzymatically active.[132] Instead, they require the skilled artisan to repeat the cycle of mutagenesis iteratively, screening and selecting until 10^{59} to 10^{112} modified PH20 polypeptides are produced and screened for activity.[133] That in no way demonstrates possession of the claimed genus.

The specification also incorrectly portrays the experimental readout—hyaluronidase activity—as a measure of "stability."[134] As Dr. Hecht explains, to assess a protein's stability directly one performs experiments that measure the energy associated with the protein's transition between its folded and unfolded

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131 EX1003, ¶ 180.

132 EX1003, ¶ 190.

133 EX1003, ¶¶ 175-77, 187-89; EX1001, 137:19-24, 137:11-36, 140:31-35, 140:46-51, 141:1-15.

134 EX1003, ¶¶ 67, 69, 179.

states.[135] Activity may or may not be influenced by stability, but is not itself a measure of stability.[136]

e) The Common Disclosure Does Not Identify a Structure-Function Relationship for Multiply-Modified, Enzymatically Active PH20 Polypeptides

The common disclosure does not identify the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.[137] Instead, it simply lists single replacements to random amino acids at random positions that were classified as "active mutants" by a hyaluronidase assay; nothing is said about the effects (if any) of substitutions on the protein's structure.[138]

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135 EX1003, ¶¶ 63-66.

136 EX1003, ¶ 67.

137 EX1003, ¶¶ 139-40, 151.

138 EX1001, 234:25-53; EX1003, ¶¶ 139-40, 142.

The common disclosure also does not identify any ***sets*** of specific amino acid replacements that correlate to structural domains or motifs that positively or negatively influence hyaluronidase activity, much less ***predictably*** increase activity to defined thresholds.[139] Again, it simply reports activity data from testing randomly generated ***single***-replacement $PH20_{1-447}$ mutants.

The common disclosure's empirically identified examples of "active mutant" single-replacement $PH20_{1-447}$ mutants also do not ***by themselves*** identify any "structure-function" relationship between "active mutants" and the set of single-replacement modified $PH20_{1-447}$ polypeptides.[140] They certainly do not do so for the much larger genus of modified PH20 polypeptides of varying lengths and between 2 and 42 substitutions.[141]

Critically, the common disclosure ***does not even contend*** that a particular amino acid replacement at a particular position (*e.g.*, 307) that makes a $PH20_{1-447}$ an "active mutant" will make any other modified PH20 polypeptide with that same amino acid replacement (plus between 1 and 41 additional replacements or

[139] EX1003, ¶¶ 55, 142-43.

[140] EX1003, ¶¶ 61, 143, 157, 159.

[141] EX1003, ¶ 157.

truncations) an "active mutant."[142] Such an assertion would have no scientific credibility—the activity of a protein such as PH20 is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.[143] Thus, even the inventors did not view their compilation of test results as identifying a structure-function correlation for multiply-modified PH20 polypeptides.

The common disclosure, thus, does not identify to a skilled artisan ***any*** structural features shared by the many, diverse "active mutant" modified PH20 polypeptides within the scope of the claims,[144] and thus cannot satisfy the written description requirement of § 112(a) as a disclosure that links a functional property to a particular structure ***shared*** by the members of the genus.

f) The Common Disclosure Does Not Describe a Representative Number of Multiply-Modified Enzymatically Active PH20 Polypeptides

The ~2,500 active mutant single-replacement $PH20_{1-447}$ polypeptides in the disclosure are not representative of the various genera within the claims.[145]

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142 EX1003, ¶¶ 168, 192-93.

143 EX1003, ¶¶ 56-57.

144 EX1003, ¶ 157.

145 EX1003, ¶¶ 61, 143, 155, 159.

First, these single-replacement $PH20_{1-447}$ examples are not representative of the trillions and trillions of $PH20_{1-447}$ polypeptides with between ***2 and 42 substitutions*** at any of hundreds of positions within the protein.[146] The latter group of proteins is structurally distinct from single replacement PH20 polypeptides, both as to their sequences and as to the various secondary structures and structural motifs within the folded proteins that result when multiple amino acid substitutions are incorporated and from the distinct interactions those substitutions can cause with their neighboring residues.[147] The effects of numerous substitutions on the PH20 protein's various secondary structures and structural motifs are not described or discussed in the common disclosure, and the magnitude of structural changes resulting from the concurrent substitutions encompassed by the claims was unknowable in 2011.[148] The overall activity of a protein with multiple substitutions also will not be due to one amino acid, but to the unique structure of each protein that reflects ***the totality*** of effects of those many substitutions.[149]

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146 *See* § IV.D.1; EX1003, ¶¶ 61, 143, 159.

147 EX1003, ¶¶ 55-56, 58, 60, 156, 159.

148 EX1003, ¶¶ 157-58, 229.

149 EX1003, ¶¶ 61, 141.

More specifically, introducing a first amino acid substitution often affects the neighbors of that original/replaced amino acid by, for example, (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, and/or (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).[150] Introducing a second substitution in that region may reverse those interactions (or not) with each neighboring residue, and a third substitution may do the same, with up to 21 rounds permitted by even the narrowest claims, each potentially impacting each interaction.[151] The data associated with a single amino acid substitution thus cannot be representative of the properties of any of these downstream, multiply-substituted mutants, which will have an unknowable combination of substitutions that each uniquely impact the properties of the mutated protein.[152]

Enzymatically active single-replacement $PH20_{1-447}$ polypeptides also are not representative of enzymatically active, multiply modified PH20 polypeptides that incorporate changes that alone render PH20 proteins inactive (*e.g.*, truncations terminating below position 429, or single substitutions that render $PH20_{1-447}$

150 EX1003, ¶¶ 56-58.

151 EX1003, ¶¶ 58-60, 142.

152 EX1003, ¶¶ 143, 159.

inactive).[153] That is because an ***active*** single-replacement $PH20_{1-447}$ polypeptide does not also contain the distinct structural features that render the latter types of PH20 polypeptides enzymatically ***inactive***. For example, an enzymatically active $PH20_{1-447}$ protein with a single amino acid substitution (*e.g.*, L307W) would not be considered representative of a PH20 that combines that L307W substitution with truncations at the C terminus ending at positions between 409 to 433 because the common disclosure would have led a skilled artisan to expect that PH20 proteins terminating at those positions would be inactive.[154] A skilled artisan could not have predicted—based on the examples in the common specification, all of which are limited to single-replacement $PH20_{1-447}$ polypeptides—whether enzymatic activity could be restored to such severely truncated PH20 mutants, much less the precise additional changes that would do so.[155]

The common disclosure thus provides a very narrow set of working examples relative to the diversity of modified PH20 polypeptides being claimed.[156] The examples are restricted to ***one type of change*** (a single amino acid

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153 EX1003, ¶¶ 161-64.

154 EX1003, ¶¶ 167-69.

155 EX1003, ¶ 168.

156 EX1003, ¶ 155.

replacement) in ***one type of PH20 polypeptide*** (SEQ ID NO: 3).[157] By contrast, the claims encompass changes in 37 different unmodified PH20 sequences, and include, in addition to one identified replacement at position 307, anywhere from 1 to 41 (claim 1) to 20 (claims 25-26) additional changes.[158] A simple illustration demonstrates how ***non-representative*** the examples are: all of the examples of single-replacement $PH20_{1-447}$ mutants fit into one box of the array below (claim 2).

	Number of Changes																					
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3																							
7																							
32																							
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157 EX1003, ¶¶ 97, 99, 103.

158 EX1003, ¶¶ 115-20.

Unlike claim 2, which requires 95% sequence identity, claim 1 permits 91% sequence identity, thus capturing an even ***larger*** genus (up to 42 permitted changes) than depicted above.

Consequently, a skilled artisan would not have viewed the Patents' examples of individual single amino acid replacements in $PH20_{1-447}$ as being ***representative*** of the diversity of modified PH20 polypeptides encompassed by the claims.[159]

g) The Claims Capture Multiply-Modified PH20 Polypeptides the Disclosure Excludes from the Class of Enzymatically Active PH20 Proteins

Patentee's position on the breadth of the claims is unknown. However, by their literal language, they capture several sub-genera of "active mutant" modified PH20 polypeptides that the common disclosure says caused single-replacement $PH20_{1-447}$ mutants to be inactive (*i.e.*, those with replacements in Tables 5/10 or in PH20 sequences terminating before position 429). Likewise, the claim language captures modified PH20 polypeptides with the six combinations of replacements the common disclosure explicitly says to not make: P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, N333A/N358A and N47A/N131A/N219A.[160] The claims thus improperly capture multiply-modified PH20 polypeptides the common

[159] EX1003, ¶ 143.

[160] *See* § V.A.2.a; EX1001, 77:46-58.

disclosure affirmatively excludes from the genus of enzymatically active PH20 polypeptides.

The common disclosure provides no exemplification of multiply-modified species of PH20 polypeptides that disregard these restrictions in the common disclosure.[161] There is no explanation of the types of substitutions that might be made to restore activity that, under the logic of the common disclosure, will result in enzymatically inactive PH20 polypeptides or which the specification teaches ***not*** to make.[162] Yet the claims encompass such proteins. The claims thus independently violate the written description requirement for the reasons articulated by the Federal Circuit in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998)—if a disclosure "unambiguously limited" the invention, but the claims circumvent that limitation, those claims are "broader than the supporting disclosure" and are unpatentable.

2. Dependent Claims 3-5, 16-24, and 27-35 Lack Written Description

a) Claims 3-4

Claims 3 and 4 specify additional functional properties of the modified PH20 polypeptides in the genus defined by claim 1: either (i) increased

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[161] EX1003, ¶ 161.

[162] EX1003, ¶ 168.

hyaluronidase activity (claim 4) or (ii) increased stability (claim 3) relative to unmodified $PH20_{1-447}$.

The reasons provided in § V.A.1 explaining why the claims generally lack written description apply with full force to claims 3 and 4.

In addition, the common disclosure's recitation of a ***desired*** level of stability or hyaluronidase activity in claims 3 and 4 does not identify ***which*** of the many trillions of PH20 polypeptides having 91% or 95% sequence identity with SEQ ID NOS: 3, 7, or 32-66 and one of nine replacements at position 307 will exhibit either of those functional properties.[163]

First, the identification of one $PH20_{1-447}$ mutation at position 307 that exhibited increased activity (L307T) compared to unmodified $PH20_{1-447}$ is not representative of each claim's genus of PH20 polypeptides with 1 to 41 additional substitutions and/or truncations, and even other substitutions at position 307 (including all other claimed substitutions, such as L307S and L307W) that, when made as single-substitutions, did ***not*** result in increased activity.[164] Notably, the patent also contains no disclosure of a PH20 protein with a substitution at position 307 that exhibits increased stability. In fact, only one of the substitutions recited in

[163] EX1003, ¶¶ 185, 191-92.

[164] EX1001, 235 (Table 9); EX1003, ¶¶ 127, 191-92.

claim 1, L307G, was even tested for "stability," and it showed ***no activity*** (0.00) in the presence of the m-cresol denaturing agent.[165]

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides (if any) exhibiting increased activity or stability.[166] The mere presence of a single substitution at position 307 in a modified PH20 certainly does not demonstrate possession of any multiply-modified PH20 polypeptide with increased activity or stability having that position 307 substitution, and the common disclosure does not contend otherwise.[167]

The common disclosure does not describe any multiply-modified PH20 polypeptides having the claimed substitutions at 307, much less those with 1 to 41 additional substitutions, and that exhibit increased enzymatic activity or increased stability.[168] Indeed, the common specification does not identify any multiply-modified PH20 polypeptides with any level of hyaluronidase activity.[169] Similarly, even if the data reported in Tables 11 and 12 was not flawed and unreliable as a

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165 EX1001, Table 11, col. 268, Table 12, col. 277.

166 EX1003, ¶¶ 157, 185, 190.

167 EX1003, ¶¶ 143, 168, 185.

168 EX1003, ¶¶ 140, 190-93.

169 EX1003, ¶¶ 130, 172.

measure of "stability" (as discussed above, it is), it too is limited to singly-substituted PH20 polypeptides, and, provides no "stability" data for multiply-modified PH20 polypeptides.[170]

Claims 3 and 4 lack written description in the common disclosure.

b) Claims 5, 16

Claims 5 and 16 require an additional functional property: that the modified PH20 polypeptide be "soluble." Each lacks written description support (i) for the same reasons identified for claim 1, and (ii) because they encompass modified PH20 polypeptides that the common disclosure suggests would be insoluble.

The common disclosure explains that "a soluble PH20 lacks all or a portion of a glycophosphatidyl anchor (GPI) attachment sequence,"[171] which was known to be hydrophobic.[172] Citing prior art, it identifies the first residue of the GPI sequence in human PH20 as position 456 (position 491 in SEQ ID NO: 6).[173] It

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170 EX1001, Tables 11, 12.

171 EX1001, 46:28-30, 72:9-10, 74:27-39.

172 EX1001, 72:33-45; EX1005, 86:18-22.

173 EX1001, 72:33-45; *also* EX1005, 2:56-61 ("Attempts to make human PH20 DNA constructs that would not introduce a lipid anchor into the polypeptide

also states that a soluble PH20 "is a polypeptide that is truncated after amino acid 482 of … SEQ ID NO: 6" (*i.e.*, 447 in SEQ ID NO:3)."[174] It thus suggests that human PH20 sequences that terminate below position 448 are soluble and those that terminate above position 456 are insoluble.[175]

Claims 5 and 16 encompass PH20 polypeptides based on SEQ ID NOS:59-66, which terminate between positions at 457 to 464 respectively (*i.e.*, beyond position 456), and does not restrict where in the PH20 polypeptide changes are made, other than the replacement at position 307. Consequently, claims 5 and 16 capture modified PH20 polypeptides that are C-terminally truncated but, per the common disclosure, ***are not*** "soluble modified PH20 polypeptide[s]" because each contains "all or a portion of" the GPI attachment sequence.[176]

Patentee may contend that some unidentified number of modified PH20 polypeptides based on SEQ ID NOS: 59-66 ***may*** be soluble, citing the common disclosure as suggesting that between 1-10 residues within the GPI anchor "can be

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resulted in either a catalytically inactive enzyme, or an insoluble enzyme") (citing EX1011).

174 EX1001, 75:17-19; EX1005, 3:57-62.

175 EX1003, ¶¶ 89-90.

176 EX1001, 46:55-61.

retained, provided the polypeptide is soluble."[177] But the common disclosure does not identify ***which*** modified PH20 polypeptides terminating above position 448 (and especially terminating between 457 and 464) ***are*** soluble, provides no examples of such soluble PH20 mutants, and provides no reason to expect that many modified PH20 polypeptides within the claim's scope are soluble.

Thus, claims 5 and 16 are unpatentable for lack of written description for this additional, independent reason.

c) Claims 17-24 and 27-35

Claims 17-24 and 27-35 do not meaningfully alter the number of PH20 polypeptides in the genus of claim 1.[178] They instead specify additional features (claims 17-23, 34-35), or pharmaceutical compositions, or methods of treatment that reference the genus of claim 1. They lack written description for the same reasons explained in § V.A.1.[179]

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177 EX1001, 74:20-26.

178 Claim 22 omits reference SEQ ID NO:7.

179 *Idenix*, 941 F.3d at 1155, 1165 (method of treatment claims involving immense genus of modified proteins invalid for lack of written description and non-enablement); *Boehringer*, PGR2020-00076, Paper 42, at 40-41 (methods of treatment claims found to lack written description because

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

"If a patent claims an entire class of … compositions of matter, the patent's specification must enable a person skilled in the art to make and use the ***entire*** class," *i.e.*, "the ***full scope*** of the invention" and so the "more one claims, the more one must enable."[180] "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."[181] "Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation."[182]

Although not required, enablement may be assessed using the *Wands* factors, which consider: "(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the

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specification did not provide an adequate written description of compositions being administered).

180 *Amgen*, 598 U.S. at 610 (emphases added).

181 *Idenix*, 941 F.3d at 1159.

182 *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention."[183]

Where the scope of the claims is large, there are few working examples disclosed in the patent, and the only guidance to practice "the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims' functional limitations—the asserted claims are not enabled."[184]

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the 10^{59}+ PH20 polypeptides having multiple amino acid replacements and/or truncations within the scope of the claims are "active mutant" PH20 polypeptides.[185]

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183 *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

184 *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, T., sitting by designation) *aff'd* 81 F.4th 1362 (Fed. Cir. 2023).

185 EX1003, ¶¶ 170-71, 190.

1. Claims 1-2, 6-15, 22, and 25-26 Are Not Enabled

The facts of this case are a textbook example of claims that are not enabled under the reasoning articulated by the Supreme Court in *Amgen*. An analysis of the common disclosure under the Federal Circuit's framework for assessing undue experimentation using the factors in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) compels the same conclusion.

a) Extreme Scope of the Claims

As explained in § IV.D.1, each of claims 1-2, 6-15, 22, and 25-26 define an immense and diverse genus of between 10^{59} and 10^{112} enzymatically active modified PH20 polypeptides. Practicing that full genus, however, raises substantial scientific questions left unanswered by the common disclosure:

(i) The claims encompass many modified PH20 polypeptides that terminate below position 429.[186] The common disclosure and the prior art, however, report that unmodified human PH20 must include residues through position 429 to have hyaluronidase activity.[187]

(ii) Several claims (e.g., 1-2, 6-10, 15, 22) encompass modified PH20 polypeptides that, per the common disclosure's guidance, would be

[186] EX1003, ¶¶ 154, 164.

[187] EX1001, 69:67-70:9; EX1003, ¶¶ 93, 152-53.

expected to be insoluble because they include all or some of the GPI anchor sequence.[188]

(iii) The mathematical "sequence identity" boundaries set by the claim language cause the claims to capture (without restriction) modified PH20 polypeptides with 2 to 42 amino acid replacements that the common disclosure instructs "are less tolerant to change or required for hyaluronidase activity"[189] or which the common disclosure affirmatively says to not make.[190]

In other words, the claims capture massive genera of modified PH20 polypeptides, most of which would have unknowable properties absent individual production and testing.[191]

Claims that capture a massive and diverse genus of proteins have routinely been found non-enabled. For example, the claims in *Amgen* covered "millions" of different, untested antibodies,[192] while in *Idenix*, a skilled artisan would

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188 EX1001, 46:28-30, 72:9-10, 74:20-26, 75:17-19; EX1005, 2:56-61, 3:57-62.

189 EX1001, 80:14-16.

190 EX1001, 77:46-58.

191 EX1003, ¶ 158.

192 598 U.S. at 603.

"understand that 'billions and billions' of compounds literally meet the structural limitations of the claim."[193] In both cases, the enormous claim scope was found non-enabled after being contrasted to the limited working examples in the patent, the existence of unpredictability, and the quantity of experimentation needed to practice the full scope of the claims (*Wands* Factors 1, 3, 4, and 7). And, as the *Idenix* court observed, one cannot rely on the knowledge and efforts of a skilled artisan to try to "fill the gaps in the specification" regarding which of the "many, many thousands" of possible compounds should be selected for screening, and which in this case is impossible.[194]

b) Limited Working Examples and Only a Research Plan for Discovering Active Mutant PH20 Polypeptides

The common disclosure provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement $PH20_{1-447}$ polypeptides, of which ~2500 were "active mutants."[195] Those examples are a tiny fraction of the 10^{59} to 10^{112} modified PH20 polypeptides covered by the claims, and provide no guidance that would help a skilled artisan navigate the "trial-and-error" methodology the common disclosure describes using to make modified PH20

193 941 F.3d at 1157.

194 *Id.* at 1159.

195 EX1003, ¶ 103.

polypeptides; indeed, none incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.[196]

The common disclosure provides no credible guidance on the full scope of the genus comprising multiple combinations of changes to PH20 polypeptides.[197] Instead, it describes an explicitly prophetic and "iterative" process for ***discovering*** active mutant PH20 polypeptides. *See* § V.A.1.d.

The purely prospective research plan in the common disclosure demands that a skilled artisan engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of ***randomized*** mutations (up to 41 rounds per starting molecule under the broadest claims) to ***discover*** which of the 10^{59}+ possible modified PH20 polypeptides having 2 to 41 replacements to any of 19 other amino acids in any of many, varying-length starting PH20 sequences might possess hyaluronidase activity.[198]

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196 EX1003, ¶¶ 155, 159, 167.

197 EX1003, ¶¶ 131, 139.

198 EX1003, ¶¶ 188-90; *see also* EX1018, 382 ("combinatorial randomization of only five residues generates a library of 205 possibilities (3.2 x 10^6 mutants), too large a number for manual screening"). Chica also credited a supposed "ground-breaking" advancement in predictive molecular modeling techniques.

Second, it provides no meaningful guidance in producing "active mutant" modified PH20 polypeptides:

(i) it does not identify ***any*** specific combination of two or more replacements within any PH20 polypeptide that yield "active mutants";

(ii) it provides no data from testing ***any*** PH20 polypeptide with two or more substitutions; and

(iii) it does not identify any regions or residues that are "associated with the activity and/or stability of the molecule" or "'critical residues involved in structural folding or other activities' of the molecule" when two or more concurrent replacements have been made.[199]

From the common disclosure and their knowledge in 2011, a skilled artisan could not predict whether a particular multiply-modified PH20 polypeptide will be enzymatically active without making and testing each one.[200]

EX1018, 384, 382. That supposed advancement, however, was later shown to be false. EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

[199] EX1003, ¶¶ 144, 158, 172, 184-85.

[200] EX1003, ¶ 190.

Regardless whether individual rounds of "iterative" production and testing might be considered "routine," the process described in the common disclosure is indistinguishable from the "***iterative, trial-and-error process[es]***" that have consistently been found to not enable broad genus claims to modified proteins.[201] Simply put, the common disclosure's prophetic, iterative and labor-intensive process requires making and screening an immense number of modified PH20 polypeptides, before which the skilled artisan will not know which multiply-modified PH20 polypeptides are within the claims' scope.[202]

c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable

Like any protein, the activity of PH20 can be unpredictably influenced by changes to its amino acid sequence.[203] Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary

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201 *Idenix*, 941 F.3d at 1161-63 (emphasis added); *see also Amgen,* 598 U.S. at 612-15; *Wyeth*, 720 F.3d at 1384-86; *Baxalta*, 597 F. Supp. 3d at 616-19; *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 n.2 (Fed. Cir. 2020).

202 EX1003, ¶¶ 172, 183-85, 189.

203 EX1003, ¶ 61.

structures or structural motifs within the protein that are important to its biological activity (*e.g.*, catalysis, ligand binding, etc.) and/or stability.[204]

As explained in § VI, below, by 2011, skilled artisans could have assessed whether certain ***single*** amino acid substitutions at certain positions would be tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.[205] That person, using a rational design approach, would have performed such an assessment by, *inter alia*, analyzing evolutionarily non-conserved positions and evaluating specific changed residues using a PH20 protein structure model using experimental evidence available before 2011 that is not disclosed in or referenced by the common disclosure.[206]

By contrast, the skilled artisan could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011.[207] Introducing ***multiple*** concurrent changes into a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity and/or stability,

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204 *Id.*

205 EX1003, ¶ 194.

206 EX1003, ¶¶ 20, 49.

207 EX1003, ¶¶ 158, 229.

and can even introduce new ones into the protein.[208] Replacing multiple amino acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.[209]

The cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure in 2011. For example, the further away the modeled amino acid sequence gets from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model became.[210] In addition, depending on the structural template used to produce the model, regions of the protein not supported by a corresponding structure cannot be reliably used to assess particular changes.[211] And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.[212]

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208 EX1003, ¶¶ 59-60, 185.

209 EX1003, ¶¶ 55, 58, 61.

210 EX1003, ¶¶ 158, 190, 229; EX1004, ¶¶ 168-169.

211 EX1003, ¶¶ 158, 229; EX1004, ¶¶ 158-160; EX1012, 4, 8.

212 EX1003, ¶ 51, 190; EX1059, 1225-26; EX1018, 378.

Consequently, a skilled artisan could not have used conventional rational design techniques to identify, much less predict the outcome of attempts to make, the enormous number of PH20 polypeptide sequences that incorporate the myriad possible combinations of between 2 and up to 42 substitutions the claims encompass.[213] Stated another way, practicing the full scope of the claims would have been well beyond the ability of the skilled artisan's ability to reasonably predict which multiply-modified PH20 polypeptides would be enzymatically active, and, even if possible, doing so would have taken an extreme amount of time and effort even for a small handful of the vast universe of multiply-modified polypeptides within the claims.[214]

d) Other Wands Factors and Conclusion

The remaining *Wands* factors either support the conclusion that practicing the full scope of the claims would require undue experimentation or are neutral.

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed.[215]

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213 EX1003, ¶¶ 61, 158, 229.

214 EX1003, ¶¶ 158, 190.

215 EX1003, ¶¶ 158, 229.

Likewise, while there was significant knowledge in the public art about hyaluronidases, there was no solved structure of the PH20 protein, experimental reports generally reported on ***loss of activity*** from mutations, and did not predictably teach how to introduce changes that ***enhanced*** stability or activity. Indeed, the non-enabled patent disclosure at issue in *Amgen* dates to the same 2011 timeframe as the common disclosure.

Practicing the full scope of claims 1-2, 6-15, 22, and 25-26 thus would have required a skilled artisan to engage in undue experimentation, which renders those claims non-enabled.

2. Dependent Claims 3-5, 16-24, and 27-35 Are Not Enabled

a) Claims 3-4

Claims 3 and 4 require the modified PH20 polypeptides to have increased activity (*i.e.*, >100% of unmodified PH20) or increased resistance to or stability in denaturing conditions.

The reasons why claims 1-2, 6-15, 22, and 25-26 are not enabled (*see* § V.B.1) establish why claims 3 and 4 are also not enabled. Specifically, a skilled artisan could not have predicted which of the trillions of PH20 polypeptides having up to 41 changes beyond a required change at position 307 would exhibit increased

activity or stability compared to an unmodified PH20.[216] Instead, a skilled artisan would need to make-and-test each molecule in order to practice the "full scope" of the claims.[217]

b) Claims 5, 16

Because claims 5 and 16 encompass a substantial portion of the genus defined by claim 1, they are not enabled for the same reasons.

Additionally, as explained in § V.A.2.b, the common disclosure suggests that PH20 polypeptides (modified or unmodified) that extend past position 456 would be "insoluble." Based on it and published literature, a skilled artisan would have expected the presence of the hydrophobic GPI sequence in the PH20 protein could cause aggregation, loss of activity, and/or reduced expression.[218] The common disclosure reinforces that these problems can occur, but provides no guidance as to how solve them and no examples of modified PH20 polypeptides extending past position 456 that are soluble. Claims 5 and 16 are thus not enabled.

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216 EX1003, ¶¶ 185, 190.

217 *Id.*

218 EX1003, ¶¶ 89-90, 196; EX1001, 51:2-4, 72:33-45; *also* EX1005, 2:56-61.

c) Claims 17-24, 27-35

The remaining claims employ the same or substantially the same genus definition used in claim 1 and recite either further modifications to the modified polypeptides, pharmaceutical compositions, or methods of treatment using the claimed genus. These claims do not add requirements that limit the numbers of polypeptides in the claim 1 genus.[219] They are therefore not enabled for the same reasons.[220]

C. Inactive PH20 Polypeptides Are Not Useful and Do Not Remedy the § 112(a) Deficiencies of the Claims

Patentee may contend the claims do not require the modified PH20 polypeptides to be "active mutants." Such a contention, even if accepted, does not solve the written description and enablement problems of the claims.

First, it ignores that at least ***a portion*** of the claimed genus ***does*** require the modified PH20 polypeptides to be "active mutants." *See* § V.B.2.a. Claim 4 defines a "sub-genus" of modified PH20 polypeptides that is within the scope of claim 1 and that must exhibit increased hyaluronidase activity. The failure of the

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[219] Claim 22 limits the genus by removing SEQ ID NO:7, but defines an immense genus otherwise identical to claim 1.

[220] *See, e.g.*, *Idenix*, 941 F.3d at 1155, 1165.

common disclosure to enable or describe that subgenus demonstrates that claim 1 is unpatentable.[221]

Second, the common disclosure provides no correlation between multiply-modified PH20 polypeptides and ***either*** active or inactive mutants.[222] The skilled artisan thus must perform trial-and-error testing of each of the 10^{59}+ candidate polypeptides within the claims' scope to determine which are "active mutants" and which are "inactive mutants."[223]

Third, the only putative utility identified for "inactive" polypeptides is as "antigens in contraception vaccines."[224] That assertion is not scientifically

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221 *ABS Glob., Inc. v. Inguran*, 914 F.3d 1054, 1070, 1074 (7th Cir. 2019) ("If the specification failed to enable [a limitation] in the dependent claim, then [] the full scope of the invention is also not enabled in the independent claim, and *both* claims are invalid for non-enablement") (citing *Alcon Research, Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1367-68 (Fed. Cir. 2012)).

222 EX1003, ¶ 143.

223 EX1003, ¶¶ 173-74, 182-84.

224 EX1001, 75:57-59, 194:48-67.

credible.[225] While the specification cites two studies in guinea pigs,[226] it ignores numerous publications before 2011 that showed that immunizing mammals with PH20 did ***not*** cause contraception.[227] Moreover, Patentee reported that clinical studies of unmodified $PH20_{1-447}$ in 2018 showed that "[a]lthough some antisperm antibodies are associated with decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex."[228] Notably, Patentee publicly reported this clinical result before filing the application that issued as the '590 Patent. A skilled artisan thus would have

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225 EX1003, ¶ 113.

226 EX1001, 194:48-67; EX1022, 1142-43; EX1023, 1133-34.

227 *See* EX1019, 325, 331-33 ("recombinant mPH20 is not a useful antigen for inclusion in immunocontraceptive vaccines that target mice"); EX1020, 179-81 ("immunization [of rabbits] with reproductive antigens … are unlikely to result in reduced fertility …"); EX1021, 30310, 30314 ("PH-20 is not essential for fertilization, at least in the mouse …").

228 EX1024, 87-88; *see also* EX1061, 1154; EX1003, ¶¶ 110-11.

expected that "inactive mutant" PH20 polypeptides would have no utility at all,[229] and would not have accepted the common disclosure's assertion that "inactive mutants" are useful as contraceptive vaccines, particularly in humans.[230]

Finally, the common disclosure does not identify ***any*** inactive PH20 mutants that exhibit contraceptive effects in humans (contrary to Patentee's clinical evidence).[231] It likewise provides no guidance about which epitopes (if any) on the PH20 protein might induce contraceptive effects, much less show that "inactive mutants" preserve such epitopes.[232] Thus, a skilled artisan could not have reasonably predicted from the common disclosure whether any "inactive mutant" PH20 polypeptides would contain such (unidentified) epitopes or induce antibody production sufficient to confer contraceptive effects.[233]

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229 *Id.*; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App'x. 26, 30 (Fed. Cir. 2007).

230 EX1003, ¶¶ 112-13; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

231 EX1003, ¶ 113.

232 *Id.*

233 EX1003, ¶¶ 112-13.

Therefore, at most, the common disclosure presents only a "research proposal" to discover "inactive mutants" with contraceptive utility.[234] It does not demonstrate possession of or enable the immense and diverse genus of PH20 polypeptides claimed, regardless of whether the claims are appropriately limited to "active mutants" or, instead, include "inactive mutants."

D. The Original Claims of the '731 Application Do Not Cure the Written Description and Enablement Deficiencies

The specifications of the pre-AIA '731 Application and AIA '590 Patent are substantially identical, and neither supports the challenged claims as § 112(a) requires by either. The claims are both PGR eligible and unpatentable under § 112(a).

The original claims of the '731 Application provide no additional guidance demonstrating written description or enablement of the claimed genera of multiply-modified PH20 polypeptides. Those original claims claimed equivalently broad genera via sequence identity language (*e.g.*, 85% to SEQ ID NOS: 3, 7 or 32-66) (claims 1-3) or having up to "75 or more amino acid replacements" (claim 4). Dependent claims listed single positions (claim 12) or replacements (claims 13-16)

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234 *See Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("[t]he utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research").

in those polypeptides. And, while certain claims contemplated 2-3 particular combinations of amino acid replacements (from dozens listed), others encompassed substitutions at unspecified locations.[235]

The original claims do not provide § 112 support for the challenged claims.[236]

VI. Challenged Claims 1-2 and 5-35 Are Unpatentable Under § 103

Claims 1-2, 6-15, 22, and 25-26 define genera that encompass one or more of three specific modified PH20 polypeptides: L307W $PH20_{1-447}$, L307T $PH20_{1-447}$, and L307S $PH20_{1-447}$. *See* § IV.D.2. Because these mutants would have been obvious from the '429 Patent in view of Chao and the knowledge of a skilled artisan, each is unpatentable. Claims 5, 16-24, and 27-35 are also obvious, as each recites attributes met by L307W, L307T, or L307S $PH20_{1-447}$, or is suggested by the '429 Patent alone or with other prior art.

A. The Prior Art

The '429 Patent (EX1005) is owned by Patentee, was originally filed in 2003, and issued on Aug. 3, 2010.

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235 EX1026, at 335.

236 *See, e.g.*, *Ariad Pharms.*, 598 F.3d at 1349; *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993).

Chao (EX1006) was published in "Biochemistry" in 2007. Chao is not discussed in the common disclosure of the '590 Patent and '731 Application and was not cited during examination.

Knowledge of the skilled artisan relevant to obviousness is described in the testimony of Drs. Hecht (EX1003) and Park (EX1004), and is also documented in the prior art, including Patentee's earlier-published application, WO297 (EX1007).

B. Because L307W, L307T, and L307S PH20$_{1-447}$ Would Have Been Obvious, Claims 1-2, 6-15, and 25-26 Are Unpatentable

Patentee's '429 Patent would have motivated a skilled artisan to produce modified PH20$_{1-447}$ polypeptides having a single amino acid substitution in non-essential regions of the protein. Guided by her familiarity with rational protein design and the teachings of the '429 Patent and Chao, the artisan would have readily identified single amino acid substitutions in non-essential regions of PH20$_{1-447}$ that would have been tolerated (*i.e.*, a PH20$_{1-447}$ with that single substitution would retain its enzymatic activity). L307W PH20$_{1-447}$, L307T PH20$_{1-447}$, and L307S PH20$_{1-447}$ are three such examples. Because claims 1-2, 6-15, and 25-26 encompass at least one of these obvious variants of PH20$_{1-447}$, each is unpatentable.

1. Patentee's '429 Patent Motivates a Skilled Artisan to Make Single Amino Acid Substitutions in Non-Essential Regions of PH20$_{1-447}$

Patentee's '429 Patent, filed in 2003, describes its invention as soluble PH20 hyaluronidase glycoproteins ("sHASEGPs") that are enzymatically active at

neutral pH.[237] It exemplifies and claims one such "sHASEGP" that terminates at position 447 (positions 36-482 of SEQ ID NO: 1).[238]

The '429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, in pharmaceutical compositions, and combined with other therapeutic agents (*e.g.*, antibodies, chemotherapeutics), and illustrates administering such combinations subcutaneously to treat cancer and hyaluronidase disorders.[239] $PH20_{1-447}$ was approved by the FDA as Hylenex® in 2005.[240] The '429 Patent's teachings combined with the status of $PH20_{1-447}$ as an approved human therapeutic before 2011 would have induced a skilled artisan to focus on this particular PH20 polypeptide.[241]

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237 EX1005, 6:4-10, 10:30-59.

238 EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

239 EX1005, 8:25-9:4, 54:40-65, 56:34-57:36, 60:38-61:4, 63:41-61, 74:10-29, 76:19-77:36, 99:28-100:47.

240 EX1049, 1.

241 EX1003, ¶ 195.

Patentee's '429 Patent defines sHASEGPs as including wild-type $PH20_{1-447}$ and "equivalent" proteins "with amino acid substitutions that do not substantially alter activity" of the protein.[242] It explains:

> Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity …[243]

The '429 Patent also explains that single amino acid substitutions can include "conservative" substitutions in Table 1, but that "[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions."[244]

The '429 Patent thus teaches making a ***particular*** type of modification (a single amino acid substitution) in ***particular*** locations (non-essential regions of PH20) in a ***particular*** PH20 sequence ($PH20_{1-447}$) to yield equivalents of $PH20_{1-447}$

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242 EX1005, 9:65-10:13; *see also id.* at 18:64-19:6 ("equivalent" proteins).

243 EX1005, 16:14-22.

244 EX1005, 16:24-36.

(*i.e.*, those that do not substantially alter the activity or function of $PH20_{1-447}$).[245]

The '429 Patent also motivates skilled artisans to undertake this effort to design and produce such single-amino acid substituted $PH20_{1-447}$ proteins because it assures them their efforts will be successful.[246] As it states, skilled artisans recognized that such "single amino acid substitutions in non-essential regions" of $PH20_{1-447}$ "do not substantially alter biological activity" of $PH20_{1-447}$.[247] As such, a skilled artisan would have expected a $PH20_{1-447}$ mutant with a single amino acid substitution in a non-essential region to have the same utility, therapeutic applications, and other characteristics that the '429 Patent identifies for wild-type $PH20_{1-447}$ and other sHASEGPs.[248]

2. Chao Provides Information Useful for Engineering the Changes to $PH20_{1-447}$ that the '429 Patent Suggests

In 2011, a skilled artisan looking to implement the '429 Patent's suggestion to make a single-amino acid modification in a non-essential region of $PH20_{1-447}$ would have recognized such changes could best be accomplished using rational design, which here involves determining (i) which regions are non-essential in

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245 EX1003, ¶ 206; EX1004, ¶ 32.

246 EX1003, ¶ 207.

247 EX1005, 16:4-21.

248 EX1003, ¶¶ 199-202, 207, 222.

PH20, and (ii) which single amino acids to substitute into positions in those non-essential regions.[249]

The ’429 Patent was written eight years before 2011. Given that, a skilled artisan would have looked for additional published insights into the structure of human hyaluronidase enzymes like PH20, like Chao (EX1006).[250] Chao reported an experimentally determined structure for human HYAL1, and provided new insights into the shared characteristics of human hyaluronidase enzymes.[251]

First, by superimposing the HYAL1 and bee venom hyaluronidase structures, Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues in it that interact with HA.[252]

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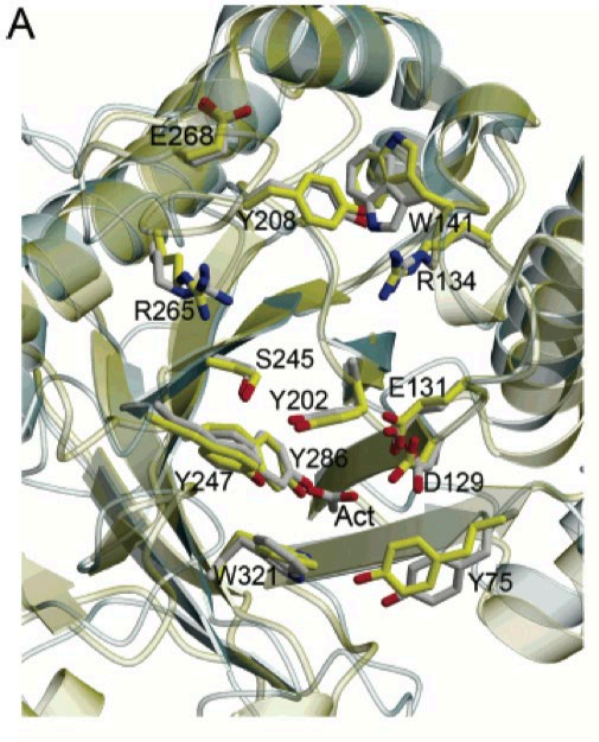
249 EX1003, ¶¶ 212-14.

250 EX1003, ¶¶ 86, 209-211; EX1004, ¶ 88.

251 EX1003, ¶¶ 81-86; EX1004, ¶ 88; EX1006, 6912-17.

252 EX1006, 6917 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1004, ¶¶ 89-91; EX1003, ¶¶ 81-82.



The ’429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20,[253] and taught that hyaluronidase domains share similarity among and between species, including residues necessary for enzymatic activity.[254]

Second, using an alignment of five human hyaluronidases, Chao identified predicted secondary structures (*e.g.*, β-sheets, α-helices) (Figure 3, below), as well as invariant conserved positions (blue), residues involved in catalysis (red),

[253] EX1005, 4:12-22, 86:49-53, 88:14-24.

[254] EX1005, 2:6-67, 4:11-22.

conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).[255]

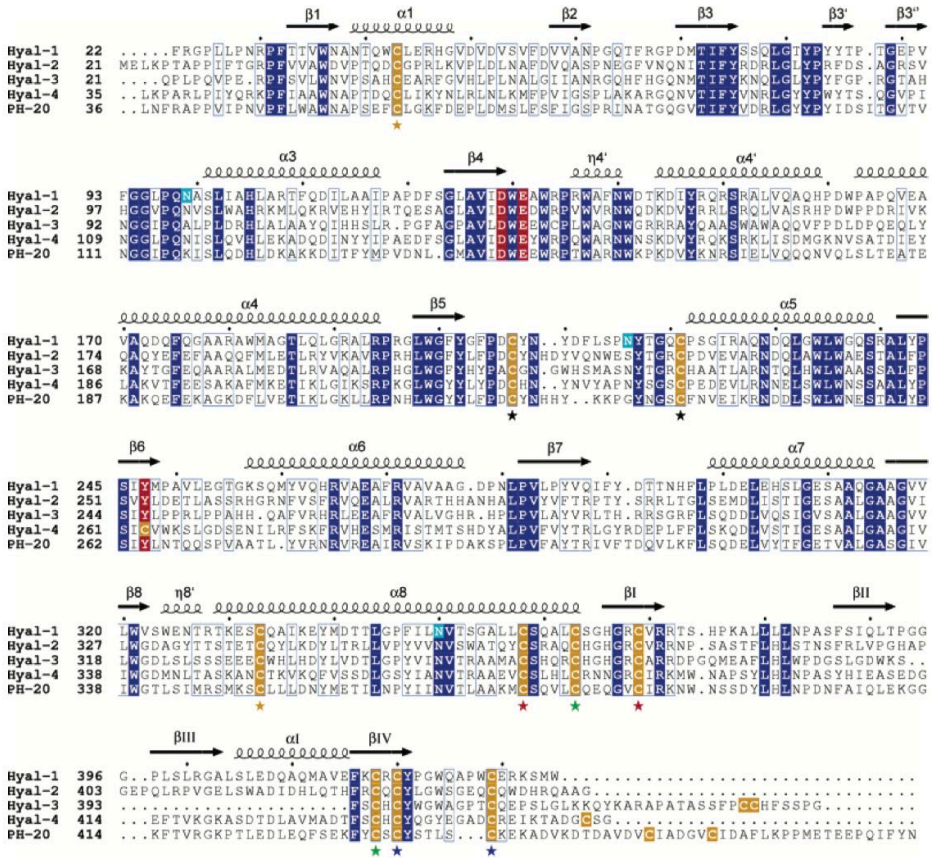


FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative replacements are blocked in blue. Pairs of cysteine residues that form disulfide bonds are indicated by stars with matching colors. Secondary structure units are labeled as in Figure 2B.

Third, Chao reported the presence of "a novel, EGF-like domain" in the C-terminal region of human hyaluronidases that was "closely associated" with the

255 EX1006, 6916; EX1003, ¶¶ 83, 211; EX1004, ¶ 92.

catalytic domain (discussed above, § V.A.1.b.iii), and identified a characteristic pattern for the Hyal-EGF domain in PH20 at positions 337-409.[256]

3. A Skilled Artisan Would Have Identified Position 307 as Being in a Non-Essential Region of $PH20_{1-447}$ in 2011

To implement the '429 Patent's suggestion to produce modified $PH20_{1-447}$ polypeptides with single amino acid substitutions in non-essential regions that retain hyaluronidase activity, the skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011.[257] The person would have done that using conventional sequence alignment tools in conjunction with the information in the '429 Patent and in Chao, as well as information publicly known in 2011.[258]

A multiple-sequence alignment identifies non-essential regions in PH20—they are the sequences between essential residues and are positions at which variations occur at a frequency above ~5% (illustrated using Chao below).[259]

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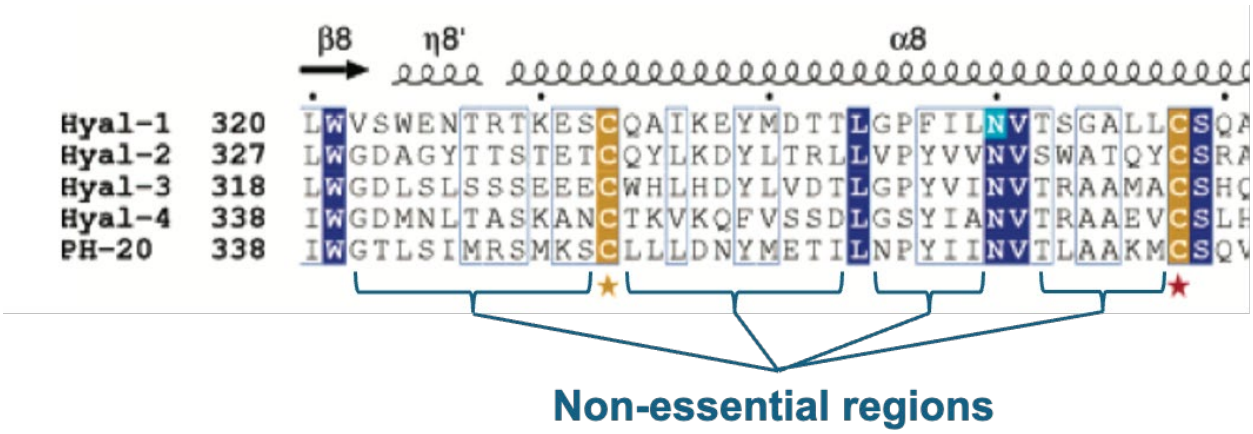
256 EX1006, 6911; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84-85.

257 EX1003, ¶¶ 212-214; EX1004, ¶¶ 22, 25-30, Appendix D-3.

258 EX1003, ¶¶ 20-21, 213-215; EX1004, ¶¶ 22-24; EX1017, 224-26.

259 EX1004, ¶¶ 31-32, Appendix D-2; EX1003, ¶¶ 213-214; EX1006, 6916.

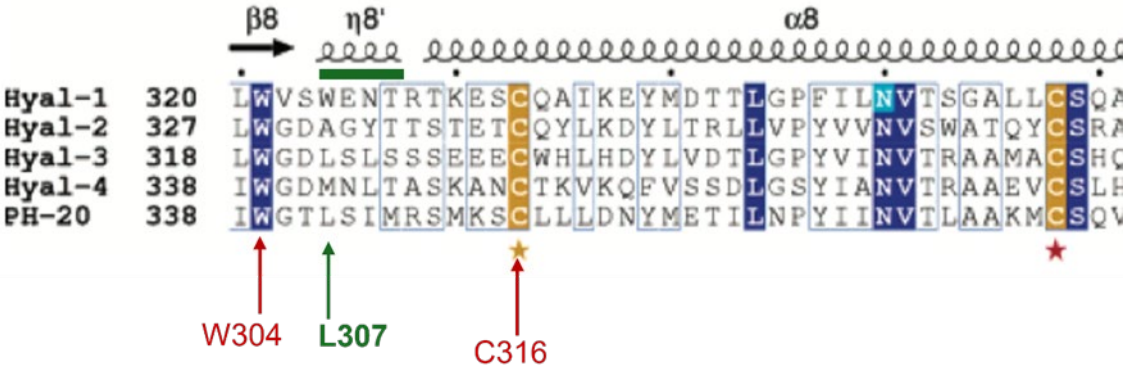


Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps. He first identified 88 homologous hyaluronidase protein sequences that had been published by December 29, 2011.[260] Dr. Park then prepared a multiple-sequence alignment of the 88 homologous proteins, similar to what Chao did with the five human hyaluronidases, and from that alignment identified essential (Appendix D-3) and non-essential (Appendix D-2) residues.[261]

[260] EX1004, ¶¶ 27, 150-153; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

[261] EX1004, ¶¶ 28-32, 154-155, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

Position 307 is within a non-essential region of $PH20_{1-447}$, which is shown by Dr. Park's analysis, and also by Chao's Figure 3; both report the same bounding essential residues (*i.e.*, W304 and C316) (below).[262]



Following the guidance and information in the '429 Patent and Chao, and assessing information publicly available in December 2011 using conventional sequence analysis tools, a skilled artisan would have readily identified position 307 as a position within a non-essential region $PH20_{1-447}$.[263]

4. A Skilled Artisan Would Have Viewed Tryptophan, Threonine, or Serine as Obvious Single Amino Acid Substitutions for Leucine at Position 307 of $PH20_{1-447}$

The multiple-sequence alignment reveals a second powerful insight: it identifies ***which*** amino acids have been tolerated at specific positions in the amino

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[262] EX1003, ¶ 217; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.

[263] EX1003, ¶ 220; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

acid sequence of homologous, stable and active naturally occurring hyaluronidase enzymes.[264] This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms those variations in the sequences of a protein that do not yield stable and active forms of the protein.[265] Using a multiple-sequence alignment, a skilled artisan can readily compile a list of amino acids tolerated at positions within non-essential regions of PH20.[266]

Dr. Park did this: using his multiple-sequence alignment of the 88 hyaluronidase proteins known by December 2011, he identified the different amino acids that occur at positions corresponding to position 307 in PH20 in homologous hyaluronidases, and how many proteins contain each residue (below).[267] The wild-

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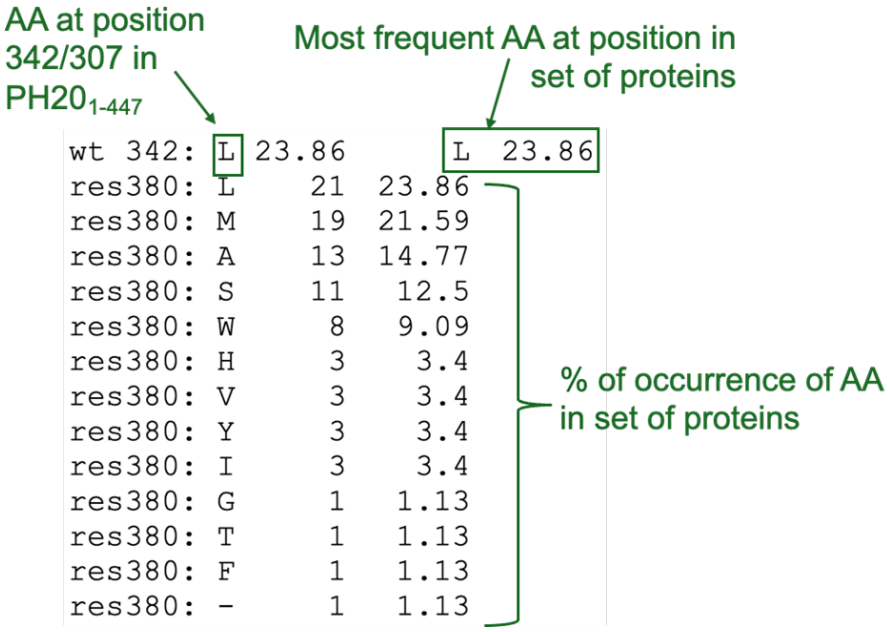
264 EX1003, ¶ 214; EX1004, ¶¶ 21-22.

265 EX1003, ¶ 214; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 ("Evolution provides a tremendously useful model for protein design. … By considering the common features of the sequences of these proteins, it is possible to deduce the key elements that determine protein structure and function—even in absence of any explicit structural information."); EX1014, 351.

266 EX1003, ¶¶ 214-215; EX1004, ¶¶ 21-22.

267 EX1004, ¶¶ 30-32, 41-43, 106, Appendix D-1; EX1003, ¶¶ 215, 217-19.

type residue at position 307 in PH20 is leucine (L), which occurs in ~24% of the proteins (including PH20). Several homologous proteins contain tryptophan (W), serine (S), or threonine (T).[268]



A skilled artisan would have considered position 307 to be a position within a non-essential region of PH20$_{1-447}$ at which a single amino acid substitution could be made pursuant to the guidance in the '429 Patent.[269]

The skilled artisan also would have selected tryptophan (W), threonine (T), and serine (S) as obvious choices for such a single substitution at position 307 in

[268] EX1003, ¶¶ 218, 220; EX1004, ¶¶ 106, 114, 121.

[269] EX1003, ¶¶ 217, 220.

$PH20_{1-447}$.[270] While leucine is the most prevalent amino acid found at positions corresponding to 307 in PH20, many different amino acids are tolerated at this position in homologous proteins, as shown by Chao and Dr. Park's multiple-sequence alignment, including tryptophan, threonine and serine.[271] Tryptophan occurs at a position corresponding to 307 in PH20 in 11 naturally occurring hyaluronidase enzymes, including human HYAL1, while threonine occurs at that position in 8 such proteins, and serine occurs at that position in the bee venom hyaluronidase protein.[272] Consequently, a skilled artisan would have considered each of tryptophan, threonine, and serine to have been obvious candidates to substitute for leucine at position 307 of position 307 in $PH20_{1-447}$ pursuant to the guidance in the '429 Patent.[273]

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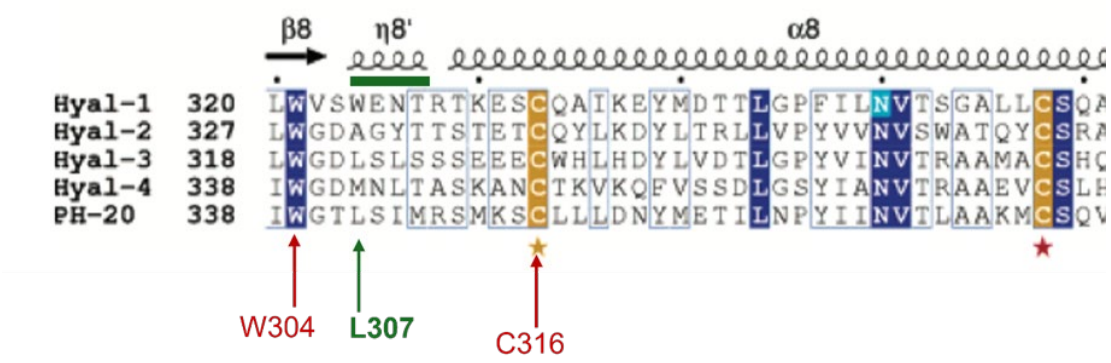
[270] EX1003, ¶ 220; EX1004, ¶¶ 41-42, 106.

[271] EX1004, ¶¶ 43, 106, 114, 121; EX1003, ¶¶ 218-219; EX1006, 6916.

[272] EX1004, ¶ 106.

[273] EX1003, ¶ 220.



5. A Skilled Artisan Would Have Reasonably Expected the L307W, L307T, and L307S Substitutions in $PH20_{1-447}$ to Yield Enzymatically Active PH20 Proteins

a) Patent Owner Cannot Contradict Its Past Representations to the PTO

Replacing the leucine (L) at position 307 with tryptophan (W), threonine (T), or serine (S) yields a $PH20_{1-447}$ with a single amino acid substitution in a non-essential region of the polypeptide.[274] In its '429 Patent, Patentee stated:

> Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.[275]

Patentee also secured claims in the '429 patent to modified $PH20_{1-447}$ proteins with at least one substitution (*e.g.*, claim 1), despite not providing examples of PH20 proteins with any substitutions. Patentee, thus, made and relied

[274] *See* § VI.B.3; EX1003, ¶ 217; EX1004, ¶ 32.

[275] EX1005, 16:17-20.

on its statements that a skilled artisan would have expected ***any*** single amino acid substitution in ***any*** non-essential position of $PH20_{1-447}$ to not substantially affect the activity of the enzyme. Patentee should not be permitted to now contend a skilled artisan would not have reasonably expected that the L307W, L307T, or L307S substitutions in $PH20_{1-447}$ would yield an enzyme with substantially the same activity as unmodified $PH20_{1-447}$.

b) Skilled Artisans Would Reasonably Expect L307W, L307T, and L307S to be Tolerated in $PH20_{1-447}$

Independently, a skilled artisan would have reasonably expected the L307W, L307T, and L307S substitutions to not substantially alter the biological activity (hyaluronidase activity) of $PH20_{1-447}$. Both experts noted that naturally occurring homologous hyaluronidase proteins contain tryptophan, threonine, or serine at positions corresponding to position 307 in PH20 (including for tryptophan in human HYAL1 (Chao)), which suggests that each of tryptophan, threonine, and serine would be tolerated at position 307 in $PH20_{1-447}$.[276]

In addition, Dr. Park's sequence alignment also shows that many (11) different amino acids occur in homologous proteins at positions corresponding to position 307 in PH20.[277] The diversity of characteristics of the amino acids that

[276] EX1003, ¶ 214; EX1004, ¶¶ 106, 114, 121.

[277] EX1004, ¶ 106.

occur at positions corresponding to 307 in PH20 (*e.g.*, polar vs. non-polar, small vs. large side chains, etc.) would have led a skilled artisan to believe that many different kinds of amino acids will be tolerated at position 307 in PH20.[278] That would reinforce the belief of the skilled artisan that each of tryptophan, threonine and serine would be tolerated at position 307 of $PH20_{1-447}$.

c) A PH20 Structural Model Confirms that $PH20_{1-447}$ Would Tolerate Tryptophan, Threonine, and Serine at 307

Dr. Park assessed whether single amino acid substitutions in $PH20_{1-447}$ would be tolerated, including L307W, L307T, and L307S, using a PH20 protein structural model generated by SWISS-MODEL using Chao's HYAL1 structure as the template, as would have been done in 2011 by a skilled artisan.[279]

Dr. Park explains that his PH20 model was reliable in the region of position 307 of PH20 based on QMEAN values,[280] and would be very similar to a PH20

[278] EX1003, ¶ 219; EX1004, ¶ 106.

[279] EX1004, ¶¶ 39-40, 156-157; EX1003, ¶¶ 226, 228; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

[280] EX1004, ¶¶ 158-160 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

model generated by SWISS-MODEL in 2011 (*e.g.*, it used 165 conserved positions in the backbone of the two proteins).[281]

Dr. Park also devised a consistent, objective methodology for assessing substitutions using the $PH20_{1-447}$ model.[282] Factors he considered included, *inter alia*, the number of neighboring residues at position 307 (*i.e.*, those within 5 Å), the various possible interactions between neighbors (*e.g.*, hydrophobic, charged, van der Walls, steric, etc.), and solvent accessibility.[283] Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*, hydrophobic-hydrophilic, effects on secondary structures, size related issues such as steric clashes or creation/filling of "holes" in the structure).[284]

Dr. Park assessed the environment of position 307 visually by comparing the wild-type with the version incorporating substituted amino acids at position 307

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281 EX1004, ¶¶ 161-162, 166; EX1038, 3382-4; EX1017, 229-230; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

282 EX1004, ¶¶ 102-103; *see generally id.* at § IV.C (description of Dr. Park's methodology); EX1003, ¶¶ 215-216.

283 EX1004, ¶¶ 44-47, 53-60, 65-85, Appendix D-5; EX1035, 1408, Table 2; EX1043, 2, Table 1.

284 EX1004, ¶¶ 62-63, 85.

using functionality within the viewer (PyMol) and as a modeled sequence generated from the $PH20_{1-447}$ sequence incorporating the single substitution in SWISS-MODEL.[285] These technologies were available in 2011.[286] He used his methodology to assess substitutions representing diverse interactions, and confirmed it provided a consistent, objective and unbiased evaluation of substitutions.[287]

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed (below).[288]

Score	***Expected Impact***	***Expected Toleration***
1	Significantly Destabilized	Likely Not Tolerated
2	Neutral or Minor Impacts	Tolerated
3	Improved Stability	Tolerated

Dr. Park assigned a score of 2 for each of the L307W, L307T, and L307S substitutions in $PH20_{1-447}$, indicating each would be expected to be tolerated.[289]

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285 EX1004, ¶¶ 61, 107, 113, 115, 119, 172-74; EX1003, ¶¶ 226, 228.

286 EX1004, ¶¶ 156, 161-162, 166, 170, 172-174; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4; EX1003, ¶¶ 20-22.

287 EX1004, ¶¶ 102-103; EX1003, ¶¶ 215-216.

288 EX1004, ¶¶ 85-87.

289 EX1004, ¶¶ 120, 126, 132, Appendix C.

Initially, Dr. Park observed that in the wild-type environment, position 307 is a solvent exposed residue, and is within a short (4 residue) sequence that lacks strict secondary structure.[290] He observed that this lack of strict secondary structure around position 307 explains why many different (11) amino acids are tolerated in homologous proteins at positions corresponding to position 307 in PH20.[291]

Dr. Park also explained that in the wild-type PH20 protein, L307 does not have significant stabilizing or destabilizing interactions with other residues in PH20, and is not near residues in PH20 that are important to catalysis.[292] In addition, he found that the hydrophobic side chain of leucine extends into the solvent exposed environment but is nonetheless tolerated (below left).[293] He found that leucine's side chain is oriented toward the HA substrate when it complexed with PH20, and may have a role in binding of HA by PH20 (below right).[294]

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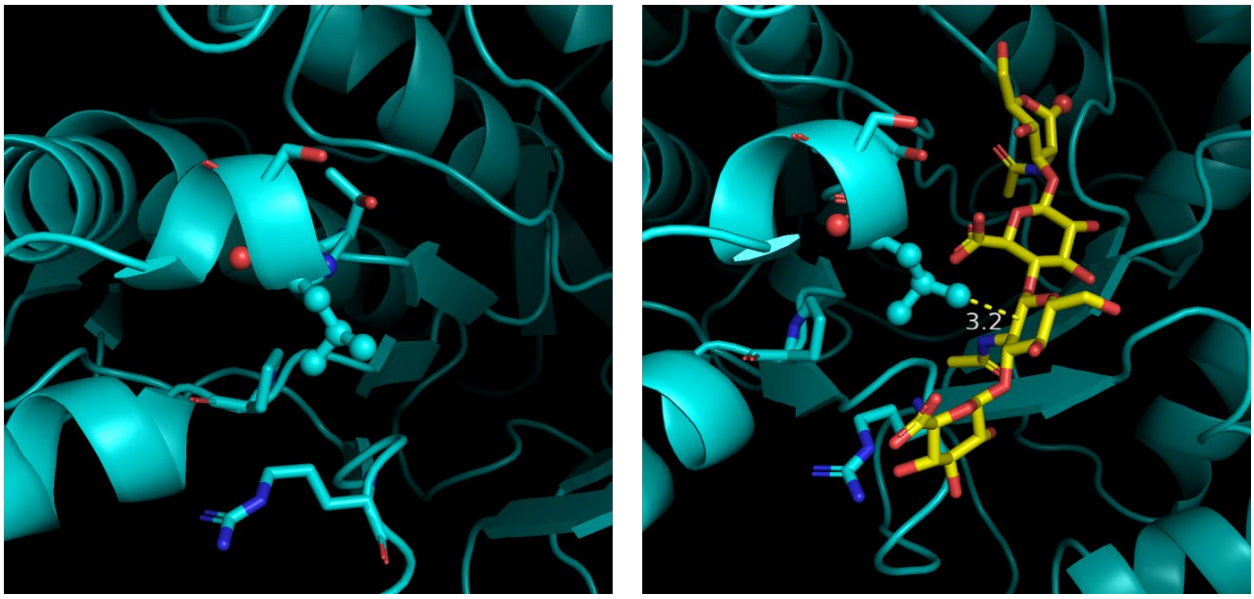
290 EX1004, ¶¶ 108-109; EX1006, 6913, 6916 (Chao identifies 307 as being in a 3_{10} helix sequence designated η8').

291 EX1004, ¶ 108.

292 EX1004, ¶¶ 109-110.

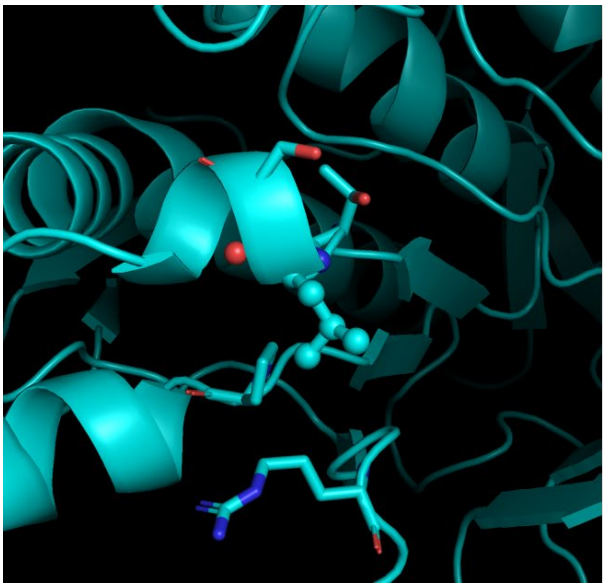
293 EX1004, ¶ 109.

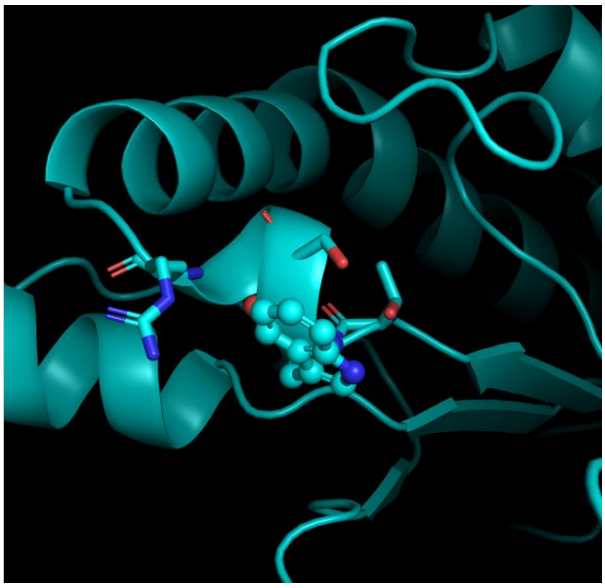
294 EX1004, ¶¶ 111.



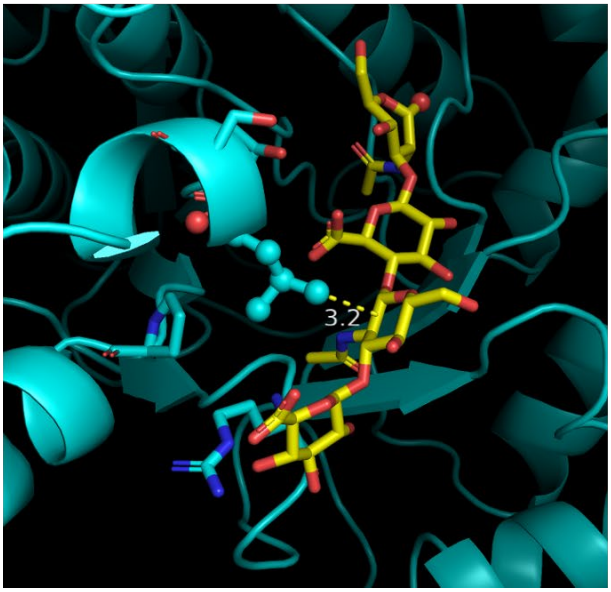
Dr. Park then evaluated tryptophan, threonine, and serine as single amino acid substitutions at position 307 of PH20 using PH20 molecular models. For the L307W PH20 substitution, the hydrophobic side chain of tryptophan extends into the solvent environment (below right), analogous to leucine in the wild-type PH20 (below left) and similar to how tryptophan's side chain is positioned in human HYAL1.[295]

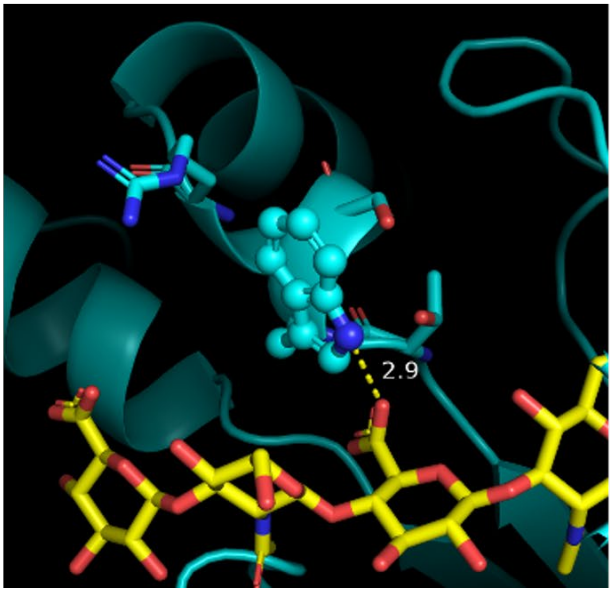
[295] EX1004, ¶¶ 109, 116-117.





Dr. Park also found that while the L307W substitution eliminates one possible interaction with substrate that occurs with L307 (below left), it also appears to form a new favorable interaction with the substrate (below right).[296]





[296] EX1004, ¶¶ 111, 118.

Dr. Park consequently found that the L307W substitution in PH20 would be neutral.[297]

Dr. Park also evaluated the L307S and L307T substitutions and concluded each would be tolerated by PH20.[298] Both the L307S and L307T substitutions will introduce a hydrophilic residue (serine or threonine) into the hydrophilic solvent environment of position 307 in PH20.[299] The L307S substitution in PH20 also yields a conformation similar to the corresponding residue in bee venom hyaluronidase, which is serine.[300] And each of the L307S and L307T substitutions in PH20 can form new favorable interactions with the HA substrate (below, left and right, respectively).[301]

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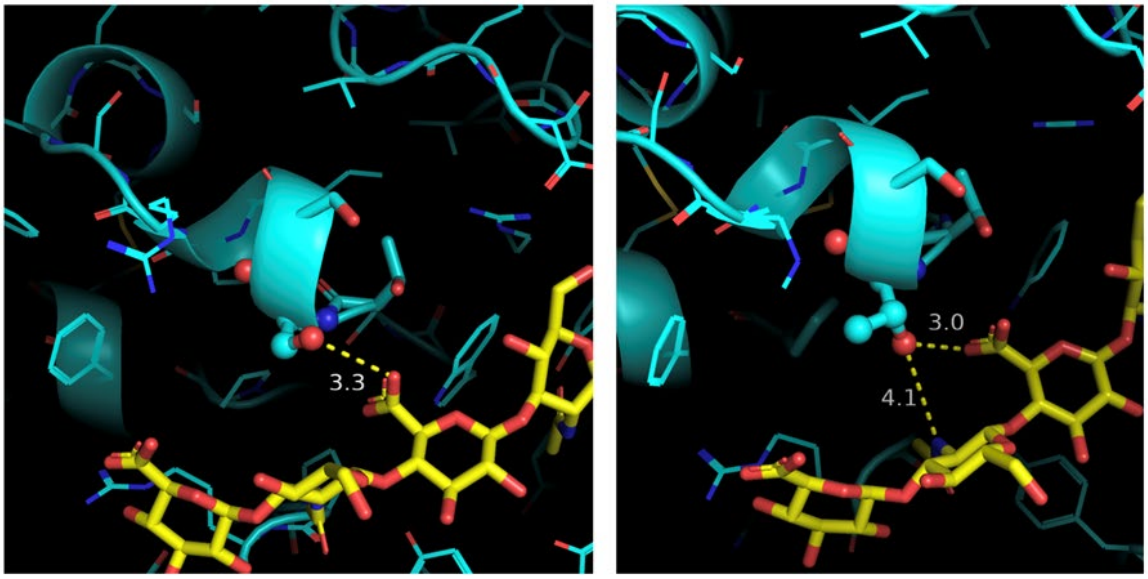
297 EX1004, ¶ 120.

298 EX1004, ¶¶ 126, 132.

299 EX1004, ¶¶ 123, 129.

300 EX1004, ¶¶ 123, 130.

301 EX1004, ¶ 124, 130.



Dr. Park's visualization-based assessment was a prevalent technique used in 2011.[302] Similarly, his technique of assessing interactions between neighbors and assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications.[303]

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[302] EX1017, 228 ("… a structural biologist's intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this."); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 226-228.

[303] EX1004, ¶¶ 48-52; EX1031, 459, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 228.

Dr. Hecht reviewed Dr. Park's analysis and conclusions and for the same reasons agreed that the L307W, L307T, and L307S single substitutions would likely have been tolerated in $PH20_{1-447}$.[304] For example, because leucine is tolerated at position 307 in PH20, a skilled artisan would expect other hydrophobic residues like tryptophan to be tolerated there.[305] The L307S and L307T substitutions, conversely, introduce hydrophilic residues into the compatible solvent accessible environment of position 307 in PH20.[306] And all three substitutions would yield $PH20_{1-447}$ mutants having favorable interactions with the HA substrate that could offset any lost favorable interactions between L307 and HA.[307]

The common disclosure defines an "active mutant" as a modified PH20 polypeptide with at least ~40% of the activity of unmodified $PH20_{1-447}$.[308] Drs. Hecht and Park each independently concluded that the L307W, L307T, and L307S

[304] EX1003, ¶ 230.

[305] EX1003, ¶ 231.

[306] EX1003, ¶ 232.

[307] EX1003, ¶ 233.

[308] EX1001, 75:48-53; *also id.* at 79:30-34.

single substitutions would have been tolerated by $PH20_{1-447}$.[309] A skilled artisan thus would have reasonably expected that the L307W, L307T, and L307S $PH20_{1-447}$ polypeptides would exhibit at least 40% of the activity of unmodified $PH20_{1-447}$.[310]

Based on the '429 Patent, Chao, and information available in 2011, the L307W, L307T, and L307S $PH20_{1-447}$ mutant polypeptides would have been obvious to a skilled artisan in 2011. And because claims 1-2, 6-15, and 25-26 each encompass one or more of these single-replacement mutants, each claim is unpatentable.

C. Dependent Claims 5, 16-24, and 27-35 Are Obvious

For the reasons below, each of claims 5, 16-24, and 27-35 defines subject matter that would have been obvious to a skilled artisan.

1. Claims 5, 16

Claims 5 and 16 require the modified PH20 polypeptide to be "a soluble PH20 polypeptide" and, in the case of claim 16, "C-terminally truncated."

The '429 Patent indicates that $PH20_{1-447}$ is a soluble form of the PH20 protein because it omits the C-terminal residues above position 448 (483)

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309 EX1003, ¶¶ 230-233; EX1004, ¶¶ 120, 126, 132.

310 EX1003, ¶ 235.

containing the GPI anchor sequence.[311] A skilled artisan would have expected that changing leucine (L) to tryptophan, threonine, and serine at position 307 would not affect the solubility of $PH20_{1-447}$ as it would not meaningfully alter the overall structure of the protein.[312]

2. Claims 17-19

Claims 17-19 require the modified PH20 polypeptide to "comprise[] one or more post-translational modifications" including glycosylation (claims 17-18) and be a "glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues" (19).

The '429 Patent teaches (i) that human PH20 must be glycosylated to exhibit activity, and (ii) expression of $PH20_{1-447}$ in mammalian (CHO) host cells that yield active forms of $PH20_{1-447}$.[313] It further teaches that "N- and O-linked glycans are attached to polypeptides through asparagine-N-acetyl-D-glucosamine … linkages," and claims PH20 polypeptides (including $PH20_{1-447}$) having asparagine-linked sugar moieties.[314] Frost reports that the recombinant production of $PH20_{1-447}$ in

311 EX1005, 3:57-62; 87:52-88:24.

312 EX1003, ¶¶ 196, 203, 222.

313 EX1005, 95:13-30; 40:41-51, 89:53-91:67; 88:5-9.

314 EX1005, 3:27-35, claims 1, 6.

CHO cells "resulted in a 447 amino acid 61 kDA glycoprotein with a properly processed amino terminus and 6 N-linked glycosylation sites."[315]

Based on the '429 Patent and knowledge in the art, a skilled artisan would have found it obvious to produce any of L307W, L307S, and L307T $PH20_{1-447}$ in a CHO cell, and that doing so will cause six N-linked glycosylation sites to be glycosylated.[316]

3. Claims 24, 27-33

Claim 24 specifies a pharmaceutical composition comprising any modified PH20 polypeptide in the genus of claim 1. Claims 27-30 add a "therapeutically active agent formulated in the same composition or in a separate composition" (27), and that the active agent may be a "drug" (28) or "chemotherapeutic agent" (29) or "antibody" (30).

Claims 31-33 concern methods of treating "hyaluronan-associated disease" (30) such as cancer (31) or a "solid tumor" by administering any of the modified PH20 polypeptides captured by claim 1.

The '429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*,

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315 EX1013, 432.

316 EX1003, ¶¶ 197-98, 203-04.

$PH20_{1-447}$), alone or with other therapeutic agents including antibodies and agents used in treating cancer and hyaluronan-associated disease.[317] It similarly describes and claims methods of administering them subcutaneously using formulations that combine an enzymatically active "sHASEPGs" (*e.g.*, $PH20_{1-447}$ with one substitution) with another therapeutic agent, which together enable delivery of the therapeutic agent after injection.[318]

Because the L307W, L307T, and L307S $PH20_{1-447}$ polypeptides would be expected to have a comparable structure and activity as unmodified $PH20_{1-447}$, a skilled artisan would have believed each would be equivalently useful in the pharmaceutical compositions, methods of administration, and methods of treatment described in the '429 Patent.[319] Indeed, in the '429 Patent, Patentee secured claims encompassing pharmaceutical compositions containing substituted PH20 polypeptides and chemotherapeutic agents despite the absence of any

[317] EX1005, 8:60-9:4, 54:40-55:35, 56:28-57:21, 55:61-56:9, 56:66-57:21, 63:41-44, 73:4-74:29, claims 14, 29, 33.

[318] EX1005, 8:25-38, 56:28-56, 57:22-36, 58:59-59:12, 63:40-64:4, 76:18-77:37, claim 27.

[319] EX1003, ¶¶ 199-202, 222.

exemplification.[320] Claims 24 and 27-33 also impose no restrictions on the makeup of the pharmaceutical composition. A skilled artisan would have found such compositions and methods of administration/treatment obvious from the '429 Patent.[321]

4. Claims 20-23, 34-35

Claims 20-21 and 34-35 concern conjugation of a modified PH20 polypeptide to (i) a polymer (claim 20) that may be polyethylene glycol (claim 21), (ii) a moiety such as a toxin, drug, label, or multimerization domain (claim 34) or (iii) to an Fc domain (claim 35). Claim 22 specifies that the modified PH20 polypeptide further comprises a heterologous signal sequence, while claim 23 specifies a chimeric peptide comprising the modified PH20 polypeptides of claim 1.

A skilled artisan would have found these further modifications to the L307W, L307T, or L307S $PH20_{1-447}$ mutants obvious from the '429 Patent.[322] The '429 Patent teaches $PH20_{1-447}$ proteins with mutations ("sHASEPGs") can be (i)

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320 EX1005, claims 29, 30, 50.

321 EX1003, ¶¶ 199-202, 207.

322 EX1003, ¶¶ 203, 205.

"modif[ied]" "with polymers such as polyethylene glycol";[323] (ii) conjugated to "one or more targeting agents" (*e.g.*, any moiety that specifically binds to a receptor);[324] (iii) attached to a label,[325] and (iv) incorporated into fusion (*i.e.*, "chimeric") proteins.[326] It also teaches expression of modified PH20 polypeptides that incorporate a heterologous signal sequence.[327]

D. There Is No Nexus Between the Claims and Any Evidence of Putative Secondary Indicia

Well-established law holds that evidence of secondary indicia cannot support non-obviousness if it does not have nexus to the claims. A key question in a nexus analysis is whether such evidence is commensurate with the scope of the claims. The answer here is a definitive no.

Patentee is likely to dispute that the L307W, L307T, and L307S $PH20_{1-447}$ substitutions are obvious. For example, Patentee may contend that the L307T variant is reported to have unexpectedly increased (108%) hyaluronidase activity

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[323] EX1005, 3:64-4:1, 4:45-53, 26:20-28:4.

[324] EX1005, 18:33-52.

[325] EX1005, 38:40-49, 40:15-21.

[326] EX1005, 18:33-52, 47:10-22, 51:25-30.

[327] EX1005, 34:33-37; 88:28-90:15 ("Kappa leader sequence" used in expression of PH20 polypeptides).

as a single substitution mutant. Demonstrating that modest increase in activity for one mutant out of the ~10^{59} and 10^{112} modified PH20 polypeptides encompassed by the claims, however, utterly fails to establish a nexus between that evidence and the claims. The argument also would be inapplicable to the other claimed single-substitution mutants, which generally exhibit reduced activity relative to unmodified $PH20_{1-447}$.[328] Indeed, the claimed L307G mutant exhibits only ***32%*** of the activity of the unmodified $PH20_{1-447}$.[329] As explained in § V.A.1, the single-substitution L307W, L307T, and L307S $PH20_{1-447}$ mutants are not representative of the numerous, structurally different proteins encompassed by the claims, particularly those expected to be inactive. No evidence or explanation is provided in the common disclosure that resolves this confusion.

If Patentee advances evidence or arguments concerning nexus, consideration of that issue should be deferred until after institution, and Petitioner reserves its right to contest such evidence.

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[328] EX1001, Table 9, column 235.

[329] EX1001, Table 9, column 235.

VII. The Board Should Not Exercise Its Discretion Under § 324(a) or § 325(d)

No litigation involving the '590 Patent is pending, making discretionary denial unwarranted under the factors in *Apple Inc. v. Fintiv, Inc.,* IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020).

The examination record also does not warrant the Board exercising its discretion to not institute. As explained in § IV.C, no obviousness rejections were raised during prosecution.[330] The present obviousness grounds also rely on Chao (EX1006), which was not cited or considered during examination, and are supported by evidence not available to the Examiner (*e.g.*, expert testimony of Drs. Hecht and Park).

Also, while certain rejections based on the form or clarity of the claims were addressed during examination,[331] the Examiner erred by not rejecting the claims for lack of written description and non-enablement. *See* §§ V.A and V.B.

There is no proper basis for the Board to exercise its discretion to not institute trial.

VIII. CONCLUSION

For the foregoing reasons, the challenged claims are unpatentable.

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330 EX1002, 834-38.

331 EX1002, 835-36, 894-98, 907-908.

Dated: February 21, 2025

Respectfully Submitted,

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,060,590
1002	File History of U.S. Patent No. 12,060,590
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Branden & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '590 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," Methods in Enzymology, 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," Protein Eng'g & Design, Ch. 10, 223-237 (2010)
1018	Chica et al., "Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design," Curr. Opin. Biotechnol., (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," Reprod., 127:325-334 (2004)
1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," Am. J. Reprod. Immunol., (3):174-82 (2002)
1021	Baba et al., "Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg," J. Biol. Chem., 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," Biol Reprod., 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 56(5):1133-41 (1997)
1024	Rosengren et al., "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects," BioDrugs, 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	[Reserved]
1028	[Reserved]
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," FEBS Letters, 3:545-548 (1993)

No.	Exhibit Description
1030	Sills, "Retraction," Science, 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," J. Mol. Biol., 353:459-473 (2005)
1032	Wang & Moult, "SNPs, Protein Structure, and Disease," Hum. Mutation, 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," Structure, 8:1025-1035 (2000)
1034	"Negative Results," Nature: Editorials, 453:258 (2008)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," Protein Sci., 12:1406-1417 (2003)
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1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with L307W Mutation
1071	Swiss Model Printout of PH20 Model with L307S Mutation
1072	Swiss Model Printout of PH20 Model with L307T Mutation
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1074	Swiss Model Printout of PH20 Model with L307Y Mutation
1075	Swiss Model Printout of PH20 Model with L307G Mutation

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,593 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

Dated: February 21, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 21st day of February, 2025, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00030
U.S. Patent No. 12,054,758

PETITION FOR POST GRANT REVIEW

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I. Introduction

Petitioner Merck Sharp & Dohme LLC ("Merck") requests post grant review of claims 1-40 of U.S. Patent No. 12,054,758 ("'758 Patent").

The '758 Patent claims are unpatentable for three independent reasons.

The first two are linked to the extreme breadth of the claims, which aim to capture any enzymatically active modified human hyaluronidase ("PH20") polypeptide within genera having between 10^{59} and 10^{112} distinct species. That results from the claim language, which specifies each PH20 polypeptide (i) ***must have*** one amino acid substitution at position 317, and (ii) ***may have*** between 20 and 41 additional substitutions at ***any*** of 430+ positions, and to ***any*** of 19 other amino acids. The scale of these genera is unfathomable. A collection of one molecule of each polypeptide in the smallest genus exceeds the weight of the Earth, and practicing the full scope of the narrowest claimed genus would require many lifetimes of "making and testing" using the patent's methodology.

These immensely broad claims, measured against the common disclosure of the '758 Patent and its ultimate parent '731 Application,[1] utterly fail the written description and enablement requirements of § 112(a). That renders every claim of the '758 Patent unpatentable. It also precludes the claims from a valid § 120

[1] 13/694,731 ('731 Application) (EX1026).

benefit claim to the ’731 Application, the only non-provisional application filed before March 16, 2013, thus making the ’758 Patent PGR eligible.

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by the enzymatically active, multiply-modified PH20 polypeptides within each claimed genus. The disclosed examples also are not representative of these structurally diverse genera: each has only ***one*** amino acid substitution in ***one*** PH20 sequence (1-447), while the claims encompass PH20 proteins with myriad ***undescribed*** combinations of 5, 10, 15, or 20+ substitutions anywhere within PH20 sequences of varying length. The claims even capture mutated PH20 polypeptides the disclosure says to avoid (*e.g.*, $PH20_{1\text{-}447}$ mutants rendered inactive by a single substitution, inactive truncated forms). The disclosure is nothing more than a research plan, lacking any blaze marks, and does not describe the claimed genera.

Regarding enablement, the common disclosure has equally fatal problems: it identifies ***no*** enzymatically active modified PH20 with 2 or more substitutions, much less affirmatively guides the selection of ***which*** combinations of substitutions yield such enzymes. The only process it discloses for making such multiply-substituted PH20 mutants is prophetic, and uses the “trial-and-error discovery” methodology the Supreme Court has found incapable of enabling a

much smaller genus of polypeptides.[2] And practicing the full scope of the claims requires scientists to repeat this "make-and-test" methodology innumerable times until they had made and tested between 10^{59} and 10^{112} unique proteins. That is far more than undue experimentation—it is impossible.

Finally, claims 1-2, 5-6, 8, and 10-40 are unpatentable because each captures at least one obvious $PH20_{1-447}$ mutant that changes a ***single*** residue in a non-essential region of PH20—leucine at position 317 to glutamine ("L317Q"). But Patentee's '429 Patent (EX1005) directs artisans to make such single amino acid substitutions in non-essential regions of $PH20_{1-447}$ (and expressly claimed them). Skilled artisans implementing that guidance in 2011 would have found Chao (EX1006)—a 2007 paper ignored in the common disclosure and never cited to the Office. Skilled artisans, using their knowledge and collective teachings of Chao and the '429 Patent, would have (i) readily identified position 317 as being in a non-essential region of PH20, and (ii) found it obvious to change leucine to glutamine at position 317. They also would have reasonably expected both mutants to retain enzymatic activity because that is what Patentee said in its '429 Patent ("Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter

[2] *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023).

biological activity").[3] Because the claims capture these obvious species, they are unpatentable, along with the dependent claims.

The '758 Patent claims are unpatentable. The Board should institute trial.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the '758 Patent's issuance. Petitioner certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '758 Patent.

The '758 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

A patent is PGR eligible if it issued from an application filed after March 16, 2013 "if the patent contains … at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought." *See Inguran, LLC v. Premium Genetics (UK) Ltd.*, Case PGR2015-00017, Paper 8 at 16-17 (P.T.A.B. Dec. 22, 2015); *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17

[3] EX1005, 16:17-22.

at 8 (P.T.A.B. Jan. 29, 2016); *Collegium Pharm., Inc. v. Purdue Pharma L.P.*, 2021 WL 6340198, at *14-18 (P.T.A.B. Nov. 19, 2021) (same) *aff'd Purdue Pharma L.P. v. Collegium Pharm., Inc.*, 86 F.4th 1338, 1346 (Fed. Cir. 2023); *Intex Recreation Corp. v. Team Worldwide Corp.*, 2020 WL 2071543, at *26 (P.T.A.B. Apr. 29, 2020) (same).

Only one of the applications to which the '758 Patent claims benefit under 35 U.S.C. § 120 and/or § 121—U.S. Application No. 13/694,731 (the '731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011) and WO 01/3087 ("WO087"). The '731 Application, however, alters several passages of the provisional disclosures, adds new examples and tested mutants and makes other changes.[4]

The '731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '758 Patent (§§ V.A, V.B). The same is true for the '758 Patent, whose

[4] EX1026, 153:15-163:26, 324-34, 19:25-26, 28; EX1051; EX1052.

disclosure relative to the claims is generally the same as the '731 Application.[5] The '758 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the '731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

Merck Sharp & Dohme LLC is the real party-in-interest for this Petition.

2. Related Proceedings

PGR2025-00003, PGR2025-00004, PGR2025-00006, PGR2025-00009, and PGR2025-00017 are related proceedings.

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[5] The "common disclosure" refers to the shared disclosure of the '758 Patent and the '731 Application (EX1026). Citations are to the '758 Patent; EX1015 correlates citations to the '731 Application. The disclosures are highly similar but not identical. *See* EX1068, ¶ 6. Relative to the '731 Application, the '758 Patent makes three changes: (i) it removes positions 282, 298, and 431 from the list of positions to avoid changing in enzymatically active PH20 proteins relative to the '731 Application (EX1045, 78), (ii) it removes the mutant designated "I083K" from Table 9's list of "Active" mutants and added I208K (*id.*, 218), and (iii) it modifies Table 3 to remove substitutions L and W from position 288 (*id.*, 80).

3. Counsel and Service Information

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III. Grounds

The grounds advanced in this Petition are:

(a) Claims 1-40 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.

(b) Claims 1-40 are unpatentable under 35 U.S.C. § 112 as not being enabled.

(c) Claims 1-2, 5-6, 8, and 10-40 are unpatentable as obvious under 35 U.S.C. § 103 based on the ’429 Patent (EX1005), Chao (EX1006), and knowledge held by a person of ordinary skill in the art.

Petitioner’s grounds are supported by the evidence submitted with this Petition, including testimony from Dr. Michael Hecht (EX1003) and Dr. Sheldon Park (EX1004).

In this Petition, “PH20” refers to the human PH20 hyaluronidase protein. The full-length PH20 protein (SEQ ID NO: 6) includes a 35 amino acid signal

sequence, which is absent in mature forms of PH20, yielding positional numbers that differ from SEQ ID NO: 6 by 35 residues.[6] The annotation "$PH20_{1\text{-}n}$" refers to a sequence of 1-n residues in PH20 (*e.g.*, $PH20_{1\text{-}447}$ is SEQ ID NO: 3), and "AxxxB" is used to identify the position of a substitution (*e.g.*, "L317Q").

IV. Background on the '758 Patent

A. Field of the Patent

The '758 Patent concerns the human PH20 hyaluronidase enzyme, and structurally altered forms of that protein that retain enzymatic activity.[7]

1. Protein Structures

Proteins are comprised of sequences of amino acids. A protein's activity, however, derives from its unique, three-dimensional shape—its structure.[8] That is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary structures and structural motifs, which are packed into compact domains that define the protein's overall structure (tertiary structure).[9]

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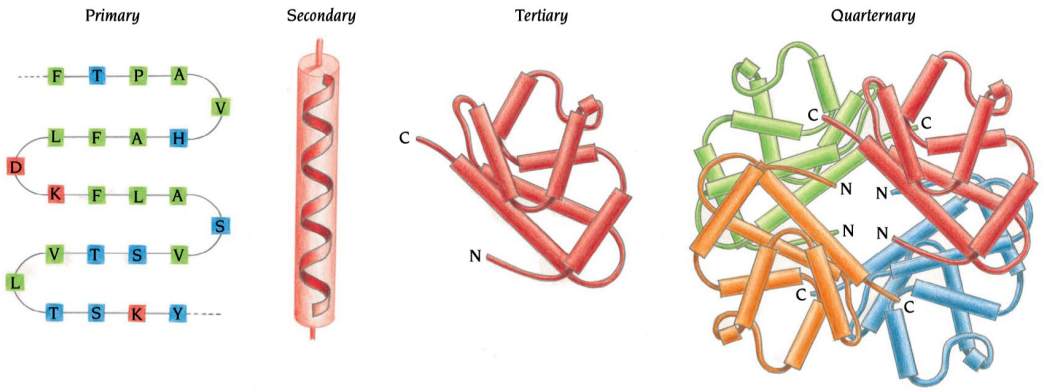
6 EX1003, ¶ 15.

7 EX1001, 4:16-19.

8 EX1003, ¶ 36.

9 EX1014, 3-4, 24-32, Figure 1.1; EX1039, 136-37 (Figure 3-11); EX1003, ¶¶ 36-40.



Secondary structures, such as α-helices or β-strands, are formed and stabilized by different but characteristic patterns of amino acids (below).[10]

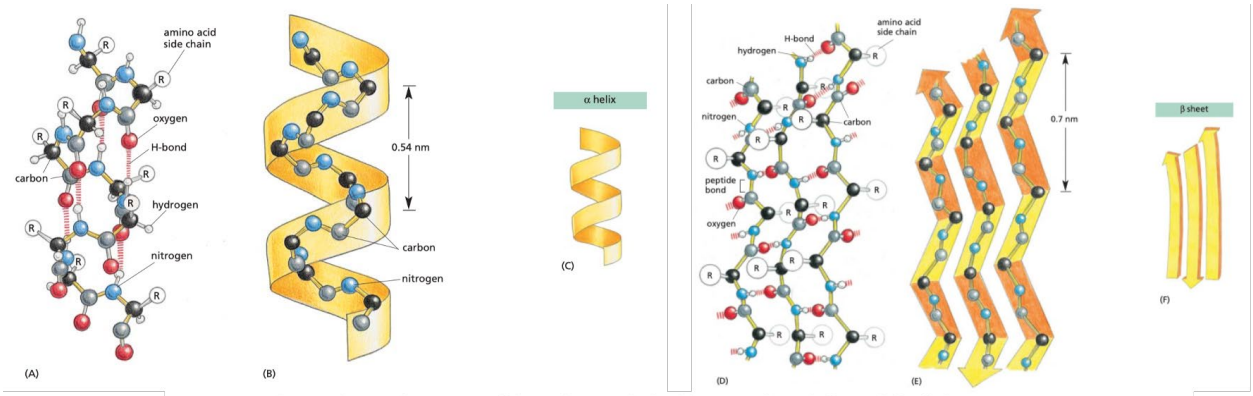


Figure 3–7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N–H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N–H groups point up in this diagram and that all of the C=O groups point down (toward the C-terminus); this gives a polarity to the helix, with the C-terminus having a partial negative and the N-terminus a partial positive charge. (D, E, and F) The β sheet. In this example, adjacent peptide chains run in opposite (antiparallel) directions. Hydrogen-bonding between peptide bonds in different strands holds the individual polypeptide chains (strands) together in a β sheet, and the amino acid side chains in each strand alternately project above and below the plane of the sheet. (A) and (D) show all the atoms in the polypeptide backbone, but the amino acid side chains are truncated and denoted by R. In contrast, (B) and (E) show the backbone atoms only, while (C) and (F) display the shorthand symbols that are used to represent the α helix and the β sheet in ribbon drawings of proteins (see Panel 3–2B).

[10] EX1039, 134; EX1014, 14-22, Figures 2.2, 2.5, Table 2.1; EX1047, 2031-32; EX1003, ¶¶ 40-43.

Intervening sequences between those characteristic sequences are important too; they direct and facilitate positioning and arrangement of the various secondary structures into structural motifs and the protein's tertiary structure.[11]

Changes to a protein's amino acid sequence can affect the folding, formation and stability of these various structures that define the protein's overall shape. For example, changing even a single residue known to be critical to the protein's structure or activity can render a protein inactive.[12]

Making many concurrent changes to a protein's sequence can cause myriad effects on the protein's structure, especially when they are in or affect the same region(s) of the protein.[13] For example, it can disrupt the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of secondary structures, and disrupt folding and positioning of the secondary structures and structural motifs into the protein's tertiary structure.[14] Multiple changes in different regions of the amino acid sequence also cause unfavorable

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11 EX1003, ¶¶ 44-46; EX1014, 21-22.

12 EX1003, ¶¶ 54, 150; EX1004, ¶¶ 20, 25.

13 EX1003, ¶ 158.

14 EX1003, ¶¶ 55-56, 142; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

spatial interactions that destabilize or impair folding.[15] Consequently, in 2011, predicting the effects of the myriad interactions that may be disrupted by multiple concurrent substitutions was beyond the capacity of skilled artisans and available computational tools.[16]

2. Hyaluronidase Enzymes

PH20 is one of five structurally similar hyaluronidases in humans and is homologous—evolutionarily related to—hyaluronidases in many species.[17] It breaks down hyaluronan ("HA") by selectively hydrolyzing glycosidic linkages.[18] PH20 exists naturally as a GPI anchored protein; deletion of its GPI-anchoring sequence yields a soluble, neutral active enzyme.[19]

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15 EX1003, ¶¶ 57-59.

16 EX1003, ¶¶ 50, 158, 190, 229; EX1004, ¶¶ 157-159.

17 EX1007, 10:18-30; EX1006, 6911, 6916 (Figure 3); EX1003, ¶¶ 33, 77.

18 EX1003, ¶ 77; EX1008, 819.

19 EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 89, 196; EX1029, 546, Figure 1.

Before 2011, many essential residues in PH20 were known. Several are in the shared catalytic site of the protein;[20] mutating certain residues in or near that site can abolish enzymatic activity.[21] Conserved cysteine residues that stabilize the protein structure are another example,[22] as are certain conserved asparagine residues involved in glycosylation.[23]

In 2007, Chao reported an experimentally determined structure of the human HYAL1 hyaluronidase, and used an alignment of the five human hyaluronidases to illustrate shared secondary structures and conserved residues in these proteins.[24] Among its findings was that human hyaluronidases contain a unique structure—the Hyal-EGF domain.[25] Using its sequence analysis, an earlier structure of bee

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[20] EX1006, 6914-16, Figure 3; EX1007, 35:28-36:10; EX1011, 810-14; EX1008, 824-25; EX1009, 6912-17.

[21] EX1011, 812-14; EX1010, 9435-39, Table 1.

[22] EX1006, 6914-16, Figure 3; EX1011, 810-11; EX1005, 88:21-22.

[23] EX1005, 7:9-27; EX1007, 36:12-20; EX1010, 9433, 9435-40.

[24] EX1006, 6914-18.

[25] EX1006, 6916-18; EX1010, 9439-40; EX1003, ¶¶ 84-86; EX1004, ¶¶ 97-99.

venom hyaluronidase and a computer model of the protein structures, Chao identified residues in the catalytic site that interact with HA.[26]

3. Protein Engineering

In 2011, skilled artisans used two general approaches to engineer changes into proteins.[27] In "rational design," skilled artisans employed computational tools—sequence alignments and protein structure models—to study the protein and then select where and what changes to introduce.[28] For example, a "multiple-sequence alignment" ("MSA")[29] produced by aligning known sequences of homologous, naturally occurring proteins identifies positions with no or little amino acid variation ("conserved" / "essential" residues) and positions where different amino acids occur ("non-conserved" / "non-essential" residues).[30] A

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[26] EX1006, 6912-13, 6916-18, Figures 2C, 4A; EX1033, 1028-29, 1035; EX1010, 9434, 9436, Figure 1.

[27] EX1003, ¶ 47.

[28] EX1016, 181-82; EX1017, 223, 236; EX1003, ¶¶ 48-50.

[29] EX1017, 224-27; EX1016, 181-86 (Figure 1); EX1003, ¶¶ 48-50; EX1004, ¶¶ 22-23, 29.

[30] EX1003, ¶¶ 213-14; EX1004, ¶¶ 21-22, 25, 30-31; EX1016, 181-84; EX1017, 224-25; EX1014, 351.

structural model using the protein's sequence but based on a known structure of a homologous protein enabled assessment of interactions between amino acids at a particular positions.[31] In 2011, using rational design techniques, a skilled artisan could assess, with varying effort, effects of changing one or a few amino acids, but could not use those techniques to predict the effects of many concurrent changes, given the escalating complexity of numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.[32]

"Directed evolution" techniques arose due to the limits of rational design.[33] They use "trial-and-error" experiments to find mutants with randomly distributed changes that exhibit desired properties, but require creation and screening of large libraries of mutants, each with one amino acid randomly changed at one position in its sequence.[34] Importantly, until a desired mutant is made, found and tested,

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31 EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶ 37; *also id.* 33-36; EX1003, ¶¶ 224, 226.

32 EX1003, ¶¶ 50, 158; EX1004, ¶¶ 157-159.

33 EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

34 EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

whether it exists and its sequence are unknown.[35] Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale of experimentation this approach requires.[36] The '758 Patent embodies this approach.[37]

B. Person of Ordinary Skill in the Art

While the '758 Patent claims priority to provisional applications dating to December 30, 2011 and benefit to the '731 Application (filed December 28, 2012), they are not supported as § 112(a) requires by those earlier-filed applications. *See* §§ II.A, V.A, V.B. Regardless, the prior art of the grounds was published before December 2011, and the obviousness grounds use that date to assess the knowledge and perspectives of the skilled artisan.

In 2011, a person of ordinary skill in the art would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production

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35 EX1003, ¶ 184.

36 EX1003, ¶¶ 52-53.

37 EX1003, ¶¶ 138, 173, 183, 186.

of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).[38]

C. Prosecution History

Only one office action issued during examination of the '758 Patent. In it, several indefiniteness rejections were imposed (*e.g.*, unclear references to "modifications", use of "Fe" instead of "Fc", failure to define "c-terminally truncated").[39] Patentee overcame these indefiniteness rejections by amending the claims to address the identified deficiencies.[40] It raised no issues relevant to the present grounds.

D. The Challenged Claims

The claim terms are either expressly defined in the common disclosure or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition. A clear understanding of the ***breadth*** of the claims, however, is important, as it shows that

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[38] EX1003, ¶ 13.

[39] EX1002, 477-78.

[40] EX1002, 549-51.

each claim captures a massive genus of structurally distinct mutant PH20 polypeptides that is neither adequately described in nor enabled by the common disclosure of the ’731 Application and the ’758 Patent.

1. The Claims Encompass a Staggering Number of Modified PH20 Polypeptides

The claims define an incredibly broad and diverse genus of “modified PH20 polypeptides,” which the common disclosure defines as “a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement … in its sequence of amino acids compared to a reference unmodified PH20 polypeptide.”[41]

Claim 1 defines the genus as containing modified PH20 polypeptides that:

- ***must*** contain ***one*** amino acid replacement at position 317 (*i.e.*, from L to any of A, I, K, M, Q, and R); and
- ***may*** contain ***additional*** modifications, provided each polypeptide retains ***at least 91% sequence identity*** to one of 37 unmodified sequences (SEQ ID NOs: 3, 7, or 32-66), ranging in length from 430 (SEQ ID NO:32) to 474 residues (SEQ ID NO:7).

Certain dependent claims restrict these parameters:

(i) claims 2 and 25-26 limit (*inter alia*) sequence identity to 95%,

[41] EX1001, 48:38-43.

(ii) claims 8-16 and 25-26 narrow the comparator sequences (*e.g.*, omit SEQ ID NO: 7, require SEQ ID NOs: 35 or 32, or list SEQ ID NOs: 604-606, 608, or 609),

(iii) certain claims require the position 317 substitutions to be Q (6, 10, 13-14, 25-26) or K (7, 9), and

(iv) claims 3-5 add functional requirements (*e.g.*, increased "stability" or activity, solubility).

Claims 17-24 and 27-40 depend from claim 1 but do not alter the parameters governing the number of PH20 polypeptides in each genus. Claims 17-23 specify additional features of the PH20 polypeptides while claims 24 and 27-40 define pharmaceutical compositions and methods of use.

The specification explains that "sequence identity can be determined by standard alignment algorithm programs …"[42] and provides an example, explaining a polypeptide that is "'at least 90% identical to' refers to percent identities from 90 to 100% relative to the reference polypeptide" where "no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides."[43]

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42 EX1001, 60:16-18.

43 EX1001, 60:51-60.

It further explains that "differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence" and that "[d]ifferences are defined as [] amino acid substitutions, insertions or deletions."[44] Also, "amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids" (*e.g.*, 10-18 of the 19 alternative amino acids).[45] Except for position 317, no language in the claims restricts ***where*** substitutions can occur within the modified PH20 sequence, or ***which*** of 19 other amino acids can be substituted at those positions.

The sequence identity parameters capture an immense number of modified PH20 polypeptides, each with a unique amino acid sequence.[46] The polypeptides may have up to 21-42 total changes but must have one substitution at position 317. Claims 1-5, 8, 11-12, 15, 17-24, and 27-40 permit six position 317 alternatives (A, I, K, M, Q, and R) while claims 6-7, 9-10, 13-14, 16, and 25-26 permit one (Q or

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44 EX1001, 60:61-61:2; *see also id.* at 5:1-2, 47:43-47, 56-58.

45 EX1001, 130:2-9; *see also id.* at 135:22-24.

46 EX1003, ¶¶ 120, 122.

K). Dr. Park's calculations identify the number of distinct polypeptides captured by these parameters:[47]

Claims	*Max Length*	*Max Changes*	*Pos. 317 Choices*	*# of Distinct Polypeptides*
1, 3-5, 17-21, 23-24, 27-40	474	42	6	3.79×10^{112}
2	474	23	6	3.11×10^{66}
6, 7	474	42	1	6.32×10^{111}
8, 22	465	41	6	8.47×10^{109}
9, 10	465	41	1	1.41×10^{109}
11	433	38	6	6.01×10^{101}
12	430	38	6	4.59×10^{101}
13	433	38	1	1.00×10^{101}
14	430	38	1	7.66×10^{100}
15	447	40	6	8.37×10^{106}
16	447	40	1	1.40×10^{106}
25	430	21	1	4.40×10^{59}
26	433	21	1	5.08×10^{59}

[47] EX1004, ¶¶ 165-169, Appendix F.

2. Claims 1-6, 8, and 10-40 Encompass One Particular Mutant: L317Q PH20$_{1-447}$

Claims 1-6, 8, and 10-40 each capture a modified PH20$_{1-447}$ polypeptide that changes leucine at position 317 to glutamine (Q) ("L317Q"). This single-replacement PH20$_{1-447}$ mutant is: (i) 99.7% identical to SEQ ID NO: 3 (1 change / 447 residues), (ii) 96.5% identical to SEQ ID NO: 35 (15 changes / 433 residues), and (iii) 95.9% identical to SEQ ID NO: 32 (18 changes / 430 residues).[48]

3. The Claims Are Restricted to One of Two Alternative Embodiments in the Patents: "Active Mutants"

When a specification discloses alternative embodiments, the claim language may limit the claims to only one.[49] That is the case here: the specification describes two mutually exclusive categories of "modified PH20 polypeptides" (*i.e.*, "active mutants" vs. "inactive mutants") but the claims are limited to one (*i.e.*, "active mutants").

According to the specification:

- "***Active mutants***" are modified PH20 polypeptides that "exhibit at least 40% of the hyaluronidase activity of the corresponding PH20

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48 EX1003, ¶ 136.

49 *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008).

polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[50]

- "***Inactive mutants***" are modified PH20 polypeptides that "generally exhibit less than 20% … of the hyaluronidase activity of a wildtype or reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7."[51]

It then classifies mutants into tables of "active" and "inactive" mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).[52]

The common disclosure reports no examples of an "active mutant" modified PH20 with two or more replacements.[53] Notably, it reports no examples of an enzymatically active $PH20_{1-447}$ that incorporates: (i) a mutation that preserved

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50 EX1001, 75:51-56; *see also id.* at 79:33-37 ("active mutants" "can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide …"); *id.* at 79:30-33.

51 EX1001, 115:53-61. *See also id*. at 261:61-65 (mutants with <20% activity "were rescreened to confirm that the dead mutants are inactive" in Table 10).

52 EX1001, 80:64-82:12, 227:5-7, 116:46-67, 262:21-24 ("reconfirmed inactive mutants are set forth in Table 10."); EX1003 ¶¶ 98, 100-101, 107.

53 *E.g.*, EX1003, ¶¶ 141, 172.

activity in Tables 3 and 9 ("active mutants") plus (ii) a second mutation that eliminated activity in Tables 5 and 10 ("inactive mutants").

The specification also portrays "active" and "inactive" mutants as having distinct utilities requiring mutually exclusive properties.

- "Active mutants" are portrayed as being therapeutically useful ***because they possess hyaluronidase activity***. For example, the specification explains that ***due to*** having hyaluronidase activity, "the modified PH20 polypeptides can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents."[54]
- "Inactive mutants" are portrayed as being therapeutically useful ***because they lack hyaluronidase activity***. Their only identified utility is "as antigens in contraception vaccines," which is implausible (*see* § V.C) but ostensibly requires them to lack activity.[55]

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[54] EX1001, 174:7-13; *see also id*. at 4:33-36, 73:37-51, 174:7-187:40; EX1003, ¶ 108.

[55] EX1001, 72:63-65; *see also id.* at 187:41-42, 75:60-62, 187:40-60 (for "contraception" "the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.").

The specification does not portray "active mutants" as having contraceptive utility even though they may differ by only one amino acid from an inactive mutant; it proposes using them instead ***in combination*** with contraceptive agents.[56]

The claim language reinforces that each is limited to the "active mutant" embodiment.

First, every claim requires modified PH20 polypeptides with one of six replacements at position 317 that yielded an "active mutant" as a single-replacement $PH20_{1-447}$ polypeptide (*i.e.*, L317A, L317I, L317K, L317M, L317Q, or L317R). All six mutants are identified as "Active Mutants" in Table 3 and all have >100% activity per Table 9.[57]

Second, claim 4 restricts the genus of active mutants in claim 1 (*i.e.*, those with hyaluronidase activity) to modified PH20 polypeptides that have at least 100% of the activity of unmodified PH20.[58]

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[56] EX1001, 150:23-36; EX1003, ¶ 113; EX1060, 1711.

[57] EX1001, 85-86 (Table 3), 251-252 (Table 9), 97:47-59; EX1003, ¶¶ 127-128.

[58] Claim 3 requires mutants with increased resistance to or stability in denaturing conditions. The specification portrays increased stability as an additional attribute of an "active mutant." EX1001, 52:41-47, 127:1-21, 172:59-62, 307:20-308:44.

Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one amino acid modification," but can also "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity.***"[59] This aligns with the specification's prophetic methodology for discovering PH20 polypeptides with multiple changes, which selects "active mutants" with one substitution, randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity.[60] This also tracks the claims, which require one substitution and permit others.

Patentee may contend the claims should be read as encompassing both alternative embodiments (*i.e.*, "active" and "inactive" mutants). Reading the claims in that manner is incorrect. It also exacerbates the § 112 problems, as every claim still necessarily includes (and thus must describe and enable) the full sub-genus of "active mutants" in claim 1 defined by claim 4.[61]

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[59] EX1001, 48:38-53; *see also id*. at 47:61-65, 76:9-12, 77:4-11, 81:5-82:12.

[60] EX1001, 134:56-67; *see also id*. at 42:46-53.

[61] EX1003, ¶ 135.

V. All Challenged Claims Are Unpatentable Under § 112 and None Are Entitled to Benefit to Any Pre-March 13, 2013 Application

Claims 1-40 are unpatentable because each lacks written description in and was not enabled by the common disclosure of the '758 Patent and the '731 Application in 2011.

As explained in § IV.D.1, the claim language defines enormous genera: between 10^{59} and 10^{112} distinct polypeptides. Their real-world scope is absurd—to practice the claims' full scope requires a skilled artisan to make-and-test at least ~10^{59} mutants. Simply producing one molecule of each mutant—required to know if each is active or inactive or exhibits increased stability—which, in the case of the genera's many multi-substituted mutants, would be would consume an aggregate mass (~3.93 x 10^{37} kg) that exceeds the mass of the Earth (~6 x 10^{24} kg).[62] Testing every polypeptide within the claims' scope in search of "active mutants" is impossible—literally.

Relative to that broad scope, the '758 Patent and the '731 Application provide only a meager disclosure: ***singly***-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones. It nowhere demonstrates possession of the vast remainder of multiply-modified

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[62] EX1003, ¶¶ 123, 189; *see also, e.g.*, EX1039, 136-37 (cell theoretically can make 10^{390} forms of a polypeptide with 300 amino acids).

polypeptides in the claims' scope, nor does it enable a skilled artisan to practice that full-range of mutant polypeptides without undue experimentation.

A. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.[63] "To fulfill the written description requirement, a patent owner 'must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent."[64] If the claims define a genus, the written description must "show that one has truly invented a genus …," "[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus."[65]

"[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the

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63 *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

64 *Idenix Pharm., LLC v. Gilead Scis., Inc.,* 941 F.3d 1149, 1163 (Fed. Cir. 2019).

65 *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

members of the genus so that one of skill in the art can visualize or recognize the members of the genus."[66] "One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent … [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus."[67]

A disclosure that fails to "provide sufficient blaze marks to direct a POSA to the specific subset" of a genus with the claimed function or characteristic does not satisfy § 112(a).[68] And "merely drawing a fence around the outer limits of a purported genus" is insufficient.[69] Instead, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."[70]

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66 *Idenix*, 941 F.3d at 1164.

67 *AbbVie*, 759 F.3d at 1299-1300.

68 *Idenix*, 941 F.3d at 1164.

69 *Ariad*, 598 F.3d at 1350-54.

70 *Ariad*, 598 F.3d at 1349.

Three cases are especially probative. First, in *AbbVie*, the Federal Circuit found a disclosure of 300 examples of IL-12 antibodies to not be representative of a functionally defined antibody genus:

> Although the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.[71]

It also criticized patentee's attempt to use a prophetic description for the remaining claim scope, portraying it as "only a research plan, leaving it to others to explore the unknown contours of the claimed genus" and a "trial and error approach."[72]

Second, *Idenix* addressed claims to methods of treatment with a broad genera of compounds defined by formulas analogous to the challenged claims here: "eighteen position-by-position formulas describing 'principal embodiments' of compounds that may treat HCV," each with "more than a dozen options" at each position (totaling "more than 7,000 unique configurations").[73] The court criticized the specification's failure to indicate which of the thousands of compounds would be effective, and found that "provid[ing] lists or examples of supposedly effective

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71 *AbbVie*, 59 F.3d at 1300-1301.

72 *Id.*

73 *Idenix*, 941 F.3d at 1158-64.

nucleosides," without "explain[ing] what makes them effective, or why" deprives a skilled artisan "of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result" because they "fail[] to provide sufficient blaze marks to direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV."[74]

Finally, the Board in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found.*, PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) considered claims that used "90% sequence homology" language to capture "a broad genus of amino acid sequence homologues" but (like here) imposed no restrictions on where particular amino acids replacements could be made, thus causing the claim "to cover, at minimum, thousands of amino acid sequences."[75] The Board found fatal the specification's failure to "explain what, if any, structural features exist (*e.g.*, remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification" and noted the homology limitation "serves to merely draw a fence around the outer

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74 *Id.* at 1164.

75 *Boehringer*, at 16. The claims were directed to compositions and methods of using proteins. *Id.* at 6.

limits of a purported genus [which] is not an adequate substitute for describing a variety of materials constituting the genus" for purposes of section 112(a).[76]

The deficiencies of the claims here dwarf those in these three cases. They define much larger, much less predictable, and much more diverse genera of modified PH20 polypeptides, and the common disclosure is far more limited. Because the common disclosure neither discloses a representative number of species within each immense claimed genus, nor identifies sufficient structural features common to the members of each claimed genus, it fails to demonstrate possession of the genera defined by the claims of the '758 Patent.

1. Claims 1-2, 6-16, and 25-26 Lack Written Description

a) The Claims Capture Massive and Diverse Genera of Enzymatically Active PH20 Polypeptides

The genera of modified PH20 polypeptides defined by the sequence identity language of claims 1-2, 6-16, and 25-26 are not only immense, but structurally and functionally diverse. They capture PH20 mutants with 2 substitutions, 3 substitutions, and so on up to a number set by the sequence identity boundary (*i.e.*, 21 for the narrowest claims (*e.g.* claims 25 and 26) to 42 for the broadest (claim 1)). The optional substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the

[76] *Id.* at 35-36.

sequence), to any of 19 other amino acids, and arranged in any manner.[77] They thus capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with up to 42 substitutions that mix polar, charged, aliphatic, and aromatic amino acids together in any manner.[78]

Each claim also encompasses substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 37 alternative sequences that terminate at positions 430 to 474. The claims' sequence identity language also captures PH20 polypeptides that terminate at positions before 430. For example, claims referencing SEQ ID NO:32 that allow between 21 and 42 changes (and can be any mixture of deletions and substitutions) will capture a PH20 terminating at position 416 or below. But removing so many residues from the C-terminus of PH20 can render it inactive, and the disclosure does not describe or suggest that the claimed position 317 substitution renders such mutants active.[79] The claims, however, capture such polypeptides.

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77 EX1003, ¶ 119; EX1001, 60:61-61:1, 47:43-47, 47:56-58, 42:1-7.

78 EX1003, ¶¶ 119-20.

79 EX1003, ¶¶ 164-67.

b) The Claims Capture Modified PH20 Polypeptides the Common Disclosure Says to Avoid or Not Make

The claims' unconstrained sequence identity language capture three categories of PH20 mutants a skilled artisan would understand the disclosure to be saying to avoid. Each raises unique questions relative to the remainder of the genus and are thus "sub-genera" of PH20 mutants that are not representative of other "sub-genera" within the claimed genera. But instead of providing guidance that navigates this confusing landscape, the patent simply instructs the skilled artisan "to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein."[80] The common disclosure thus does not describe any of these sub-genera within the claims' scope.

(i) Multiply-Modified PH20 Mutants to Not Make

The common disclosure affirmatively addresses only six, specific modified PH20 polypeptides with more than one identified (*i.e.*, position and amino acid) substitution, but its guidance is to ***not make those polypeptides***:

> [W]here the modified PH20 polypeptide contains only two amino acid replacements, the amino acid replacements are ***not*** P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A or N333A/N358A. In a

[80] EX1001, 78:37-42; EX1003, ¶ 193.

> further example, where the modified PH20 polypeptide contains only three amino acid replacements, the amino acid replacements are ***not*** N47A/N131A/N219A.[81]

No explanation is provided why these particular combinations of replacements should be avoided, and nor any data testing their activity or other characteristics.[82] The substitutions are not included in Tables 5 and 10 (*i.e.*, "inactive mutants") and N219A $PH20_{1-447}$ showed increased activity (129%).[83] Nothing in the claim language excludes these combinations.

(ii) Substitutions to Avoid in Active Mutants

The common disclosure indicates that active mutant modified PH20 polypeptides should not incorporate amino acid substitutions that rendered $PH20_{1-447}$ inactive, stating:

> ***To retain hyaluronidase activity***, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.[84]

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81 EX1001, 77:49-61 (emphases added).

82 EX1003, ¶¶ 146-47; EX1001, 49:30-35.

83 EX1001, 245 (Table 9).

84 EX1001, 80:17-19 (emphases added).

It identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10 that are made at other positions.[85] It does not limit this observation to single-replacement $PH20_{1-447}$ mutants, or suggest that any of these substitutions that render $PH20_{1-447}$ inactive should be included in enzymatically active, multiply-modified PH20 polypeptides (much less identify specific combinations including them).[86] Instead, by stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that the ***claimed*** enzymatically active multiply-modified PH20 polypeptides do not and should not contain them.[87] The sequence identity claim parameters, however, capture such mutants.

(iii) PH20 with Significant C-terminal Truncations Can Lose Activity

The common disclosure does not describe and provides no guidance concerning "active mutant" PH20 polypeptides having fewer than 447 residues,

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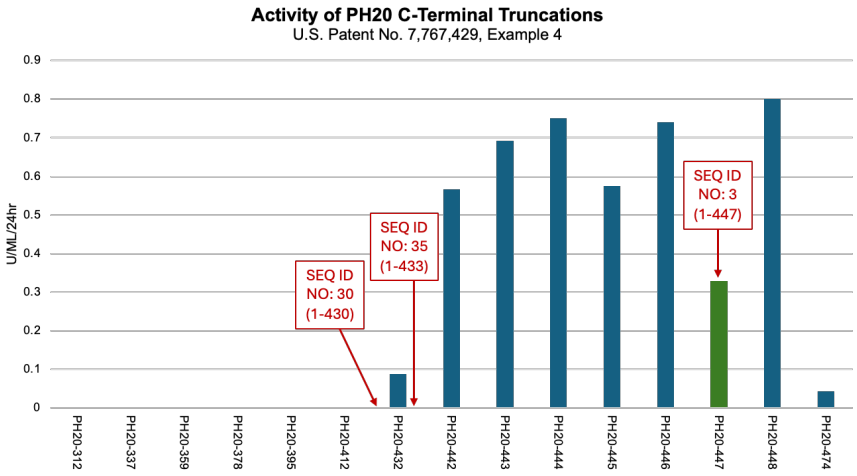
85 EX1001, 80:19-59 ("For example, generally modifications are not made at a position corresponding to position …").

86 EX1003, ¶¶ 151, 161-62, 169.

87 EX1003, ¶¶ 148-51, 162; EX1001, 80:17-59, 70:49-59.

particularly multiply-modified PH20 mutants terminating significantly before that position.[88]

But the common disclosure and the prior art report that wild-type PH20 polypeptides terminating at or below position 442 have ***significantly reduced or no*** hyaluronidase activity. For example, Patentee's '429 Patent reported that PH20 mutants terminating below position 432 residues lacked hyaluronidase activity, while those terminating between positions 432 and 448 had widely varying activities (below):[89]



Position (w/leader)	Mutant	U/ML/24hr	Normalized to PH20(1-447)
347	PH20-312	0	0.00
372	PH20-337	0	0.00
394	PH20-359	0	0.00
413	PH20-378	0	0.00
430	PH20-395	0	0.00
447	PH20-412	0	0.00
467	**PH20-432**	**0.089**	**27.05**
477	PH20-442	0.567	172.34
478	PH20-443	0.692	210.33
479	PH20-444	0.75	227.96
480	PH20-445	0.575	174.77
481	PH20-446	0.74	224.92
482	**PH20-447**	**0.329**	**100.00**
483	PH20-448	0.8	243.16
509	PH20-474	0.044	13.37

88 EX1003, ¶¶ 94, 97, 167-69; EX1001, 74:13-19.

89 EX1005, 87:52-88:24 ($PH20_{1-442}$ activity "decreased to approximately 10%"); EX1013, Figure 2, 430-32 ("[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA"); EX1003, ¶ 91.

The ’429 Patent also reported that “a very narrow range spanning … [437-447] … defined the minimally active domain” of human PH20, and elsewhere observed this “minimally active” human PH20 domain contains at least residues 1-429.[90]

The common disclosure reiterates these findings, stating that PH20 polypeptides must extend to at least position 429 to exhibit hyaluronidase activity:

> A mature PH20 polypeptide … containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue ***464*** of SEQ ID NO: 6 [position ***429*** without signal] … ***is the minimal sequence required for hyaluronidase activity***.[91]

In 2007, Chao reported that the C-terminal region of human hyaluronidases contains a unique domain (“Hyal-EGF”) linked to a characteristic pattern of sequences.[92] In PH20, the Hyal-EGF domain runs from positions 337-409.[93] In

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[90] EX1005, 6:65-7:7 (“… sHASEGP from amino acids 36 to Cys 464 [429] … comprise the minimally active human sHASEGP hyaluronidase domain”); EX1003, ¶ 90.

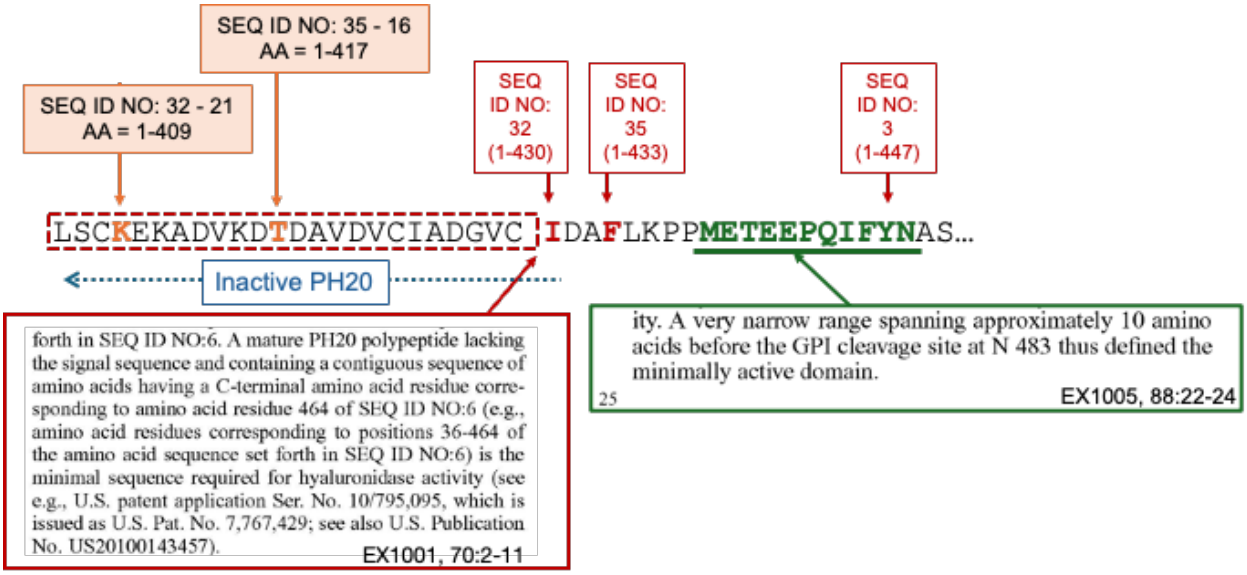
[91] EX1001, 70:2-11 (emphases added); *also* EX1003, ¶ 93.

[92] EX1006, 6912; EX1003, ¶¶ 84-86.

[93] EX1004, ¶¶ 97-99; EX1003, ¶ 92.

2009, Zhang showed the Hyal-EGF domain was necessary for hyaluronidase activity.[94]

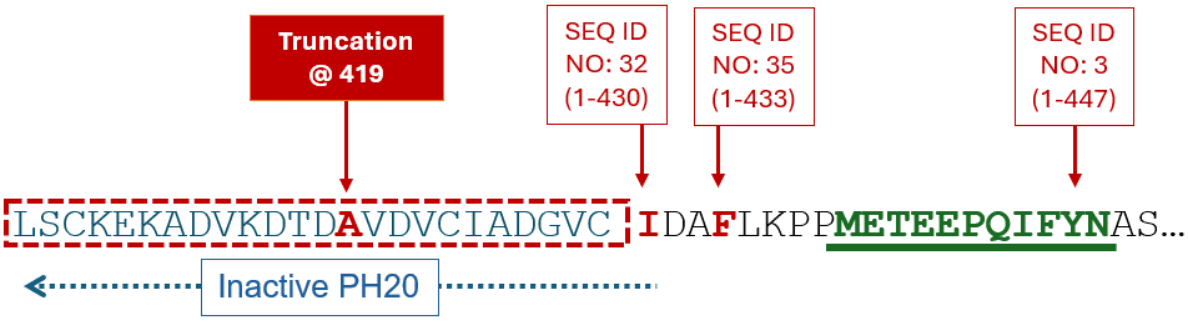
The C-terminus of PH20 is illustrated below, showing (i) the positions where SEQ ID NOS: **3** (447), **32** (430) and **35** (433) terminate, (ii) the "minimally active domain" at 437-447, and (iii) residues below position 429.[95] Positions resulting from deletion of 21 or 16 residues from SEQ ID NOS: 32 and 35 end before position 429.



94 EX1010, 9438; EX1003, ¶ 87.

95 EX1003, ¶ 153.

Consequently, a skilled artisan in 2011 would have believed that PH20 polypeptides that terminate before position 430 would be inactive (*e.g.*, at position 419, below).[96]



The common disclosure provides no examples of (or guidance concerning) PH20 mutants truncated below position 447 with one or more substitutions and that are enzymatically active. It thus ignores the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433.[97] The claims nonetheless capture modified PH20 polypeptides with truncations down to and beyond position 419.[98]

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96 EX1003, ¶¶ 92-93, 165-166.

97 EX1003, ¶¶ 92-93, 95, 97, 168.

98 EX1003, ¶¶ 164-66.

c) Empirical Test Results of Single-Replacement Modified PH20 Polypeptides Do Not Identify Multiply-Modified Enzymatically Active PH20 Polypeptides

The empirical results in the common disclosure provide no predictive guidance to a skilled artisan about the structural features of multiply-modified PH20 polypeptides within the claimed genera that are enzymatically active.

(i) The Data Concerning Single-Replacements Is Not Probative of Multiple-Replacement Mutants

The common disclosure reports results from testing a portion of a randomly generated library of ~6,743 single-replacement $PH20_{1-447}$ polypeptides.[99] These mutants were generated via a mutagenesis process which substituted one of ~15 amino acids into random positions in $PH20_{1-447}$ "such that each member contained a single amino change."[100] Approximately 5,917 were tested, while ~846 were uncharacterized.[101] More than half (~57%) of these mutants were classified as

[99] EX1001, 127:22-33, 194:44-46, 194:24-30.

[100] EX1001, 194:24-33.

[101] EX1003, ¶¶ 103-104. Inconsistent numbers of tested mutants and classifications of mutants are reported but not explained: (i) Table 3 lists 2,516 single-replacement $PH20_{1-447}$ mutants as "active mutants," but Table 9 identifies only 2,376 mutants that exhibit >40% hyaluronidase activity; (ii)

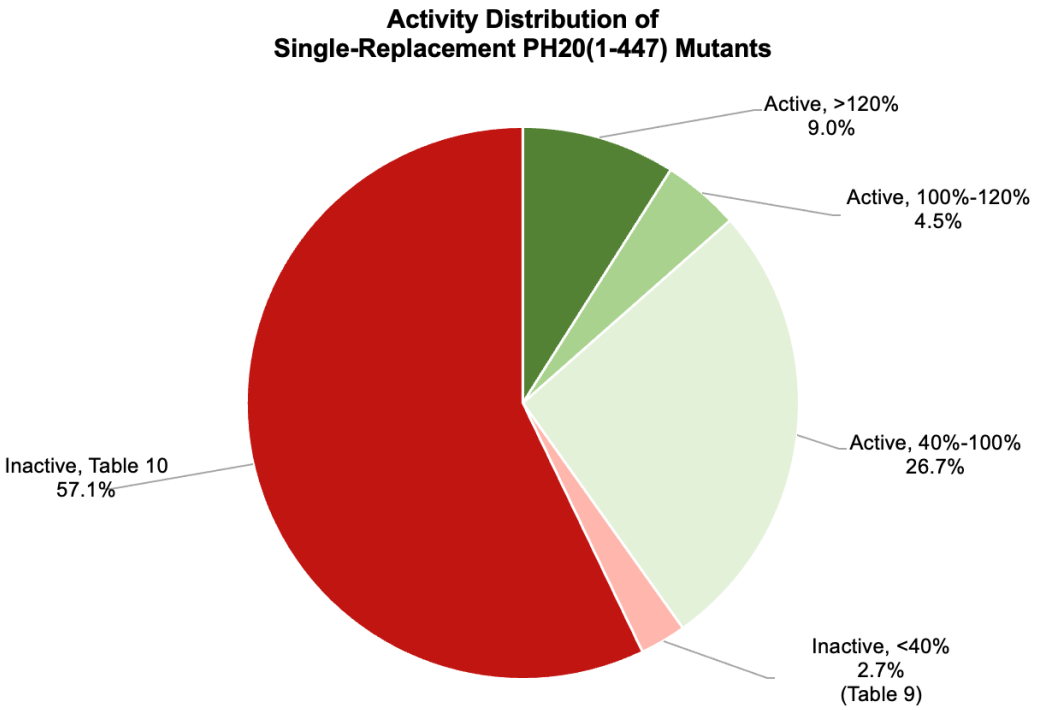
"inactive mutants," while ~30% (1335) were reported to have less activity than unmodified $PH20_{1-447}$ (20%-100%).[102] In other words, ~87% of the single-replacement $PH20_{1-447}$ polypeptides had ***less*** activity than unmodified $PH20_{1-447}$.[103]

Activity vs. Unmodified PH20	**Number**	**% of Tested (5916)**
Active Mutants (Table 9)		
>120%	532	9.0%
100%-120%	267	4.5%
40%-100%	1577	26.7%
Inactive Mutants (Table 9)		
<40%	160	2.7%
Inactive Mutants (Table 10)		
Table 10 'inactive mutants"	3,380	57.1%

Tables 5 and 10 list 3,368 and 3,380 $PH20_{1-447}$ "inactive mutants," respectively.

[102] EX1003, ¶ 105.

[103] *Id.*



The measured activity of single-replacement $PH20_{1-447}$ mutants shows no trends or correlations even for single-replacement $PH20_{1-447}$ polypeptides.[104] Instead, numerous examples show that even introducing different amino acids at the same position in $PH20_{1-447}$ resulted in (i) increased activity, (ii) decreased activity, or (iii) inactive mutants (below).[105]

104 EX1003, ¶¶ 106, 142-43.

105 Data from Tables 3, 5, 9, 10.

Position	Inactive	Decreased Activity	Increased Activity
008	P	L, M	I
067	R	L, Y	V
092	H	M, T	C, L, V
165	C	A, R, Y	D, F, N, S, V, W
426	K, S	E, G, N, Q, Y	P

The data on activities of tested single-replacement $PH20_{1-447}$ mutants is not analyzed or explained in the common disclosure—it is simply presented. There is no attempt to extrapolate its results to any combinations of substitutions in PH20 polypeptides, or to assess the impact of a single substitution on the protein's structure.[106] The quality of the data is also questionable: no control values or statistical assessments are provided.[107] All the data shows is that most of the tested single-substitution mutants impaired PH20's activity.[108]

The results from single substitutions provide no insights into PH20 polypeptides with multiple concurrent mutations, which together can cause complex and unpredictable effects on a protein's structure and resulting

[106] EX1003, ¶ 139.

[107] EX1003, ¶ 106.

[108] EX1003, ¶ 138.

function.[109] The patent's empirical test results thus provide no guidance to a skilled artisan about which of the many possible PH20 mutants with different sets of 2-42 substitutions will be enzymatically active.[110]

(ii) Purported Stability Data Is Not Reliable or Probative

The common disclosure reports results in Tables 11 and 12 from two runs of "stability" testing of ~409 single-replacement $PH20_{1-447}$ polypeptides.[111] Table 11 reports the hyaluronidase activity of single-replacement $PH20_{1-447}$ mutants tested at 4° C and 37° C, and in the presence of a "phenolic preservative" (m-cresol),[112] while Table 12 compares relative activities under pairs of these conditions.[113]

The data in Tables 11 and 12 provides no meaningful insights.[114] For example, unsurprisingly, single-replacement $PH20_{1-447}$ polypeptides showed higher activity at 37° C than at 4° C, given that PH20 exists at the former temperature in

[109] EX1003, ¶¶ 139, 142.

[110] EX1003, ¶¶ 140, 143.

[111] EX1001, 267:63-270:23.

[112] EX1001, 270:24-281 (Table 11).

[113] EX1001, 281-293:24 (Table 12).

[114] EX1003, ¶ 76.

humans.[115] And all that testing with m-cresol showed was that only a few mutants were able to resist its effects, with no explanation why.[116]

With one exception, there is no evidence the measured activity data was attributable to improved stability of PH20.[117] More directly, the common disclosure does not identify which ***combinations*** of substitutions improve stability.[118] It thus provides no probative insight regarding multiply-modified PH20 polypeptides with increased stability.[119]

The data is also largely meaningless, as many of their values fall within the range of activity observed for the positive control.[120] As the charts and table below show, the activity of unmodified $PH20_{1-447}$ varied by 97% and 87% in two rounds of testing.[121]

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115 EX1003, ¶ 73; EX1001, 170:48-57.

116 EX1003, ¶ 69.

117 EX1003, ¶ 69.

118 EX1003, ¶¶ 75-76.

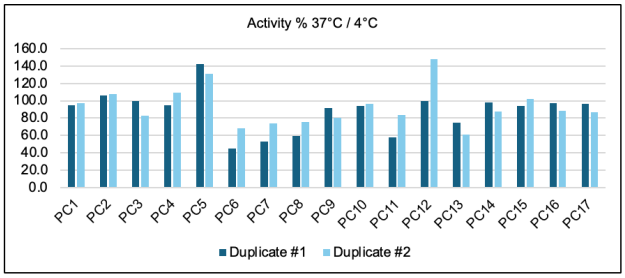
119 *Id*.

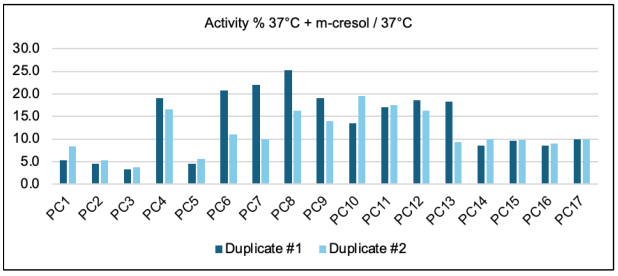
120 EX1003, ¶ 71; EX1001, 291-293 (Table 12).

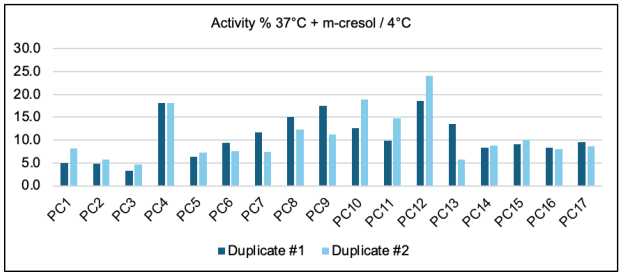
121 EX1003, ¶ 71, Appendix A-7, A-8.

Positive Control ("PC") (OHO)	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C+mcr/4°C
PC1	94.998	5.230	4.970	96.871	8.456	8.190
PC2	105.798	4.480	4.740	108.066	5.246	5.670
PC3	100.000	3.330	3.330	82.778	3.759	4.590
PC4	94.762	19.070	18.070	109.539	16.529	18.110
PC5	142.024	4.480	6.360	130.947	5.595	7.330
PC6	45.115	20.770	9.370	68.017	11.035	7.510
PC7	53.324	21.950	11.710	74.253	9.960	7.400
PC8	59.581	25.240	15.040	75.872	16.231	12.310
PC9	91.844	19.050	17.500	80.371	13.977	11.230
PC10	93.828	13.470	12.630	96.630	19.454	18.800
PC11	57.773	17.040	9.850	83.536	17.573	14.680
PC12	100.000	18.560	18.560	148.226	16.239	24.070
PC13	74.325	18.290	13.600	61.119	9.286	5.680
PC14	98.132	8.480	8.320	87.677	10.006	8.770
PC15	93.817	9.620	9.020	102.223	9.745	9.960
PC16	96.922	8.560	8.300	87.993	9.064	7.980
PC17	96.648	9.910	9.580	86.891	9.938	8.630

KEY
Coloration of Percent (%) Activity Values
n/a
>120
between 100 and 120
between 80 and 100
between 40 and 80
between 20 and 40
between 10 and 20
between 0 and < 10







	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C + m-cresol	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol	% Activity at 37°C+mcr/4°C
High	142.02	25.24	18.56	148.23	19.45	24.07
Low	45.12	3.33	3.33	61.12	3.76	4.59
Range	96.91	21.91	15.23	87.11	15.70	19.48
Average	88.17	13.38	10.64	93.00	11.30	10.64
Mean	94.76	13.47	9.58	87.68	9.96	8.63

As Dr. Hecht observes, this "significant variation raises serious doubts about how probative or instructive the values of individual tested mutants that fall within the range of variability observed for the control can possibly be."[122] The data not only fails to identify specific combinations of substitutions that yield PH20 mutants with increased resistance to or stability in denaturing conditions, it is unreliable.

d) The Common Disclosure's Research Plan Does Not Identify Multiply-Mutated Enzymatically Active PH20 Polypeptides

The common disclosure does not describe any multiply-modified PH20 polypeptides that are "active mutants." Instead, it simply presents ***the idea*** of multiply-modified PH20 polypeptides. First, it observes that "[a] modified PH20 polypeptide can have up to 150 amino acid replacements," "[t]ypically" contains between 1 and 50 amino acid replacements and "can include any one or more other

[122] EX1003, ¶¶ 70-72; *see also* EX1001, 293:30-40 (positive control also varied).

modifications**,** in addition to at least one amino acid replacement as described herein."[123] It also contends a modified PH20 polypeptide with "a sequence of amino acids that exhibits" between 68% and 99% sequence identity with any of unmodified Sequence ID Nos. 74-855 "***can*** exhibit altered, such as improved or increased, properties or activities compared to the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[124]

None of these statements identify ***any*** actual multiply-modified PH20 polypeptides (*i.e.*, particular sets of specific amino acid substitutions), much less provide results from testing any. They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides.

The common disclosure also describes no methods that produce any specific multiply-modified, enzymatically active PH20 polypeptides. What it provides instead is a prophetic research plan requiring "iterative" make-and-test experiments that ***might discover*** multiply-modified enzymatically active PH20 polypeptides:

> The method provided herein [] is ***iterative***. In one example, after the method is performed, any modified hyaluronan-degrading enzymes identified as exhibiting stability … ***can be modified or further modified*** to increase or optimize the

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123 EX1001, 48:43-53.

124 EX1001, 96:66-97:13 (emphasis added).

> stability. A secondary library ***can be*** created by introducing additional modifications in a first identified modified hyaluronan-degrading enzyme. … The secondary library ***can be*** tested using the assays and methods described herein.[125]

This prophetic research plan is effectively meaningless—it does not indicate that any active mutant multiply-modified PH20 polypeptides will be found, much less identify ***which*** multiply-modified PH20 polypeptides are active mutants.[126]

An alternative focus is then proposed: mutations can be "targeted near" "critical residues" which supposedly "can be identified because, when mutated, a normal activity of the protein is ablated or reduced."[127] But Tables 5 and 10 show that at least one substitution at each of 405 positions between positions 1 and 444 of $PH20_{1-447}$ resulted in an inactive mutant.[128] In other words, the common disclosure's guidance is to target locations "near" ~90% of the amino acids in

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[125] EX1001, 134:55-67 (emphases added); *see also id.* at 42:46-53, 128:1-6; EX1003, ¶¶ 173-177.

[126] EX1003, ¶¶ 173, 184-85, 190; EX1001, 44:1-3; *see generally id.*, 127:22-67, 128:9-129:51, 130:11-134:54.

[127] EX1001, 135:1-26; EX1003, ¶¶ 178-79.

[128] EX1003, ¶ 180, Appendix A-3.

$PH20_{1\text{-}447}$, which is no different than targeting every residue in the protein.[129] It is, like the first proposed "iterative" process, meaningless.

These prophetic research plans, based entirely on unfocused, iterative "make-and-test" experiments, provide no direction to the skilled artisan about which of the trillions and trillions of possible multiply-modified PH20 polypeptides are enzymatically active.[130] Instead, they require the skilled artisan to repeat the cycle of mutagenesis iteratively, screening and selecting until 10^{59} to 10^{112} modified PH20 polypeptides are produced and screened for activity.[131] That in no way demonstrates possession of the claimed genus.

The specification also incorrectly portrays the experimental readout—hyaluronidase activity—as a measure of "stability."[132] As Dr. Hecht explains, to assess a protein's stability directly one performs experiments that measure the energy associated with the protein's transition between its folded and unfolded

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129 EX1003, ¶ 180.

130 EX1003, ¶ 190.

131 EX1003, ¶¶ 175-77, 187-89; EX1001, 129:59-64, 129:52-130:9, 133:5-9, 133:20-25, 133:42-56.

132 EX1003, ¶¶ 67, 69, 179.

states.[133] Activity may or may not be influenced by stability but is not itself a measure of stability.[134]

e) The Common Disclosure Does Not Identify a Structure-Function Relationship for Multiply-Modified, Enzymatically Active PH20 Polypeptides

The common disclosure does not identify the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.[135] Instead, it simply lists single replacements to random amino acids at random positions that were classified as "active mutants" by a hyaluronidase assay; nothing is said about the effects (if any) of substitutions on the protein's structure.[136]

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133 EX1003, ¶¶ 63-66.

134 EX1003, ¶ 67.

135 EX1003, ¶¶ 139-40, 151.

136 EX1001, 227:5-33; EX1003, ¶¶ 139-40, 142.

The common disclosure also does not identify any ***sets*** of specific amino acid replacements that correlate to structural domains or motifs that positively or negatively influence hyaluronidase activity, much less ***predictably*** increase activity to defined thresholds.[137] Again, it simply reports activity data from testing randomly generated ***single***-replacement $PH20_{1-447}$ mutants.

The common disclosure's empirically identified examples of "active mutant" single-replacement $PH20_{1-447}$ mutants also do not ***by themselves*** identify any "structure-function" relationship between "active mutants" and the set of single-replacement modified $PH20_{1-447}$ polypeptides.[138] They certainly do not do so for the much larger genus of modified PH20 polypeptides of varying lengths and between 2 and 42 substitutions.[139]

Critically, the common disclosure ***does not even contend*** that a particular amino acid replacement at a particular position (*e.g.*, 317) that makes a $PH20_{1-447}$ an "active mutant" will make any other modified PH20 polypeptide with that same amino acid replacement (plus between 1 and 41 additional replacements or

[137] EX1003, ¶¶ 55, 142-43.

[138] EX1003, ¶¶ 61, 143, 157, 159.

[139] EX1003, ¶ 157.

truncations) an "active mutant."[140] Such an assertion would have no scientific credibility—the activity of a protein such as PH20 is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.[141] Thus, even the inventors did not view their compilation of test results as identifying a structure-function correlation for multiply-modified PH20 polypeptides.

The common disclosure, thus, does not identify to a skilled artisan ***any*** structural features shared by the many, diverse "active mutant" modified PH20 polypeptides within the scope of the claims,[142] and thus cannot satisfy the written description requirement of § 112(a) as a disclosure that links a functional property to a particular structure ***shared*** by the members of the genus.

[140] EX1003, ¶¶ 168, 192-93.

[141] EX1003, ¶¶ 56-57.

[142] EX1003, ¶ 157.

f) The Common Disclosure Does Not Describe a Representative Number of Multiply-Modified Enzymatically Active PH20 Polypeptides

The ~2,500 active mutant single-replacement $PH20_{1-447}$ polypeptides in the disclosure are not representative of the claimed genera or the various sub-genera within the claims.[143]

First, these single-replacement $PH20_{1-447}$ examples are not representative of the trillions and trillions of $PH20_{1-447}$ polypeptides with between ***2 and 42 substitutions*** at any of hundreds of positions within the protein.[144] The latter group of proteins is structurally distinct from single replacement PH20 polypeptides, both as to their sequences and as to the various secondary structures and structural motifs within the folded proteins that result when multiple amino acid substitutions are incorporated and from the distinct interactions they can cause with neighboring residues.[145] The effects of numerous substitutions on the PH20 protein's various secondary structures and structural motifs are not described or discussed in the common disclosure, and the magnitude of structural changes resulting from the

143 EX1003, ¶¶ 61, 143, 155, 159.

144 *See* § IV.D.1; EX1003, ¶¶ 61, 143, 159.

145 EX1003, ¶¶ 55-56, 58, 60, 156, 159.

concurrent substitutions encompassed by the claims was unknowable in 2011.[146] The overall activity of a protein with multiple substitutions also will not be due to one amino acid, but to the unique structure of each protein that reflects ***the totality*** of effects of those many substitutions.[147]

More specifically, introducing a first amino acid substitution often affects the neighbors of that original/replaced amino acid by, for example, (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, and/or (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).[148] Introducing a second substitution in that region may reverse those interactions (or not) with each neighboring residue, and a third substitution may do the same, with up to 21 rounds permitted by even the narrowest claims, each potentially impacting each interaction.[149] The data associated with a single amino acid substitution thus cannot be representative of the properties of any of these downstream, multiply-substituted mutants, which will have an unknowable

146 EX1003, ¶¶ 157-58, 229.

147 EX1003, ¶¶ 61, 141.

148 EX1003, ¶¶ 56-58.

149 EX1003, ¶¶ 58-60, 142.

combination of substitutions that each uniquely impact the properties of the mutated protein.[150]

Enzymatically active single-replacement $PH20_{1-447}$ polypeptides also are not representative of enzymatically active, multiply modified PH20 polypeptides that incorporate changes that alone render PH20 proteins inactive (*e.g.*, truncations terminating below position 429, or single substitutions that render $PH20_{1-447}$ inactive).[151] That is because an ***active*** single-replacement $PH20_{1-447}$ polypeptide does not also contain the distinct structural features that render the latter types of PH20 polypeptides enzymatically ***inactive***. For example, an enzymatically active $PH20_{1-447}$ protein with a single amino acid substitution (*e.g.*, L317Q) would not be considered representative of a PH20 that combines that L317Q substitution with truncations at the C terminus ending at positions between 409 to 433 because the common disclosure would have led a skilled artisan to expect that PH20 proteins terminating at those positions would be inactive.[152] A skilled artisan could not have predicted—based on the examples in the common specification, all of which are limited to single-replacement $PH20_{1-447}$ polypeptides—whether enzymatic

150 EX1003, ¶¶ 143, 159.

151 EX1003, ¶¶ 161-64.

152 EX1003, ¶¶ 167-69.

activity could be restored to such severely truncated PH20 mutants, much less the precise additional changes that would do so.[153]

The common disclosure thus provides a very narrow set of working examples relative to the diversity of modified PH20 polypeptides being claimed.[154] The examples are restricted to ***one type of change*** (a single amino acid replacement) in ***one type of PH20 polypeptide*** (SEQ ID NO: 3).[155] By contrast, the claims encompass changes in 37 different unmodified PH20 sequences, and include, in addition to one identified replacement at position 317, anywhere from 1 to 41 (claim 1) or 22 (claim 2) or 20 (claims 25-26) additional changes.[156] A simple illustration demonstrates how ***non-representative*** the examples are: all of the examples of single-replacement $PH20_{1\text{-}447}$ mutants fit into one box of the array below (which depicts the scope of claim 2).

153 EX1003, ¶ 168.

154 EX1003, ¶ 155.

155 EX1003, ¶¶ 97, 99, 103.

156 EX1003, ¶¶ 115-20.

	Number of Changes																					
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3																							
7																							
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Unlike claim 2, which requires 95% sequence identity, claim 1 permits 91% sequence identity, thus capturing an even ***larger*** genus (up to 42 permitted changes) than depicted above.

Consequently, a skilled artisan would not have viewed the Patents' examples of individual single amino acid replacements in $PH20_{1\text{-}447}$ as being ***representative*** of the diversity of modified PH20 polypeptides encompassed by the claims.[157]

[157] EX1003, ¶ 143.

g) The Claims Capture Multiply-Modified PH20 Polypeptides the Disclosure Excludes from the Class of Enzymatically Active PH20 Proteins

Patentee's position on the breadth of the claims is unknown. However, by their literal language, they capture several sub-genera of "active mutant" modified PH20 polypeptides that the common disclosure says caused single-replacement $PH20_{1-447}$ mutants to be inactive (*i.e.*, those with replacements in Tables 5/10 or in PH20 sequences terminating before position 429). Likewise, the claim language captures modified PH20 polypeptides with the six combinations of replacements the common disclosure explicitly says to not make: P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, N333A/N358A, and N47A/N131A/N219A.[158] The claims thus improperly capture multiply-modified PH20 polypeptides the common disclosure affirmatively excludes from the genus of enzymatically active PH20 polypeptides.

The common disclosure provides no exemplification of multiply-modified species of PH20 polypeptides that disregard these restrictions in the common disclosure.[159] There is no explanation of the types of substitutions that might be made to restore activity that, under the logic of the common disclosure, will result

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158 *See* § V.A.2.a; EX1001, 77:49-61.

159 EX1003, ¶ 161.

in enzymatically inactive PH20 polypeptides or which the specification teaches ***not*** to make.[160] Yet the claims encompass such proteins.

The claims thus independently violate the written description requirement for the reasons articulated by the Federal Circuit in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998)—if a disclosure "unambiguously limited" the invention, but the claims circumvent that limitation, those claims are "broader than the supporting disclosure" and are unpatentable.

2. Dependent Claims 3-5, 17-24, and 27-40 Lack Written Description

a) Claims 3-4

Claims 3 and 4 specify additional functional properties of the modified PH20 polypeptides in the genus defined by claim 1: either (i) increased hyaluronidase activity (claim 4) or (ii) increased stability (claim 3) relative to unmodified $PH20_{1-447}$.

The reasons provided in § V.A.1 explaining why the claims generally lack written description apply with full force to claims 3 and 4.

In addition, the common disclosure's recitation of a ***desired*** level of stability or hyaluronidase activity in claims 3 and 4 does not identify ***which*** of the many trillions of PH20 polypeptides having 91% or 95% sequence identity with SEQ ID

[160] EX1003, ¶ 168.

NOS: 3, 7, or 32-66 and one of six replacements at position 317 will exhibit either of those functional properties.[161]

First, the identification of six single-substitution $PH20_{1-447}$ mutations at position 317 that exhibited increased activity compared to unmodified $PH20_{1-447}$ is not representative of each claim's genus of PH20 polypeptides having 1 to 41 additional substitutions and/or truncations.[162] Regarding "stability," only four of the six position 317 mutants (L317A, L317I, L317K, and L317R) were tested, and they showed activities both above and below that reported for unmodified $PH20_{1-447}$; the L317Q mutant was not tested for "stability."[163]

TABLE 12-continued

	Percent (%) Activity					
	duplicate 1			duplicate 2		
	% activity at 37° C./4° C.	% activity 37° C. + m-cresol/37° C.	% activity 37° C. + m-cresol/4° C.	% activity at 37° C./4° C.	% activity 37° C. + m-cresol/37° C.	% activity 37° C. + m-cresol/4° C.
L317A	123.510	6.97	8.60	132.724	8.395	11.14
L317I	187.477	12.72	23.84	110.696	10.670	11.81
L317K	96.199	3.45	3.31	134.204	3.534	4.74
L317N	127.382	12.02	15.31	121.233	14.528	17.61
L317R	238.501	3.87	9.22	99.467	5.673	5.64
L317S	90.929	15.54	14.13	85.810	6.423	5.51
L317T	145.964	6.96	10.16	154.334	1.087	1.68
L317W	163.704	11.92	19.51	147.606	10.270	15.16

161 EX1003, ¶¶ 185, 191-92.

162 EX1001, 251-252 (Table 9); EX1003, ¶¶ 191-92.

163 EX1001, 287 (Table 12); EX1003, ¶ 71; *see* § IV.A.1.c.ii.

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides (if any) exhibiting increased activity or stability.[164] The mere presence of a single substitution at position 317 in a modified PH20 certainly does not demonstrate possession of any multiply-modified PH20 polypeptide with increased activity or stability having that position 317 substitution, and the common disclosure does not contend otherwise.[165]

The common disclosure does not describe any multiply-modified PH20 polypeptides having the claimed substitutions at position 317, much less those with 1 to 41 additional substitutions, and that exhibit increased enzymatic activity or increased stability.[166] Indeed, the common specification does not identify any multiply-modified PH20 polypeptides with any level of hyaluronidase activity.[167] Similarly, even if the data reported in Tables 11 and 12 was not flawed and unreliable as a measure of "stability" (as discussed above, it is), it too is limited to

[164] EX1003, ¶¶ 157, 185, 190.

[165] EX1003, ¶¶ 143, 168, 185.

[166] EX1003, ¶¶ 140, 190-93.

[167] EX1003, ¶¶ 130, 172.

singly-substituted PH20 polypeptides, and, provides no "stability" data for multiply-modified PH20 polypeptides.[168]

Claims 3 and 4 lack written description in the common disclosure.

b) Claim 5

Claim 5 requires an additional functional property: that the modified PH20 polypeptide be "soluble." Claim 5 lacks written description support (i) for the same reasons identified for claim 1, and (ii) because it encompasses modified PH20 polypeptides that the common disclosure suggests would be insoluble.

The common disclosure explains that "a soluble PH20 lacks all or a portion of a glycophosphatidyl anchor (GPI) attachment sequence,"[169] which was known to be hydrophobic.[170] Citing prior art, it identifies the first residue of the GPI sequence in human PH20 as position 456 (position 491 in SEQ ID NO: 6).[171] It

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168 EX1001, Tables 11, 12.

169 EX1001, 46:26-28, 72:11-12, 74:30-42.

170 EX1001, 72:35-47; EX1005, 86:18-22.

171 EX1001, 72:35-47; *also* EX1005, 2:56-61 ("Attempts to make human PH20 DNA constructs that would not introduce a lipid anchor into the polypeptide resulted in either a catalytically inactive enzyme, or an insoluble enzyme") (citing EX1011).

also states that a soluble PH20 "is a polypeptide that is truncated after amino acid 482 of … SEQ ID NO: 6" (*i.e.*, 447 in SEQ ID NO:3)."[172] It thus suggests that human PH20 sequences that terminate below position 448 are soluble and those that terminate above position 456 are insoluble.[173]

Claim 5 encompasses PH20 polypeptides based on SEQ ID NOS:59-66, which terminate between positions at 457 to 464 respectively (*i.e.*, beyond position 456), and does not restrict where in the PH20 polypeptide changes are made, other than the replacement at position 317. Consequently, claim 5 captures modified PH20 polypeptides that are C-terminally truncated but, per the common disclosure, ***are not*** "soluble modified PH20 polypeptide[s]" because each contains "all or a portion of" the GPI attachment sequence.[174]

Patentee may contend that some unidentified number of modified PH20 polypeptides based on SEQ ID NOS: 59-66 ***may*** be soluble, citing the common disclosure as suggesting that between 1-10 residues within the GPI anchor "can be retained, provided the polypeptide is soluble."[175] But the common disclosure does

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172 EX1001, 75:20-22; EX1005, 3:57-62.

173 EX1003, ¶¶ 89-90.

174 EX1001, 46:53-59.

175 EX1001, 74:23-29.

not identify ***which*** modified PH20 polypeptides terminating above position 448 (and especially terminating between 457 and 464) ***are*** soluble, provides no examples of such soluble PH20 mutants, and provides no reason to expect that many modified PH20 polypeptides within the claim's scope are soluble.

Thus, claim 5 is unpatentable for lack of written description for this additional, independent reason.

c) Claims 17-24, 27-40

The remaining dependent claims (17-24 and 27-40) do not alter the number of PH20 polypeptides in the genus of claim 1. They instead specify additional features (claims 17-23, 34-40), or pharmaceutical compositions, or methods of treatment, or methods of delivery that reference the genus of claim 1. They lack written description for the same reasons explained in § V.A.1.[176]

[176] *Idenix*, 941 F.3d at 1155, 1165 (method of treatment claims involving immense genus of modified proteins invalid for lack of written description and non-enablement); *Boehringer*, PGR2020-00076, Paper 42, at 40-41 (methods of treatment claims found to lack written description because specification did not provide an adequate written description of compositions being administered).

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

"If a patent claims an entire class of … compositions of matter, the patent's specification must enable a person skilled in the art to make and use the ***entire*** class," *i.e.*, "the ***full scope*** of the invention" and so the "more one claims, the more one must enable."[177] "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."[178] "Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation."[179]

Although not required, enablement may be assessed using the *Wands* factors, which consider: "(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the

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177 *Amgen*, 598 U.S. at 610 (emphases added).

178 *Idenix*, 941 F.3d at 1159.

179 *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention."[180]

Where the scope of the claims is large, there are few working examples disclosed in the patent, and the only guidance to practice "the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims' functional limitations—the asserted claims are not enabled."[181]

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the 10^{59}+ PH20 polypeptides having multiple amino acid replacements and/or truncations within the scope of the claims are "active mutant" PH20 polypeptides.[182]

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180 *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

181 *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, T., sitting by designation) *aff'd* 81 F.4th 1362 (Fed. Cir. 2023).

182 EX1003, ¶¶ 170-71, 190.

1. Claims 1-2, 6-16, and 25-26 Are Not Enabled

The facts of this case are a textbook example of claims that are not enabled under the reasoning articulated by the Supreme Court in *Amgen*. An analysis of the common disclosure under the Federal Circuit's framework for assessing undue experimentation using the factors in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) compels the same conclusion.

a) Extreme Scope of the Claims

As explained in § IV.D.1, each of claims 1-2, 6-16, and 25-26 define an immense and diverse genus of between 10^{59} and 10^{112} enzymatically active modified PH20 polypeptides. Practicing that full genus, however, raises substantial scientific questions left unanswered by the common disclosure:

(i) The claims encompass many modified PH20 polypeptides that terminate below position 429.[183] The common disclosure and the prior art, however, report that unmodified human PH20 must include residues through position 429 to have hyaluronidase activity.[184]

(ii) Several claims (1-2, 6-10) encompass modified PH20 polypeptides that, per the common disclosure's guidance, would be expected to be

[183] EX1003, ¶¶ 154, 164.

[184] EX1001, 70:2-11; EX1003, ¶¶ 93, 152-53.

insoluble because they include all or some of the GPI anchor sequence.[185]

(iii) The mathematical "sequence identity" boundaries set by the claim language cause the claims to capture (without restriction) modified PH20 polypeptides with 2 to 42 amino acid replacements that the common disclosure instructs "are less tolerant to change or required for hyaluronidase activity"[186] or which the common disclosure affirmatively says to not make.[187]

In other words, the claims capture massive genera of modified PH20 polypeptides, most of which would have unknowable properties absent individual production and testing.[188]

Claims that capture a massive and diverse genus of proteins have routinely been found non-enabled. For example, the claims in *Amgen* covered "millions" of different, untested antibodies,[189] while in *Idenix*, a skilled artisan would

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185 EX1001, 46:26-28, 72:11-12, 74:23-29, 75:20-22; EX1005, 2:56-61, 3:57-62.

186 EX1001, 80:17-19.

187 EX1001, 77:49-61.

188 EX1003, ¶ 158.

189 598 U.S. at 603.

"understand that 'billions and billions' of compounds literally meet the structural limitations of the claim."[190] In both cases, the enormous claim scope was found non-enabled after being contrasted to the limited working examples in the patent, the existence of unpredictability, and the quantity of experimentation needed to practice the full scope of the claims (*Wands* Factors 1, 3, 4, and 7). And, as the *Idenix* court observed, one cannot rely on the knowledge and efforts of a skilled artisan to try to "fill the gaps in the specification" regarding which of the "many, many thousands" of possible compounds should be selected for screening, and which in this case is impossible.[191]

b) Limited Working Examples and Only a Research Plan for Discovering Active Mutant PH20 Polypeptides

The common disclosure provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement $PH20_{1\text{-}447}$ polypeptides, of which ~2500 were "active mutants."[192] Those examples are a tiny fraction of the 10^{59} to 10^{112} modified PH20 polypeptides covered by the claims, and provide no guidance that would help a skilled artisan navigate the "trial-and-error" methodology the common disclosure describes using to make modified PH20

190 941 F.3d at 1157.

191 *Id.* at 1159.

192 EX1003, ¶ 103.

polypeptides; indeed, none incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.[193]

The common disclosure provides no credible guidance on the full scope of the genus comprising multiple combinations of changes to PH20 polypeptides.[194] Instead, it describes an explicitly prophetic and "iterative" process for ***discovering*** active mutant PH20 polypeptides. *See* § V.A.1.d.

The purely prospective research plan in the common disclosure demands that a skilled artisan engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of ***randomized*** mutations (up to 41 rounds per starting molecule under the broadest claims) to ***discover*** which of the 10^{59}+ possible modified PH20 polypeptides having 2 to 41 replacements to any of 19 other amino acids in any of many, varying-length starting PH20 sequences might possess hyaluronidase activity.[195]

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193 EX1003, ¶¶ 155, 159, 167.

194 EX1003, ¶¶ 131, 139.

195 EX1003, ¶¶ 188-90; *see also* EX1018, 382 ("combinatorial randomization of only five residues generates a library of 205 possibilities (3.2 x 10^6 mutants), too large a number for manual screening"). Chica also credited a supposed "ground-breaking" advancement in predictive molecular modeling techniques.

Second, it provides no meaningful guidance in producing "active mutant" modified PH20 polypeptides:

(i) it does not identify ***any*** specific combination of two or more replacements within any PH20 polypeptide that yield "active mutants";

(ii) it provides no data from testing ***any*** PH20 polypeptide with two or more substitutions; and

(iii) it does not identify any regions or residues that are "associated with the activity and/or stability of the molecule" or "'critical residues involved in structural folding or other activities' of the molecule" when two or more concurrent replacements have been made.[196]

From the common disclosure and their knowledge in 2011, a skilled artisan could not predict whether a particular multiply-modified PH20 polypeptide will be enzymatically active without making and testing each one.[197]

EX1018, 384, 382. That supposed advancement, however, was later shown to be false. EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

[196] EX1003, ¶¶ 144, 158, 172, 184-85.

[197] EX1003, ¶ 190.

Regardless whether individual rounds of "iterative" production and testing might be considered "routine," the process described in the common disclosure is indistinguishable from the "***iterative, trial-and-error process[es]***" that have consistently been found to not enable broad genus claims to modified proteins.[198] Simply put, the common disclosure's prophetic, iterative and labor-intensive process requires making and screening an immense number of modified PH20 polypeptides, before which the skilled artisan will not know which multiply-modified PH20 polypeptides are within the claims' scope.[199]

c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable

Like any protein, the activity of PH20 can be unpredictably influenced by changes to its amino acid sequence.[200] Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary

198 *Idenix*, 941 F.3d at 1161-63 (emphasis added); *see also Amgen,* 598 U.S. at 612-15; *Wyeth*, 720 F.3d at 1384-86; *Baxalta*, 597 F. Supp. 3d at 616-19; *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 n.2 (Fed. Cir. 2020).

199 EX1003, ¶¶ 172, 183-85, 189.

200 EX1003, ¶ 61.

structures or structural motifs within the protein that are important to its biological activity (*e.g.*, catalysis, ligand binding, etc.) and/or stability.[201]

As explained in § VI, below, by 2011, skilled artisans could have assessed whether certain ***single*** amino acid substitutions at certain positions would be tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.[202] That person, using a rational design approach, would have performed such an assessment by, *inter alia*, analyzing evolutionarily non-conserved positions and evaluating specific changed residues using a PH20 protein structure model using experimental evidence available before 2011 that is not disclosed in or referenced by the common disclosure.[203]

By contrast, the skilled artisan could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011.[204] Introducing ***multiple*** concurrent changes into a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity and/or stability,

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201 *Id.*

202 EX1003, ¶ 194.

203 EX1003, ¶¶ 20, 49.

204 EX1003, ¶¶ 158, 229.

and can even introduce new ones into the protein.[205] Replacing multiple amino acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.[206]

The cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure in 2011. For example, the further away the modeled amino acid sequence gets from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model became.[207] In addition, depending on the structural template used to produce the model, regions of the protein not supported by a corresponding structure cannot be reliably used to assess particular changes.[208] And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.[209]

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205 EX1003, ¶¶ 59-60, 185.

206 EX1003, ¶¶ 55, 58, 61.

207 EX1003, ¶¶ 158, 190, 229; EX1004, ¶¶ 158-159.

208 EX1003, ¶¶ 158, 229; EX1004, ¶¶ 148-150; EX1012, 4, 8.

209 EX1003, ¶ 51, 190; EX1059, 1225-26; EX1018, 378.

Consequently, a skilled artisan could not have used conventional rational design techniques to identify, much less predict the outcome of attempts to make, the enormous number of PH20 polypeptide sequences that incorporate the myriad possible combinations of between 2 and up to 42 substitutions the claims encompass.[210] Stated another way, practicing the full scope of the claims would have been well beyond the ability of the skilled artisan's ability to reasonably predict which multiply-modified PH20 polypeptides would be enzymatically active, and, even if possible, doing so would have taken an extreme amount of time and effort even for a small handful of the vast universe of multiply-modified polypeptides within the claims.[211]

d) Other Wands Factors and Conclusion

The remaining *Wands* factors either support the conclusion that practicing the full scope of the claims would require undue experimentation or are neutral.

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed.[212]

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210 EX1003, ¶¶ 61, 158, 229.

211 EX1003, ¶¶ 158, 190.

212 EX1003, ¶¶ 158, 229.

Likewise, while there was significant knowledge in the public art about hyaluronidases, there was no solved structure of the PH20 protein, experimental reports generally reported on ***loss of activity*** from mutations, and did not predictably teach how to introduce changes that ***enhanced*** stability or activity. Indeed, the non-enabled patent disclosure at issue in *Amgen* dates to the same 2011 timeframe as the common disclosure.

Practicing the full scope of claims 1-2, 6-16, and 25-26 thus would have required a skilled artisan to engage in undue experimentation, which renders those claims non-enabled.

2. Dependent Claims 3-5, 17-24, and 27-40 Are Not Enabled

a) Claims 3-4

Claims 3 and 4 require the modified PH20 polypeptides to have increased activity (*i.e.*, >100% of unmodified PH20) or increased resistance to or stability in denaturing conditions.

The reasons why claims 1-2, 6-16, and 25-26 are not enabled (*see* § V.B.1) establish why claims 3 and 4 are also not enabled. Specifically, a skilled artisan could not have predicted which of the trillions of PH20 polypeptides having up to 41 changes beyond a required change at position 317 would exhibit increased

activity or stability compared to an unmodified PH20.[213] Instead, a skilled artisan would need to make-and-test each molecule in order to practice the "full scope" of the claims.[214]

b) Claim 5

Because claim 5 encompasses a substantial portion of the genus defined by claim 1, it is not enabled for the same reasons.

Additionally, as explained in § V.A.2.b, the common disclosure suggests that PH20 polypeptides (modified or unmodified) that extend past position 456 would be "insoluble." Based on it and published literature, a skilled artisan would have expected the presence of the hydrophobic GPI sequence in the PH20 protein could cause aggregation, loss of activity, and/or reduced expression.[215] The common disclosure reinforces that these problems can occur, but provides no guidance as to how solve them and no examples of modified PH20 polypeptides extending past position 456 that are soluble. Claim 5 is thus not enabled.

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213 EX1003, ¶¶ 185, 190.

214 *Id.*

215 EX1003, ¶¶ 89-90, 196; EX1001, 51:2-4, 72:35-47; *also* EX1005, 2:56-61.

c) Claims 17-24, 27-40

The remaining claims employ the genus definition used in claim 1 and recite either further modifications to the modified polypeptides, pharmaceutical compositions, or methods (*e.g.*, methods of treatment or delivery of therapeutic agents) using the claimed genus. These claims do not add requirements that limit the numbers of polypeptides in the claim 1 genus. They are therefore not enabled for the same reasons.[216]

C. Inactive PH20 Polypeptides Are Not Useful and Do Not Remedy the § 112(a) Deficiencies of the Claims

Patentee may contend the claims do not require the modified PH20 polypeptides to be "active mutants." Such a contention, even if accepted, does not solve the written description and enablement problems of the claims.

First, it ignores that at least ***a portion*** of the claimed genus ***does*** require the modified PH20 polypeptides to be "active mutants." *See* § V.B.2.a. Claim 4 defines a "sub-genus" of modified PH20 polypeptides that is within the scope of claim 1 and that must exhibit increased hyaluronidase activity. The failure of the

[216] *See, e.g.*, *Idenix*, 941 F.3d at 1155, 1165.

common disclosure to enable or describe that subgenus demonstrates that claim 1 is unpatentable.[217]

Second, the common disclosure provides no correlation between multiply-modified PH20 polypeptides and ***either*** active ***or*** inactive mutants.[218] The skilled artisan thus must perform trial-and-error testing of each of the 10^{59}+ candidate polypeptides within the claims' scope to determine which are "active mutants" and which are "inactive mutants."[219]

Third, the only putative utility identified for "inactive" polypeptides is as "antigens in contraception vaccines."[220] That assertion is not scientifically credible. While the specification cites two studies in guinea pigs,[221] it ignores

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217 *ABS Glob., Inc. v. Inguran*, 914 F.3d 1054, 1070, 1074 (7th Cir. 2019) ("If the specification failed to enable [a limitation] in the dependent claim, then [] the full scope of the invention is also not enabled in the independent claim, and *both* claims are invalid for non-enablement") (citing *Alcon Research, Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1367-68 (Fed. Cir. 2012)).

218 EX1003, ¶ 143.

219 EX1003, ¶¶ 173-74, 182-84.

220 EX1001, 75:60-62, 187:40-60.

221 EX1001, 187:40-60; EX1022, 1142-43; EX1023, 1133-34.

numerous publications before 2011 that showed that immunizing mammals with PH20 did ***not*** cause contraception.[222] Moreover, Patentee reported that clinical studies of unmodified $PH20_{1-447}$ in 2018 showed that "[a]lthough some antisperm antibodies are associated with decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex."[223] Notably, Patentee publicly reported this clinical result before filing the application that issued as the '758 Patent. A skilled artisan thus would have expected that "inactive mutant" PH20 polypeptides would have no utility at all,[224]

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222 *See* EX1019, 325, 331-33 ("recombinant mPH20 is not a useful antigen for inclusion in immunocontraceptive vaccines that target mice"); EX1020, 179-81 ("immunization [of rabbits] with reproductive antigens … are unlikely to result in reduced fertility …"); EX1021, 30310, 30314 ("PH-20 is not essential for fertilization, at least in the mouse …").

223 EX1024, 87-88; *see also* EX1061, 1154; EX1003, ¶¶ 110-11.

224 *Id.*; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App'x. 26, 30 (Fed. Cir. 2007).

and would not have accepted the common disclosure's assertion that "inactive mutants" are useful as contraceptive vaccines, particularly in humans.[225]

Finally, the common disclosure does not identify ***any*** inactive PH20 mutants that exhibit contraceptive effects in humans (contrary to patentee's clinical evidence).[226] It likewise provides no guidance about which epitopes (if any) on the PH20 protein might induce contraceptive effects, much less show that "inactive mutants" preserve such epitopes.[227] Thus, a skilled artisan could not have reasonably predicted from the common disclosure whether any "inactive mutant" PH20 polypeptides would contain such (unidentified) epitopes or induce antibody production sufficient to confer contraceptive effects.[228]

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225 EX1003, ¶¶ 112-13; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

226 EX1003, ¶ 113.

227 *Id.*

228 EX1003, ¶¶ 112-13.

Therefore, at most, the common disclosure presents only a "research proposal" to discover "inactive mutants" with contraceptive utility.[229] It does not demonstrate possession of or enable the immense and diverse genus of PH20 polypeptides claimed, regardless of whether the claims are appropriately limited to "active mutants" or, instead, include "inactive mutants."

D. The Original Claims of the '731 Application Do Not Cure the Written Description and Enablement Deficiencies

The specifications of the pre-AIA '731 Application and AIA '758 Patent are substantially identical, and neither supports the challenged claims as § 112(a) requires by either. The claims are both PGR eligible and unpatentable under § 112(a).

The original claims of the '731 Application provide no additional guidance demonstrating written description or enablement of the claimed genera of multiply-modified PH20 polypeptides. Those original claims claimed equivalently broad genera via sequence identity language (*e.g.*, 85% to SEQ ID NOS: 3, 7 or 32-66) (claims 1-3) or having up to "75 or more amino acid replacements" (claim 4). Dependent claims listed single positions (claim 12) or replacements (claims 13-16)

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[229] *See Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("[t]he utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research").

in those polypeptides. And, while certain claims contemplated 2-3 particular combinations of amino acid replacements (from dozens listed), others encompassed substitutions at unspecified locations.[230] The original claims do not provide § 112 support for the challenged claims.[231]

VI. Challenged Claims 1-2, 5-6, 8, and 10-40 Are Unpatentable Under § 103

Claims 1-2, 6, 8, 10-16, and 25-26 define genera that encompass one specific modified PH20 polypeptide: L317Q $PH20_{1-447}$. *See* § IV.D.2. Because this mutant would have been obvious from the '429 Patent in view of Chao and the knowledge of a skilled artisan, each of those claims is unpatentable. Claims 5, 17-24, and 27-40 are also obvious, as each recites attributes met by L317Q $PH20_{1-447}$, or is suggested by the '429 Patent alone or with other prior art.

A. The Prior Art

The '429 Patent (EX1005) is owned by Patentee, was originally filed in 2003, and issued on Aug. 3, 2010.

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230 EX1026, at 335.

231 *See, e.g.*, *Ariad Pharms.*, 598 F.3d at 1349; *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993).

Chao (EX1006) was published in "Biochemistry" in 2007. Chao is not discussed in the common disclosure of the '758 Patent and '731 Application and was not cited during examination.

Knowledge of the skilled artisan relevant to obviousness is described in the testimony of Drs. Hecht (EX1003) and Park (EX1004), and is also documented in the prior art, including Patentee's earlier-published application, WO297 (EX1007).

B. Because L317Q PH20$_{1-447}$ Would Have Been Obvious, Claims 1-2, 6, 8, 10-16, and 25-26 Are Unpatentable

Patentee's '429 Patent would have motivated a skilled artisan to produce modified PH20$_{1-447}$ polypeptides having a single amino acid substitution in non-essential regions of the protein. Guided by her familiarity with rational protein design and the teachings of the '429 Patent and Chao, the artisan would have readily identified single amino acid substitutions in non-essential regions of PH20$_{1-447}$ that would have been tolerated (*i.e.*, a PH20$_{1-447}$ with that single substitution would retain its enzymatic activity). L317Q PH20$_{1-447}$ is one such example. Because claims 1-2, 6, 8, 10-16 and 25-26 encompass at least one of these obvious variants of PH20$_{1-447}$, each is unpatentable.

1. Patentee's '429 Patent Motivates a Skilled Artisan to Make Single Amino Acid Substitutions in Non-Essential Regions of PH20$_{1-447}$

Patentee's '429 Patent, filed in 2003, describes its invention as soluble PH20 hyaluronidase glycoproteins ("sHASEGPs") that are enzymatically active at

neutral pH.[232] It exemplifies and claims one such "sHASEGP" that terminates at position 447 (positions 36-482 of SEQ ID NO: 1).[233]

The '429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, in pharmaceutical compositions, and combined with other therapeutic agents (*e.g.*, antibodies, chemotherapeutics), and illustrates administering such combinations subcutaneously to treat cancer and hyaluronidase disorders.[234] $PH20_{1-447}$ was approved by the FDA as Hylenex® in 2005.[235] The '429 Patent's teachings combined with the status of $PH20_{1-447}$ as an approved human therapeutic before 2011 would have induced a skilled artisan to focus on this particular PH20 polypeptide.[236]

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232 EX1005, 6:4-10, 10:30-59.

233 EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

234 EX1005, 8:25-9:4, 54:40-65, 56:34-57:36, 60:38-61:4, 63:41-61, 74:10-29, 76:19-77:36, 99:28-100:47.

235 EX1049, 1.

236 EX1003, ¶ 195.

Patentee's '429 Patent defines sHASEGPs as including wild-type $PH20_{1-447}$ and "equivalent" proteins "with amino acid substitutions that do not substantially alter activity" of the protein.[237] It explains:

> Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity …[238]

The '429 Patent also explains that single amino acid substitutions can include "conservative" substitutions in Table 1, but that "[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions."[239]

The '429 Patent thus teaches making a ***particular*** type of modification (a single amino acid substitution) in ***particular*** locations (non-essential regions of PH20) in a ***particular*** PH20 sequence ($PH20_{1-447}$) to yield equivalents of $PH20_{1-447}$

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[237] EX1005, 9:65-10:13; *see also id.* at 18:64-19:6 ("equivalent" proteins).

[238] EX1005, 16:14-22.

[239] EX1005, 16:24-36.

(*i.e.*, those that do not substantially alter the activity or function of $PH20_{1-447}$).[240]

The '429 Patent also motivates skilled artisans to undertake this effort to design and produce such single-amino acid substituted $PH20_{1-447}$ proteins because it assures them their efforts will be successful.[241] As it states, skilled artisans recognized that such "single amino acid substitutions in non-essential regions" of $PH20_{1-447}$ "do not substantially alter biological activity" of $PH20_{1-447}$.[242] As such, a skilled artisan would have expected a $PH20_{1-447}$ mutant with a single amino acid substitution in a non-essential region to have the same utility, therapeutic applications, and other characteristics that the '429 Patent identifies for wild-type $PH20_{1-447}$ and other sHASEGPs.[243]

2. Chao Provides Information Useful for Engineering the Changes to $PH20_{1-447}$ that the '429 Patent Suggests

In 2011, a skilled artisan looking to implement the '429 Patent's suggestion to make a single-amino acid modification in a non-essential region of $PH20_{1-447}$ would have recognized such changes could best be accomplished using rational design, which here involves determining (i) which regions are non-essential in

240 EX1003, ¶ 206; EX1004, ¶ 32.

241 EX1003, ¶ 207.

242 EX1005, 16:4-21.

243 EX1003, ¶¶ 199-202, 207, 223.

PH20, and (ii) which single amino acids to substitute into positions in those non-essential regions.[244]

The ’429 Patent was written eight years before 2011. Given that, a skilled artisan would have looked for additional published insights into the structure of human hyaluronidase enzymes like PH20, like Chao (EX1006).[245] Chao reported an experimentally determined structure for human HYAL1, and provided new insights into the shared characteristics of human hyaluronidase enzymes.[246]

First, by superimposing the HYAL1 and bee venom hyaluronidase structures, Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues in it that interact with HA.[247]

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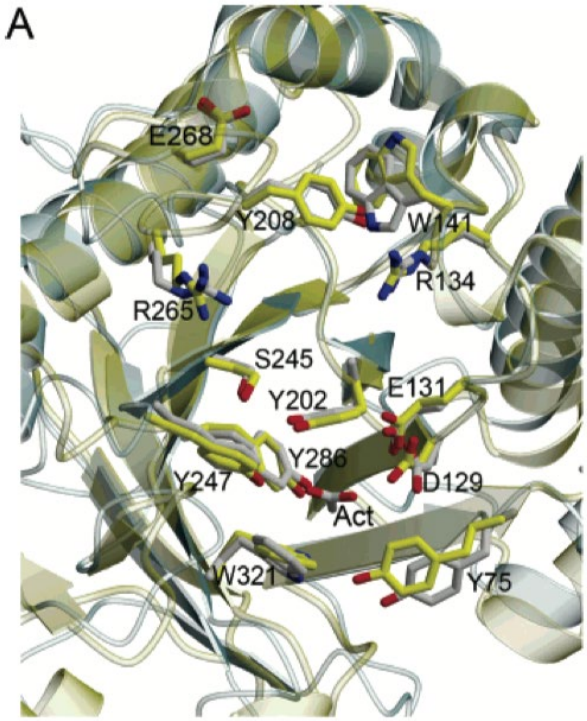
244 EX1003, ¶¶ 212-14.

245 EX1003, ¶¶ 86, 209-211; EX1004, ¶ 88.

246 EX1003, ¶¶ 81-86; EX1004, ¶ 88; EX1006, 6912-17.

247 EX1006, 6917 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1004, ¶¶ 89-91; EX1003, ¶¶ 81-82.



The ’429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20,[248] and taught that hyaluronidase domains share similarity among and between species, including residues necessary for enzymatic activity.[249]

Second, using an alignment of five human hyaluronidases, Chao identified predicted secondary structures (*e.g.*, β-sheets, α-helices) (Figure 3, below), as well as invariant conserved positions (blue), residues involved in catalysis (red),

[248] EX1005, 4:12-22, 86:49-53, 88:14-24.

[249] EX1005, 2:6-67, 4:11-22.

conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).[250]

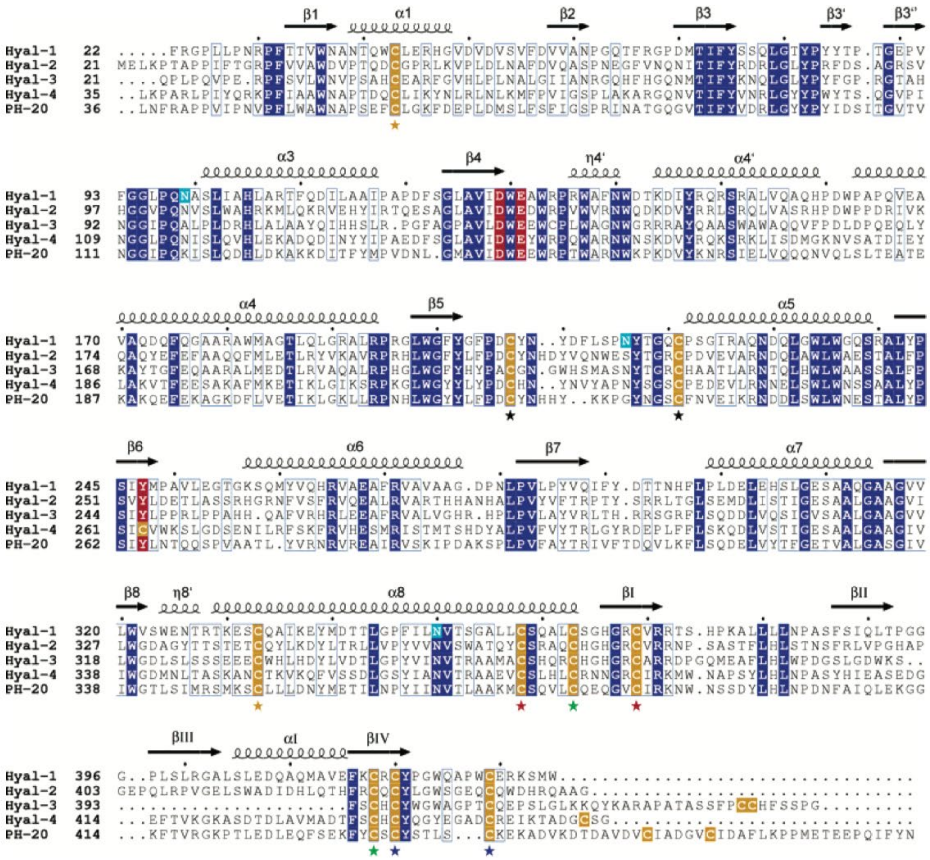


FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative replacements are blocked in blue. Pairs of cysteine residues that form disulfide bonds are indicated by stars with matching colors. Secondary structure units are labeled as in Figure 2B.

Third, Chao reported the presence of "a novel, EGF-like domain" in the C-terminal region of human hyaluronidases that was "closely associated" with the

[250] EX1006, 6916; EX1003, ¶¶ 83, 211; EX1004, ¶ 92.

catalytic domain (discussed above, § V.A.1.b.iii), and identified a characteristic pattern for the Hyal-EGF domain in PH20 at positions 337-409.[251]

3. A Skilled Artisan Would Have Identified Position 317 as Being in a Non-Essential Region of $PH20_{1-447}$ in 2011

To implement the '429 Patent's suggestion to produce modified $PH20_{1-447}$ polypeptides with single amino acid substitutions in non-essential regions that retain hyaluronidase activity, the skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011.[252] The person would have done that using conventional sequence alignment tools in conjunction with the information in the '429 Patent and in Chao, as well as information publicly known in 2011.[253]

A multiple-sequence alignment identifies non-essential regions in PH20—they are the sequences between essential residues and are positions at which variations occur at a frequency above ~5% (illustrated using Chao below).[254]

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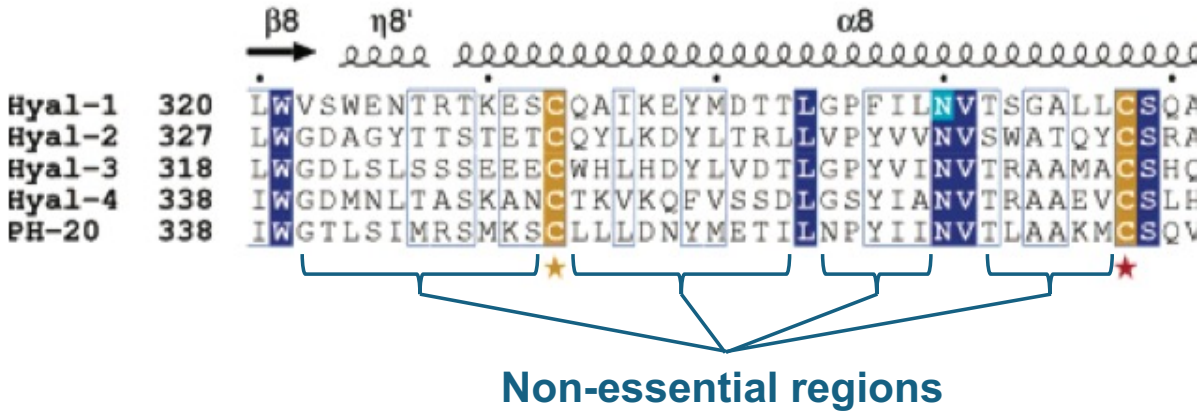
251 EX1006, 6911; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84-85.

252 EX1003, ¶¶ 212-214; EX1004, ¶¶ 22, 25-30, Appendix D-3.

253 EX1003, ¶¶ 20-21, 213-215; EX1004, ¶¶ 22-24; EX1017, 224-26.

254 EX1004, ¶¶ 31-32, Appendix D-2; EX1003, ¶¶ 213-214; EX1006, 6916.

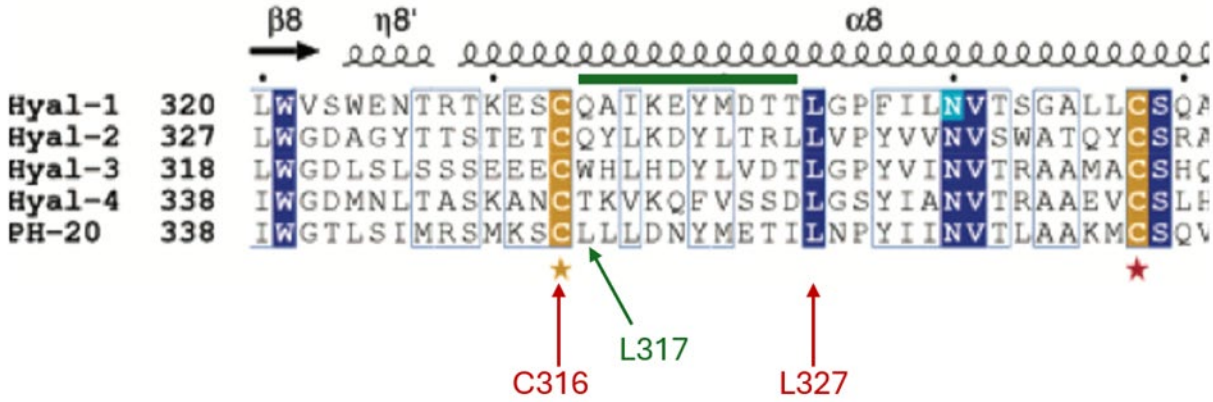


Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps. He first identified 88 homologous hyaluronidase protein sequences that had been published by December 29, 2011.[255] Dr. Park then prepared a multiple-sequence alignment of the 88 homologous proteins, similar to what Chao did with the five human hyaluronidases, and from that alignment identified essential (Appendix D-3) and non-essential (Appendix D-2) residues.[256]

[255] EX1004, ¶¶ 27, 140-143; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

[256] EX1004, ¶¶ 28-32, 144-145, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

Position 317 is within a non-essential region of $PH20_{1-447}$, which is shown by Dr. Park's analysis, and also by Chao's Figure 3; both report the same bounding essential residues (*i.e.*, C316 and L327) (below).[257]



Following the guidance and information in the '429 Patent and Chao, and assessing information publicly available in December 2011 using conventional sequence analysis tools, a skilled artisan would have readily identified position 317 as a position within a non-essential region $PH20_{1-447}$.[258]

4. A Skilled Artisan Would Have Viewed Glutamine as an Obvious Single Amino Acid Substitution for Leucine at Position 317 of $PH20_{1-447}$

The multiple-sequence alignment reveals a second powerful insight: it identifies ***which*** amino acids have been tolerated at specific positions in the amino

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257 EX1003, ¶ 217; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.

258 EX1003, ¶ 221; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

acid sequence of homologous, stable and active, naturally occurring hyaluronidase enzymes.[259] This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms those variations in the sequences of a protein that do not yield stable and active forms of the protein.[260]

Using a multiple-sequence alignment, a skilled artisan can readily compile a list of amino acids tolerated at positions within non-essential regions of PH20.[261] Dr. Park did this: using his multiple-sequence alignment of the 88 hyaluronidase proteins known by December 2011, he identified the different amino acids that

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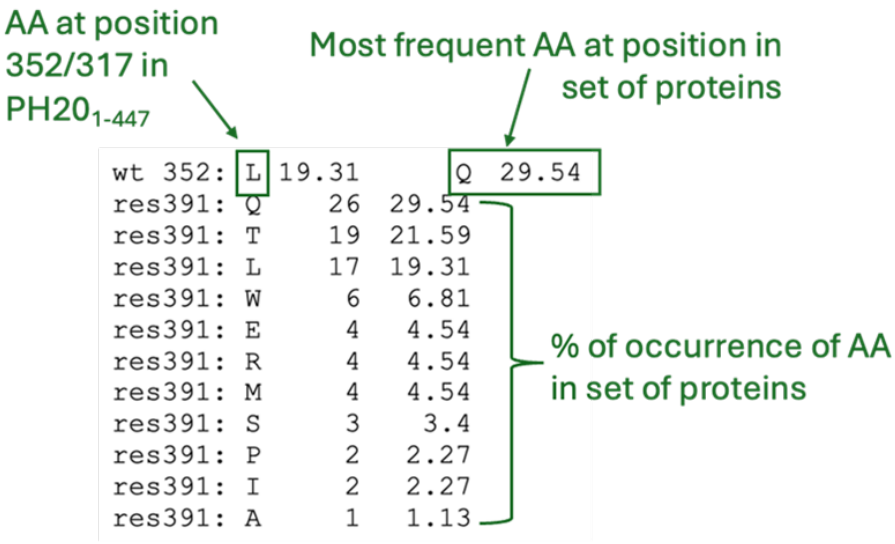
[259] EX1003, ¶ 214; EX1004, ¶¶ 21-22.

[260] EX1003, ¶ 214; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 ("Evolution provides a tremendously useful model for protein design. … By considering the common features of the sequences of these proteins, it is possible to deduce the key elements that determine protein structure and function—even in absence of any explicit structural information."); EX1014, 351.

[261] EX1003, ¶¶ 214-215; EX1004, ¶¶ 21-22.

occur at positions corresponding to position 317 in PH20 in homologous hyaluronidases, and how many proteins contain each residue (below).[262]



The wild-type residue at position 317 in PH20 is leucine (L), which occurs in ~19% of the proteins (including PH20). The most prevalent amino acid found at position 317 in this set of homologous sequences is glutamine (Q) (~30%), which is present in 26 different hyaluronidase proteins.[263]

A skilled artisan would have considered position 317 to be a position within a non-essential region of PH20$_{1-447}$ at which a single amino acid substitution could

[262] EX1004, ¶¶ 30-32, 41-43, 106, 112, Appendix D-1; EX1003, ¶¶ 215, 217-218.

[263] EX1004, ¶ 112; EX1003, ¶ 218.

be made pursuant to the guidance in the '429 Patent.[264] The skilled artisan also would have selected glutamine (Q) as an obvious choice for such a single substitution at position 317 in $PH20_{1-447}$.[265]

First, glutamine is the most prevalent amino acid found at positions corresponding to 317 in PH20: it occurs in nearly 30% of the 88 homologous hyaluronidase enzymes known by 2011 (26 different naturally occurring hyaluronidase enzymes) and in 2 of the 5 human hyaluronidases (as shown in Chao Figure 3, above).[266] The high frequency with which glutamine occurs at positions corresponding to 317 in naturally occurring hyaluronidases indicates it is likely to be tolerated in PH20 as well, and makes it an obvious amino acid to substitute into position 317 of PH20.[267]

Second, glutamine was known to have a high helix propensity, meaning it is favored in sequences that form α-helix secondary structures.[268] Chao identified the "α8" helix sequence as one such α-helix forming sequence in PH20, and position

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264 EX1003, ¶¶ 217, 221.

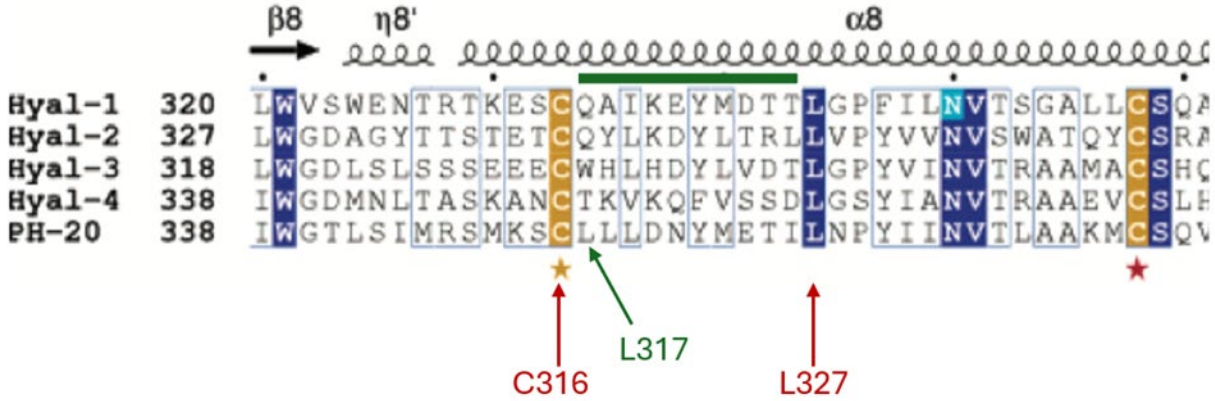
265 EX1003, ¶¶ 221-222; EX1004, ¶¶ 41-42, 106, 112.

266 EX1004, ¶¶ 43, 106, 112; EX1003, ¶¶ 218, 221.

267 EX1003, ¶¶ 222; EX1004, ¶ 112.

268 EX1050, 422-24, Table 2; EX1003, ¶ 220; EX1004, ¶¶ 69-70, 115.

317 is in the middle of that α8 helix sequence in PH20 (below).[269] Given its high propensity for supporting α-helix secondary structures, a skilled artisan would have viewed glutamine as a logical (and thus obvious) substitution for leucine at position 317 in $PH20_{1-447}$.[270]



Consequently, a skilled person would have found glutamine to be an obvious choice for a single amino acid substitution for leucine at position 317 in $PH20_{1-447}$ pursuant to the guidance in the '429 Patent.[271]

[269] EX1006, 6916, Figure 3; EX1003, ¶ 192; EX1004, ¶¶ 32, 108.

[270] EX1003, ¶ 220; EX1004, ¶¶ 32, 108, 115, 119.

[271] EX1003, ¶¶ 221-222.

5. A Skilled Artisan Would Have Reasonably Expected the L317Q Substitution in $PH20_{1-447}$ to Yield Enzymatically Active PH20 Proteins

a) Patent Owner Cannot Contradict Its Past Representations to the PTO

Replacing the leucine at position 317 with glutamine yields a $PH20_{1-447}$ with a single amino acid substitution in a non-essential region of the polypeptide.[272] In its '429 Patent, Patentee stated:

> Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.[273]

Patentee also secured claims in the '429 patent to modified $PH20_{1-447}$ proteins with at least one substitution (*e.g.*, claim 1), despite not providing examples of PH20 proteins with any substitutions. Patentee, thus, made and relied on its statements that a skilled artisan would have expected ***any*** single amino acid substitution in ***any*** non-essential position of $PH20_{1-447}$ to not substantially affect the activity of the enzyme. Patentee should not be permitted to now contend a skilled artisan would not have reasonably expected that the L317Q substitution in $PH20_{1-}$

[272] *See* § VI.B.3; EX1003, ¶ 217; EX1004, ¶ 32.

[273] EX1005, 16:17-20.

$_{447}$ would yield an enzyme with substantially the same activity as unmodified $PH20_{1-447}$.

b) Skilled Artisans Would Reasonably Expect L317Q to be Tolerated in $PH20_{1-447}$

Independently, a skilled artisan would have reasonably expected the L317Q substitution to not substantially alter the biological activity (hyaluronidase activity) of $PH20_{1-447}$. Both experts noted that many naturally occurring homologous hyaluronidase proteins contain glutamine at positions corresponding to position 317 in PH20 (including in human HYAL-1 (Chao)), which suggests glutamine would be tolerated at that position in PH20.[274]

Dr. Park's sequence alignment also shows that many (10) different amino acids occur in homologous proteins at positions corresponding to position 317 in PH20.[275] The diversity of characteristics of those amino acids at that position (*e.g.*, polar vs. non-polar, small vs. large side chains, charged or uncharged residues, etc.) suggests that many different kinds of amino acids can be tolerated at this position in PH20.[276]

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274 EX1003, ¶¶ 218-219; EX1004, ¶¶ 106, 112.

275 EX1004, ¶ 106.

276 EX1003, ¶ 219; EX1004, ¶ 106.

The high frequency of occurrence of glutamine at positions equivalent to 317 in naturally-occurring hyaluronidases, including in 2 of 4 human homologs of PH20 (Chao, Figure 3), along with glutamine's high helix propensity, also would have led a skilled artisan to reasonably expect the L317Q substitution would be tolerated in $PH20_{1-447}$.[277]

c) A PH20 Structural Model Confirms that $PH20_{1-447}$ Would Tolerate Glutamine at 317

Dr. Park assessed whether single amino acid substitutions in $PH20_{1-447}$ would be tolerated, including L317Q, using a PH20 protein structural model generated by SWISS-MODEL using Chao's HYAL1 structure as the template, as would have been done in 2011 by a skilled artisan.[278]

Dr. Park explains that his PH20 model was reliable in the region of position 317 of PH20 based on QMEAN values,[279] and would be very similar to a PH20

[277] EX1003, ¶¶ 221-222; EX1004, ¶ 112.

[278] EX1004, ¶¶ 39-40, 146-147; EX1003, ¶¶ 224-225, 227-228; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

[279] EX1004, ¶¶ 148-150 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

model generated by SWISS-MODEL in 2011 (*e.g.*, it used 165 conserved positions in the backbone of the two proteins).[280]

Dr. Park also devised a consistent, objective methodology for assessing substitutions using the $PH20_{1-447}$ model.[281] Factors he considered included, *inter alia*, the number of neighboring residues at position 317 (*i.e.*, those within 5 Å), the various possible interactions between neighbors (*e.g.*, hydrophobic, charged, van der Walls, steric, etc.), and solvent accessibility.[282] Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*, hydrophobic-hydrophilic, effects on secondary structures, size related issues such as steric clashes or creation/filling of "holes" in the structure).[283]

Dr. Park assessed the environment of position 317 visually by comparing the wild-type with the version incorporating substituted amino acids at position 317

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280 EX1004, ¶¶ 151-152, 156; EX1038, 3382-4; EX1017, 229-230; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

281 EX1004, ¶¶ 102-103; *see generally id.* at § IV.C (description of Dr. Park's methodology); EX1003, ¶¶ 215-216.

282 EX1004, ¶¶ 44-47, 53-60, 65-85, Appendix D-5; EX1035, 1408, Table 2; EX1043, 2, Table 1.

283 EX1004, ¶¶ 62-63, 85.

using functionality within the viewer (PyMol) and as a modeled sequence generated from the $PH20_{1-447}$ sequence incorporating the single substitution in SWISS-MODEL.[284] These technologies were available in 2011.[285] He used his methodology to assess substitutions representing diverse interactions, and confirmed it provided a consistent, objective and unbiased evaluation of substitutions.[286]

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed (below).[287]

Score	***Expected Impact***	***Expected Toleration***
1	Significantly Destabilized	Likely Not Tolerated
2	Neutral or Minor Impacts	Tolerated
3	Improved Stability	Tolerated

Dr. Park assigned a score of 2 for the L317Q substitution in $PH20_{1-447}$, indicating it would not be expected to significantly impact stability.[288] He

[284] EX1004, ¶¶ 61, 107, 111, 114, 118, 161-163; EX1003, ¶¶ 225, 227.

[285] EX1004, ¶¶ 146, 151-152, 160, 162-164; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4; EX1003, ¶¶ 20-22.

[286] EX1004, ¶¶ 102-103; EX1003, ¶¶ 215-216.

[287] EX1004, ¶¶ 85-87.

[288] EX1004, ¶ 119, Appendix C.

observed that in the wild-type environment, position 317 is a solvent exposed position within helix 8 of PH20.[289] He also showed that 10 different types of amino acids that occur at this position in homologous proteins, and that the neighboring residues of position 317 are both hydrophilic and hydrophobic, collectively indicating that many different amino acids are tolerated at this position.[290]

Dr. Park identified several reasons why glutamine would be tolerated at position 317 of PH20. First, it is hydrophilic, which is compatible with the environment at position 317.[291] Second, glutamine in position 317 can form hydrogen bonds with nearby residues (E31, N321), which can enhance stability around this position (below), and offset hydrophobic interactions lost by replacing wild-type leucine.[292] Overall, Dr. Park found that the L317Q substitution would have a neutral or slightly positive effect on the stability of the protein.[293]

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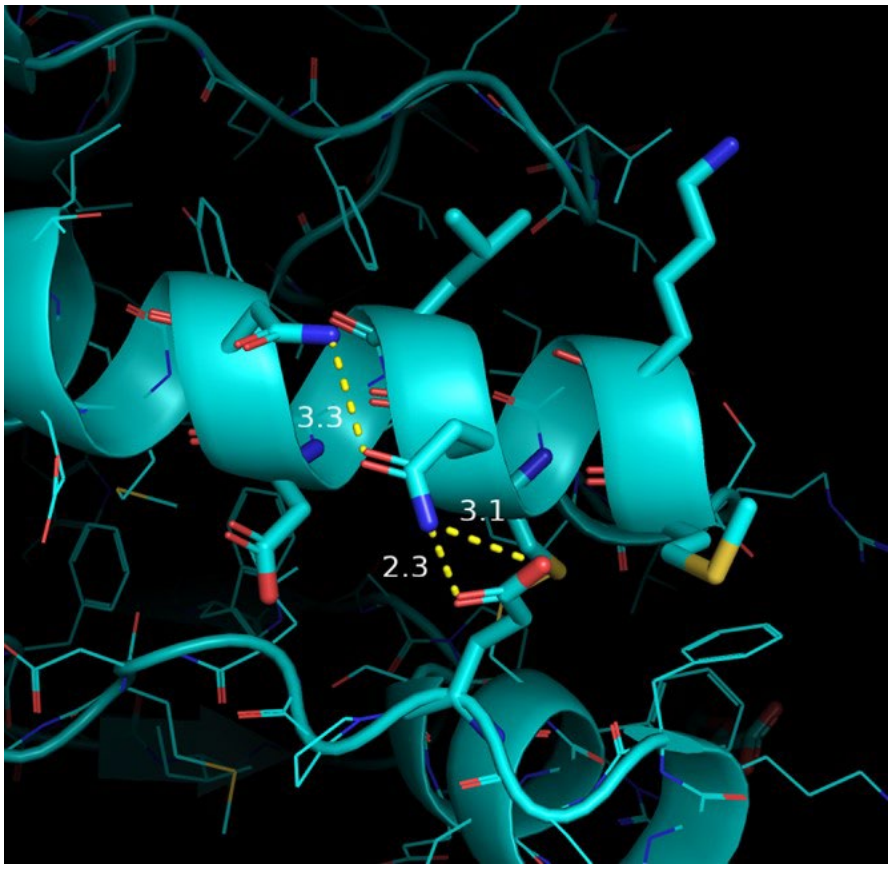
289 EX1004, ¶ 108.

290 EX1004, ¶¶ 108-110.

291 EX1004, ¶¶ 113, 115.

292 EX1004, ¶ 116.

293 EX1004, ¶ 119.



Dr. Park's visualization-based assessment was a prevalent technique used in 2011.[294] Similarly, his technique of assessing interactions between neighbors and

[294] EX1017, 228 ("… a structural biologist's intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this."); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 226-228.

assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications.[295]

Dr. Hecht reviewed Dr. Park's analysis and conclusions concerning the L317Q single substitution and agreed with them.[296] Dr. Hecht concluded that glutamine would likely have been tolerated at position 317 as a single substitution in $PH20_{1-447}$.[297] For example, he explained that glutamine's hydrophilic character would be compatible with the high solvent accessibility of position 317, and that its high helix propensity would be favorable to the α-helix structure that includes position 317.[298]

The common disclosure defines an "active mutant" as a modified PH20 polypeptide with at least ~40% of the activity of unmodified $PH20_{1-447}$.[299] Drs. Hecht and Park each independently concluded that the L317Q substitution would

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295 EX1004, ¶¶ 48-52; EX1031, 459, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 228.

296 EX1003, ¶ 227, 230.

297 EX1003, ¶¶ 230-232, 234.

298 EX1003, ¶¶ 220, 222, 231.

299 EX1001, 75:51-56; *also id.* at 79:33-37.

have been tolerated by $PH20_{1-447}$.[300] A skilled artisan thus would have reasonably expected that the L317Q $PH20_{1-447}$ polypeptide would exhibit at least 40% of the activity of unmodified $PH20_{1-447}$.[301]

Based on the '429 Patent, Chao, and information available in 2011, the L317Q $PH20_{1-447}$ mutant polypeptide would have been obvious to a skilled artisan in 2011. And because claims 1-2, 6, 8, 10-16, and 25-26 each encompass one or more of these single-replacement mutants, each claim is unpatentable.

C. Dependent Claims 5, 17-24, and 27-40 Are Obvious

For the reasons below, each of claims 5, 17-24, and 27-40 defines subject matter that would have been obvious to a skilled artisan.

1. Claim 5

Claim 5 requires the modified PH20 polypeptide to be "a soluble PH20 polypeptide."

The '429 Patent indicates that $PH20_{1-447}$ is a soluble form of the PH20 protein because it omits the C-terminal residues above position 448 (483) containing the GPI anchor sequence.[302] A skilled artisan would have expected that

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300 EX1003, ¶¶ 230-232, 234; EX1004, ¶ 119.

301 EX1003, ¶ 234.

302 EX1005, 3:57-62; 87:52-88:24.

changing leucine (L) to glutamine (Q)at position 317 would not affect the solubility of $PH20_{1-447}$ as it would not meaningfully alter the overall structure of the protein.[303]

2. Claims 17-19

Claims 17-19 require the modified PH20 polypeptide to "comprise[] one or more post-translational modifications" including glycosylation (claims 17-18) and be a "glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues" (19).

The '429 Patent teaches (i) that human PH20 must be glycosylated to exhibit activity, and (ii) expression of $PH20_{1-447}$ in mammalian (CHO) host cells that yield active forms of $PH20_{1-447}$.[304] It further teaches that "N- and O-linked glycans are attached to polypeptides through asparagine-N-acetyl-D-glucosamine … linkages," and claims PH20 polypeptides (including $PH20_{1-447}$) having asparagine-linked sugar moieties.[305] Frost reports that the recombinant production of $PH20_{1-447}$ in

303 EX1003, ¶¶ 196, 203, 223.

304 EX1005, 95:13-30, 40:41-51, 89:53-91:67, 88:5-9.

305 EX1005, 3:27-35, claims 1, 6.

CHO cells "resulted in a 447 amino acid 61 kDA glycoprotein with a properly processed amino terminus and 6 N-linked glycosylation sites."[306]

Based on the '429 Patent and knowledge in the art, a skilled artisan would have found it obvious to produce L317Q $PH20_{1-447}$ in a CHO cell, and that doing so causes six N-linked glycosylation sites to be glycosylated.[307]

1. Claims 20-23, 34-35

Claims 20-21 and 34-35 concern conjugation of a modified PH20 polypeptide to (i) a polymer (claim 20) that may be polyethylene glycol (claim 21), (ii) a moiety such as a toxin, drug, label, or multimerization domain (claim 34), or (iii) an Fc domain (claim 35). Claim 22 specifies the modified PH20 polypeptide further comprises a heterologous signal sequence, while claim 23 specifies a chimeric peptide comprising the modified PH20 polypeptides of claim 1.

A skilled artisan would have found these further modifications to the L317Q $PH20_{1-447}$ mutant obvious from the '429 Patent.[308] The '429 Patent teaches $PH20_{1-447}$ proteins with mutations ("sHASEPGs") can be (i) "modif[ied]" "with polymers

306 EX1013, 432.

307 EX1003, ¶¶ 197-98, 203-04.

308 EX1003, ¶¶ 203, 205.

such as polyethylene glycol";[309] (ii) conjugated to "one or more targeting agents" (*e.g.*, any moiety that specifically binds to a receptor);[310] (iii) attached to a label;[311] and (iv) incorporated into fusion (*i.e.*, "chimeric") proteins.[312] It also teaches expression of modified PH20 polypeptides that incorporate a heterologous signal sequence.[313]

2. Claims 24, 27-33, 36-40

Claim 24 specifies a pharmaceutical composition comprising any modified PH20 polypeptide in the genus of claim 1. Claims 27-30 add a "therapeutically active agent formulated in the same composition or in a separate composition" (27), and that the active agent may be a "drug" (28) or "chemotherapeutic agent" (29) or "antibody" (30).

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309 EX1005, 3:64-4:1, 4:45-53, 26:20-28:4.

310 EX1005, 18:33-52.

311 EX1005, 38:40-49, 40:15-21.

312 EX1005, 18:33-52, 47:10-22, 51:25-30.

313 EX1005, 34:33-37; 88:28-90:15 ("Kappa leader sequence" used in expression of PH20 polypeptides).

Claims 31-33 concern methods of treating "hyaluronan-associated disease" (30) such as cancer (31) or a "solid tumor" by administering any of the modified PH20 polypeptides captured by claim 1.

Claims 36-40 concern methods for delivery of a "therapeutic agent" by administration of a "modified PH20 polypeptide of claim 1" (36) via subcutaneous injection (37), either before the therapeutic agent (38) or in the "same composition" (40), and wherein the therapeutic agent is an antibody (39).

The '429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*, $PH20_{1-447}$), alone or with other therapeutic agents including antibodies and agents used in treating cancer and hyaluronan-associated disease.[314] It similarly describes and claims methods of administering them subcutaneously using formulations that combine an enzymatically active "sHASEPGs" (*e.g.*, $PH20_{1-447}$ with one substitution) with another therapeutic agent, which together enable delivery of the

[314] EX1005, 8:60-9:4, 54:40-55:35, 56:28-57:21, 55:61-56:9, 56:66-57:21, 63:41-44, 73:4-74:29, claims 14, 29, 33.

therapeutic agent after injection.[315] It likewise explains that the therapeutic agent and the PH20 can be subcutaneously administered together or sequentially.[316]

Because the L317Q $PH20_{1-447}$ would be expected to have a comparable structure and activity as unmodified $PH20_{1-447}$, a skilled artisan would have believed it would be equivalently useful in the pharmaceutical compositions, methods of administration, methods of treatment, and methods of delivery. described in the '429 Patent.[317] Indeed, in the '429 Patent, Patentee secured claims encompassing pharmaceutical compositions containing PH20 polypeptides with 1+ substitutions and chemotherapeutic agents despite the absence of any exemplification.[318] Claims 24 and 27-33 also impose no restrictions on the makeup of the pharmaceutical composition. A skilled artisan would have found

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315 EX1005, 8:25-38, 54:40-65, 56:28-56, 57:22-36, 58:59-59:12, 63:40-64:4, 73:4-20, 76:18-77:37, claim 27.

316 EX1005, 8:25-37, 8:60-9:4, 75:25-50, 76:19-77:33, 99:27-100:47; EX1003, ¶¶ 200-201.

317 EX1003, ¶¶ 199-202, 223.

318 EX1005, claims 29, 30, 50.

such compositions and methods of administration/delivery/treatment obvious from the ’429 Patent.[319]

D. There Is No Nexus Between the Claims and Any Evidence of Putative Secondary Indicia

Well-established law holds that evidence of secondary indicia cannot support non-obviousness if it does not have nexus to the claims. A key question in a nexus analysis is whether such evidence is commensurate with the scope of the claims. The answer here is a definitive no.

Patentee is likely to dispute that the L317Q $PH20_{1\text{-}447}$ substitution is obvious. For example, Patentee may contend the L317Q variant has unexpectedly high hyaluronidase activity as a single substitution mutant. Demonstrating that result for one mutant out of the $\sim 10^{59}$ and 10^{112} modified PH20 polypeptides encompassed by the claims, however, utterly fails to establish a nexus between that evidence and the claims. As explained in § V.A.1, the single-substitution L317Q $PH20_{1\text{-}447}$ mutant is not representative of the numerous, structurally different proteins encompassed by the claims, particularly those expected to be inactive. No evidence or explanation is provided in the common disclosure that resolves this confusion.

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[319] EX1003, ¶¶ 199-202, 207.

If Patentee advances evidence or arguments concerning nexus, consideration of that issue should be deferred until after institution, and Petitioner reserves its right to contest such evidence.

VII. The Board Should Not Exercise Its Discretion Under § 324(a) or § 325(d)

No litigation involving the '758 Patent is pending, making discretionary denial unwarranted under the factors in *Apple Inc. v. Fintiv, Inc.,* IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020).

The examination record also does not warrant the Board exercising its discretion to not institute. As explained in § IV.C, no obviousness rejections were raised during prosecution.[320] The present obviousness grounds also rely on Chao (EX1006), which was not cited or considered during examination, and are supported by evidence not available to the Examiner (*e.g.*, expert testimony of Drs. Hecht and Park).

Also, while certain indefiniteness rejections were imposed and overcome by claim amendments,[321] the Examiner erred by not rejecting the claims for lack of written description and non-enablement. *See* §§ V.A and V.B.

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[320] EX1002, 476-84.

[321] EX1002, 549-51.

There is no proper basis for the Board to exercise its discretion to not institute trial.

VIII. CONCLUSION

For the foregoing reasons, the challenged claims are unpatentable.

Dated: February 4, 2025

Respectfully Submitted,

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,054,758
1002	File History of U.S. Patent No. 12,054,758
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Brandon & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '758 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," Methods in Enzymology, 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," Protein Eng'g & Design, Ch. 10, 223-237 (2010)
1018	Chica et al., "Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design," Curr. Opin. Biotechnol., (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," Reprod., 127:325-334 (2004)
1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," Am. J. Reprod. Immunol., (3):174-82 (2002)
1021	Baba et al., "Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg," J. Biol. Chem., 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," Biol Reprod., 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 56(5):1133-41 (1997)
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1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
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1069	Swiss Model Printout of PH20 Model
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1071	Swiss Model Printout of PH20 Model with L317R Mutation
1072	Swiss Model Printout of PH20 Model with L317M Mutation
1073	[Reserved]
1074	Swiss Model Printout of PH20 Model with L317I Mutation

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,221 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

Dated: February 4, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 4th day of February, 2025, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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Paper No. 1
Filed: January 17, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00017
U.S. Patent No. 12,110,520

PETITION FOR POST GRANT REVIEW

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I. Introduction

Petitioner Merck Sharp & Dohme LLC ("Merck") requests post grant review of claims 1-35 of U.S. Patent No. 12,110,520 ("'520 Patent").

The '520 Patent claims are unpatentable for three independent reasons.

The first two are linked to the extreme breadth of the claims, which aim to capture any enzymatically active modified human hyaluronidase ("PH20") polypeptide within genera having between 10^{59} and 10^{112} distinct species. That results from the claim language, which specifies each PH20 polypeptide (i) ***must have*** one amino acid substitution at position 324, and (ii) ***may have*** between 20 and 41 additional substitutions at ***any*** of 430+ positions, and to ***any*** of 19 other amino acids. The scale of these genera is unfathomable. A collection of one molecule of each polypeptide in the smallest genus exceeds the weight of the Earth, and practicing the full scope of the narrowest claimed genus would require many lifetimes of "making and testing" using the patent's methodology.

These immensely broad claims, measured against the common disclosure of the '520 Patent and its ultimate parent '731 Application,[1] utterly fail the written description and enablement requirements of § 112(a). That renders every claim of the '520 Patent unpatentable. It also precludes the claims from a valid § 120

[1] 13/694,731 ('731 Application) (EX1026).

benefit claim to the ’731 Application, the only non-provisional application filed before March 16, 2013, thus making the ’520 Patent PGR eligible.

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by the enzymatically active, multiply-modified PH20 polypeptides within each claimed genus. The disclosed examples also are not representative of these structurally diverse genera: each has only ***one*** amino acid substitution in ***one*** PH20 sequence (1-447), while the claims encompass PH20 proteins with myriad ***undescribed*** combinations of 5, 10, 15, or 20+ substitutions anywhere within PH20 sequences of varying length. The claims even capture mutated PH20 polypeptides the disclosure says to avoid (*e.g.*, $PH20_{1\text{-}447}$ mutants rendered inactive by a single substitution, inactive truncated forms). The disclosure is nothing more than a research plan, lacking any blaze marks, and does not describe the claimed genera.

Regarding enablement, the common disclosure has equally fatal problems: it identifies ***no*** enzymatically active modified PH20 with 2 or more substitutions, much less affirmatively guides the selection of ***which*** combinations of substitutions yield such enzymes. The only process it discloses for making such multiply-substituted PH20 mutants is prophetic, and uses the “trial-and-error discovery” methodology the Supreme Court has found incapable of enabling a

much smaller genus of polypeptides.[2] And practicing the full scope of the claims requires scientists to repeat this "make-and-test" methodology innumerable times until they had made and tested between 10^{59} and 10^{112} unique proteins. That is far more than undue experimentation—it is impossible.

Finally, claims 1-2 and 5-35 are unpatentable because each captures at least one of three obvious $PH20_{1-447}$ mutants that change a ***single*** residue in a non-essential region of PH20—glutamic acid at position 324 to aspartic acid ("E324D"), asparagine ("E324N"), or arginine ("E324R"). But Patentee's '429 Patent (EX1005) directs artisans to make such single amino acid substitutions in non-essential regions of $PH20_{1-447}$ (and expressly claimed them). Skilled artisans implementing that guidance in 2011 would have found Chao (EX1006)—a 2007 paper ignored in the common disclosure and never cited to the Office. Skilled artisans, using their knowledge and collective teachings of Chao and the '429 Patent, would have (i) readily identified position 324 as being in a non-essential region of PH20, and (ii) found it obvious to change glutamic acid to aspartic acid, asparagine, or arginine at position 324. They also would have reasonably expected both mutants to retain enzymatic activity because that is what Patentee said in its '429 Patent ("Those of skill in this art recognize that, in general, single amino acid

[2] *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023).

substitutions in non-essential regions of a polypeptide do not substantially alter biological activity").[3] Because the claims capture these obvious species, they are unpatentable, along with the dependent claims.

The '520 Patent claims are unpatentable. The Board should institute trial.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the '520 Patent's issuance. Petitioner certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '520 Patent.

The '520 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

A patent is PGR eligible if it issued from an application filed after March 16, 2013 "if the patent contains … at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought." *See Inguran, LLC v. Premium Genetics (UK) Ltd.*, Case PGR2015-00017, Paper 8 at 16-17 (P.T.A.B. Dec. 22, 2015); *US*

[3] EX1005, 16:17-22.

Endodontics, LLC v. Gold Standard Instruments, LLC, PGR2015-00019, Paper 17 at 8 (P.T.A.B. Jan. 29, 2016); *Collegium Pharm., Inc. v. Purdue Pharma L.P.*, 2021 WL 6340198, at *14-18 (P.T.A.B. Nov. 19, 2021) (same) *aff'd Purdue Pharma L.P. v. Collegium Pharm., Inc.*, 86 F.4th 1338, 1346 (Fed. Cir. 2023); *Intex Recreation Corp. v. Team Worldwide Corp.*, 2020 WL 2071543, at *26 (P.T.A.B. Apr. 29, 2020) (same).

Only one of the applications to which the '520 Patent claims benefit under 35 U.S.C. § 120 and/or § 121—U.S. Application No. 13/694,731 (the '731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011) and WO 01/3087 ("WO087"). The '731 Application, however, alters several passages of the provisional disclosures, adds new examples and tested mutants and makes other changes.[4]

The '731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '520 Patent (§§ V.A, V.B). The same is true for the '520 Patent, whose

[4] EX1026, 153:15-163:26, 324-34, 19:25-26, 28; EX1051; EX1052.

disclosure relative to the claims is generally identical to the '731 Application.[5] The '520 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the '731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

Merck Sharp & Dohme LLC is the real party-in-interest for this Petition.

2. Related Proceedings

PGR2025-00003, PGR2025-00004, PGR2025-00006, and PGR2025-00009 are related proceedings.

3. Counsel and Service Information

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[5] The "common disclosure" refers to the shared disclosure of the '520 Patent and the '731 Application (EX1026). Citations are to the '520 Patent; EX1015 correlates citations to the '731 Application. The '520 Patent alters the list of positions to avoid changing in enzymatically active PH20 proteins in the '731 Application: it removes positions 282, 298, and 431. EX1045, 78; EX1068, ¶ 6.

Petitioner consents to service via e-mail at the email addresses listed above.

III. Grounds

The grounds advanced in this Petition are:

(a) Claims 1-35 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.

(b) Claims 1-35 are unpatentable under 35 U.S.C. § 112 as not being enabled.

(c) Claims 1-2 and 5-35 are unpatentable as obvious under 35 U.S.C. § 103 based on the '429 Patent (EX1005), Chao (EX1006), and knowledge held by a person of ordinary skill in the art.

Petitioner's grounds are supported by the evidence submitted with this Petition, including testimony from Dr. Michael Hecht (EX1003) and Dr. Sheldon Park (EX1004).

In this Petition, "PH20" refers to the human PH20 hyaluronidase protein. The full-length PH20 protein (SEQ ID NO: 6) includes a 35 amino acid signal sequence, which is absent in mature forms of PH20, yielding positional numbers that differ from SEQ ID NO: 6 by 35 residues.[6] The annotation "$PH20_{1-n}$" refers to

[6] EX1003, ¶ 15.

a sequence of 1-n residues in PH20 (*e.g.*, $PH20_{1-447}$ is SEQ ID NO: 3), and "AxxxB" is used to identify the position of a substitution (*e.g.*, "E324D").

IV. Background on the '520 Patent

A. Field of the Patent

The '520 Patent concerns the human PH20 hyaluronidase enzyme, and structurally altered forms of that protein that retain enzymatic activity.[7]

1. Protein Structures

Proteins are comprised of sequences of amino acids. A protein's activity, however, derives from its unique, three-dimensional shape—its structure.[8] That is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary structures and structural motifs, which are packed into compact domains that define the protein's overall structure (tertiary structure).[9]

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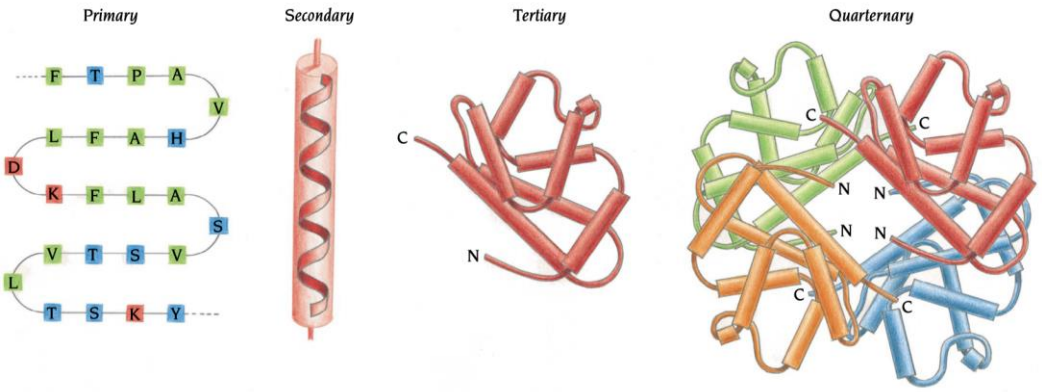
[7] EX1001, 4:16-19.

[8] EX1003, ¶ 36.

[9] EX1014, 3-4, 24-32, Figure 1.1; EX1039, 136-37 (Figure 3-11); EX1003, ¶¶ 36-40.



Secondary structures, such as α-helices or β-strands, are formed and stabilized by different but characteristic patterns of amino acids (below).[10]

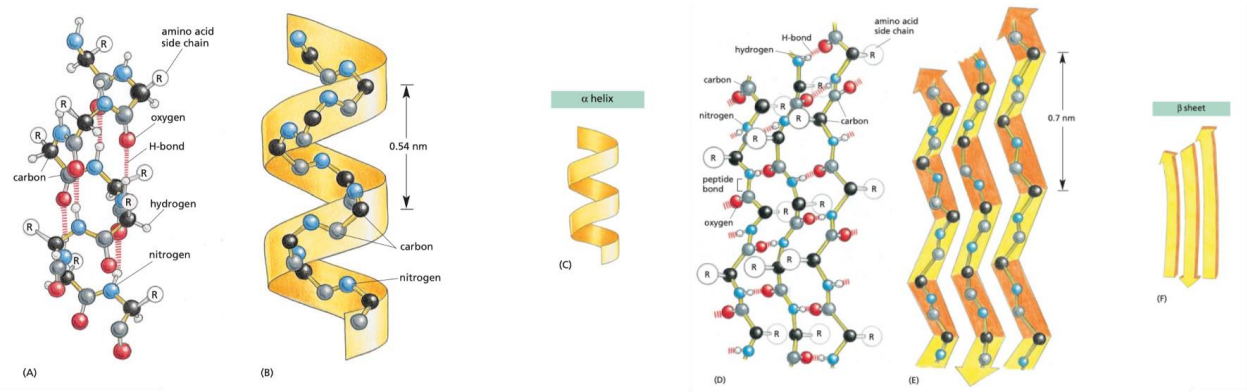


Figure 3–7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N–H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N–H groups point up in this diagram and that all of the C=O groups point down (toward the C-terminus); this gives a polarity to the helix, with the C-terminus having a partial negative and the N-terminus a partial positive charge. (D, E, and F) The β sheet. In this example, adjacent peptide chains run in opposite (antiparallel) directions. Hydrogen-bonding between peptide bonds in different strands holds the individual polypeptide chains (strands) together in a β sheet, and the amino acid side chains in each strand alternately project above and below the plane of the sheet. (A) and (D) show all the atoms in the polypeptide backbone, but the amino acid side chains are truncated and denoted by R. In contrast, (B) and (E) show the backbone atoms only, while (C) and (F) display the shorthand symbols that are used to represent the α helix and the β sheet in ribbon drawings of proteins (see Panel 3–2B).

10 EX1039, 134; EX1014, 14-22, Figures 2.2, 2.5, Table 2.1; EX1047, 2031-32; EX1003, ¶¶ 40-43.

Intervening sequences between those characteristic sequences are important too; they direct and facilitate positioning and arrangement of the various secondary structures into structural motifs and the protein's tertiary structure.[11]

Changes to a protein's amino acid sequence can affect the folding, formation and stability of these various structures that define the protein's overall shape. For example, changing even a single residue known to be critical to the protein's structure or activity can render a protein inactive.[12]

Making many concurrent changes to a protein's sequence can cause myriad effects on the protein's structure, especially when they are in or affect the same region(s) of the protein.[13] For example, it can disrupt the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of secondary structures, and disrupt folding and positioning of the secondary structures and structural motifs into the protein's tertiary structure.[14] Multiple changes in different regions of the amino acid sequence also cause unfavorable

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11 EX1003, ¶¶ 44-46; EX1014, 21-22.

12 EX1003, ¶¶ 54, 150; EX1004, ¶¶ 20, 25.

13 EX1003, ¶ 158.

14 EX1003, ¶¶ 55-56, 142; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

spatial interactions that destabilize or impair folding.[15] Consequently, in 2011, predicting the effects of the myriad interactions that may be disrupted by multiple concurrent substitutions was beyond the capacity of skilled artisans and available computational tools.[16]

2. Hyaluronidase Enzymes

PH20 is one of five structurally similar hyaluronidases in humans and is homologous—evolutionarily related to—hyaluronidases in many species.[17] It breaks down hyaluronan ("HA") by selectively hydrolyzing glycosidic linkages.[18] PH20 exists naturally as a GPI anchored protein; deletion of its GPI-anchoring sequence yields a soluble, neutral active enzyme.[19]

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15 EX1003, ¶¶ 57-59.

16 EX1003, ¶¶ 50, 158, 190, 228; EX1004, ¶¶ 172-174.

17 EX1007, 10:18-30; EX1006, 6911, 6916 (Figure 3); EX1003, ¶¶ 33, 77.

18 EX1003, ¶ 77; EX1008, 819.

19 EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 89, 196; EX1029, 546, Figure 1.

Before 2011, many essential residues in PH20 were known. Several are in the shared catalytic site of the protein;[20] mutating certain residues in or near that site can abolish enzymatic activity.[21] Conserved cysteine residues that stabilize the protein structure are another example,[22] as are certain conserved asparagine residues involved in glycosylation.[23]

In 2007, Chao reported an experimentally determined structure of the human HYAL1 hyaluronidase, and used an alignment of the five human hyaluronidases to illustrate shared secondary structures and conserved residues in these proteins.[24] Among its findings was that human hyaluronidases contain a unique structure—the Hyal-EGF domain.[25] Using its sequence analysis, an earlier structure of bee

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20 EX1006, 6914-16, Figure 3; EX1007, 35:28-36:10; EX1011, 810-14; EX1008, 824-25; EX1009, 6912-17.

21 EX1011, 812-14; EX1010, 9435-39, Table 1.

22 EX1006, 6914-16, Figure 3; EX1011, 810-11; EX1005, 88:21-22.

23 EX1005, 7:9-27; EX1007, 36:12-20; EX1010, 9433, 9435-40.

24 EX1006, 6914-18.

25 EX1006, 6916-18; EX1010, 9439-40; EX1003, ¶¶ 84-86; EX1004, ¶¶ 97-99.

venom hyaluronidase and a computer model of the protein structures, Chao identified residues in the catalytic site that interact with HA.[26]

3. Protein Engineering

In 2011, skilled artisans used two general approaches to engineer changes into proteins.[27] In "rational design," skilled artisans employed computational tools—sequence alignments and protein structure models—to study the protein and then select where and what changes to introduce.[28] For example, a "multiple-sequence alignment" ("MSA")[29] produced by aligning known sequences of homologous, naturally occurring proteins identifies positions with no or little amino acid variation ("conserved" / "essential" residues) and positions where different amino acids occur ("non-conserved" / "non-essential" residues).[30] A

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[26] EX1006, 6912-13, 6916-18, Figures 2C, 4A; EX1033, 1028-29, 1035; EX1010, 9434, 9436, Figure 1.

[27] EX1003, ¶ 47.

[28] EX1016, 181-82; EX1017, 223, 236; EX1003, ¶¶ 48-50.

[29] EX1017, 224-27; EX1016, 181-86 (Figure 1); EX1003, ¶¶ 48-50; EX1004, ¶¶ 22-23, 29.

[30] EX1003, ¶¶ 213-14; EX1004, ¶¶ 21-22, 25, 30-31; EX1016, 181-84; EX1017, 224-25; EX1014, 351.

structural model using the protein's sequence but based on a known structure of a homologous protein enabled assessment of interactions between amino acids at a particular positions.[31] In 2011, using rational design techniques, a skilled artisan could assess, with varying effort, effects of changing one or a few amino acids, but could not use those techniques to predict the effects of many concurrent changes, given the escalating complexity of numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.[32]

"Directed evolution" techniques arose due to the limits of rational design.[33] They use "trial-and-error" experiments to find mutants with randomly distributed changes that exhibit desired properties, but require creation and screening of large libraries of mutants, each with one amino acid randomly changed at one position in its sequence.[34] Importantly, until a desired mutant is made, found and tested,

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31 EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶ 37; *also id.* 33-36; EX1003, ¶¶ 223, 225.

32 EX1003, ¶¶ 50, 158; EX1004, ¶¶ 172-174.

33 EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

34 EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

whether it exists and its sequence are unknown.[35] Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale of experimentation this approach requires.[36] The '520 Patent embodies this approach.[37]

B. Person of Ordinary Skill in the Art

While the '520 Patent claims priority to provisional applications dating to December 30, 2011 and benefit to the '731 Application (filed December 28, 2012), they are not supported as § 112(a) requires by those earlier-filed applications. *See* §§ II.A, V.A, V.B. Regardless, the prior art of the grounds was published before December 2011, and the obviousness grounds use that date to assess the knowledge and perspectives of the skilled artisan.

In 2011, a person of ordinary skill in the art would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production

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35 EX1003, ¶ 184.

36 EX1003, ¶¶ 52-53.

37 EX1003, ¶¶ 138, 173, 183, 186.

of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).[38]

C. Prosecution History

Only one office action issued during examination of the '520 Patent. It raised issues that are unrelated to the present grounds.

Several rejections were based on indefiniteness of the then-pending claims (*e.g.*, unclear references to "modifications", use of "Fe" instead of "Fc", failure of a dependent claim to further limit its parent).[39] Patentee overcame these indefiniteness rejections by amending the claims to address the identified deficiencies.[40]

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[38] EX1003, ¶ 13.

[39] EX1002, 481-83.

[40] EX1002, 563-64.

The claims were also rejected for non-statutory double patenting over U.S. Patent 10,865,400 and U.S. Application 18/340,786.[41] Patentee overcame those rejections with terminal disclaimers.[42]

D. The Challenged Claims

The claim terms are either expressly defined in the common disclosure or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition. A clear understanding of the ***breadth*** of the claims, however, is important, as it shows that each claim captures a massive genus of structurally distinct mutant PH20 polypeptides that is neither adequately described in nor enabled by the common disclosure of the ’731 Application and the ’520 Patent.

1. The Claims Encompass a Staggering Number of Modified PH20 Polypeptides

The claims define an incredibly broad and diverse genus of “modified PH20 polypeptides,” which the common disclosure defines as “a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid

41 EX1002, 483-86.

42 EX1002, 564.

replacement … in its sequence of amino acids compared to a reference unmodified PH20 polypeptide."[43]

Claim 1 defines the genus as containing modified PH20 polypeptides that:

- ***must*** contain ***one*** amino acid replacement at position 324 (*i.e.*, from E to any of A, D, H, M, N, R, and S); and
- ***may*** contain ***additional*** modifications, provided each polypeptide retains ***at least 91% sequence identity*** to one of 37 unmodified sequences (SEQ ID NOs: 3, 7, or 32-66), ranging in length from 430 (SEQ ID NO:32) to 474 residues (SEQ ID NO:7).

Certain dependent claims restrict these parameters:

(i) claims 2 and 25-26 limit (*inter alia*) sequence identity to 95%,

(ii) claims 8-15 and 22 narrow the comparator sequences (*e.g.*, removing SEQ ID NO: 7 or requiring only SEQ ID NOs: 35 or 32),

(iii) claims 6 and 7 require the position 324 substitutions to be D (E324D), or one of N (E324N) or R (E324R), and

(iv) claims 3-5 and 16 add functional requirements (*e.g.*, increased "stability" or activity, solubility).

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[43] EX1001, 48:38-43. Dependent claims 24-35 reference genera of PH20 polypeptides defined by claims 1 or 6.

Claims 17-24 and 27-35 depend from claim 1 but do not alter the parameters governing the number of PH20 polypeptides in each genus. Claims 17-23 specify additional features of the PH20 polypeptides while claims 24 and 27-35 define pharmaceutical compositions and methods of use.

The specification explains that "sequence identity can be determined by standard alignment algorithm programs …"[44] and provides an example, explaining a polypeptide that is "'at least 90% identical to' refers to percent identities from 90 to 100% relative to the reference polypeptide" where "no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides."[45]

It further explains that "differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence" and that "[d]ifferences are defined as [] amino acid substitutions, insertions or deletions."[46] Also, "amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids" (*e.g.*, 10-18 of the 19

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44 EX1001, 60:16-18.

45 EX1001, 60:51-60.

46 EX1001, 60:61-61:2; *see also id.* at 5:1-2, 47:43-47, 56-58.

alternative amino acids).[47] Except for position 324, no language in the claims restricts ***where*** substitutions can occur within the modified PH20 sequence, or ***which*** of 19 other amino acids can be substituted at those positions.

The sequence identity parameters capture an immense number of modified PH20 polypeptides, each with a unique amino acid sequence.[48] The polypeptides may have up to 21-42 total changes but must have one substitution at position 324. Claims 1-5, 8, 11-12, 16-24, and 27-35 permit 7 alternatives at position 324 (A, D, H, M, N, R and S), claims 7 and 9 permit two (N or R), and claims 6, 10, 13-15 and 25-26 permit one (D). Dr. Park's calculations identify the immense number of distinct polypeptides captured by these parameters:[49]

47 EX1001, 129:67-130:7; *see also id.* at 135:22-24.

48 EX1003, ¶¶ 120, 122.

49 EX1004, ¶¶ 180-184, Appendix F.

Claims	*Max Length*	*Max Changes*	*Pos. 324 Choices*	*# of Distinct Polypeptides*
1, 3-5, 16-21, 23-24, 27-35	474	42	7	1.41×10^{109}
2	474	23	7	3.63×10^{66}
6	474	42	1	6.32×10^{111}
7	474	42	2	1.26×10^{112}
8, 22	465	41	7	9.88×10^{109}
9	465	41	2	2.83×10^{109}
10, 15	465	41	1	1.41×10^{109}
11	433	38	7	7.02×10^{101}
12	430	38	7	5.36×10^{101}
13	433	38	1	1.00×10^{101}
14	430	38	1	7.66×10^{100}
25	430	21	1	4.40×10^{59}
26	433	21	1	5.08×10^{59}

2. The Claims Encompass Three Particular Mutants: E324D, E324N, and E324R $PH20_{1-447}$

The claims' parameters also cause them to capture one or more of three modified $PH20_{1-447}$ polypeptides that change glutamic acid at position 324 to either aspartic acid (D) ("E324D"), asparagine (N) ("E324N") or arginine ("E324R"). These single-replacement $PH20_{1-447}$ mutants are: (i) 99.7% identical to SEQ ID NO: 3 (1 change / 447 residues), (ii) 96.5% identical to SEQ ID NO: 35 (15

changes / 433 residues), and (iii) 95.9% identical to SEQ ID NO: 32 (18 changes / 430 residues).[50] All three mutants satisfy claims 1-5, 8, 11-12, 16-24 and 27-35, the E324D mutant satisfies claims 6, 10, 13-15 and 25-26, and the E324N and E324R mutants each satisfy claims 7 and 9.

3. The Claims Are Restricted to One of Two Alternative Embodiments in the Patents: "Active Mutants"

When a specification discloses alternative embodiments, the claim language may limit the claims to only one.[51] That is the case here: the specification describes two mutually exclusive categories of "modified PH20 polypeptides" (*i.e.*, "active mutants" vs. "inactive mutants") but the claims are limited to one (*i.e.*, "active mutants").

According to the specification:

- "***Active mutants***" are modified PH20 polypeptides that "exhibit at least 40% of the hyaluronidase activity of the corresponding PH20

[50] EX1003, ¶ 136.

[51] *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc*., 529 F.3d 1364, 1375 (Fed. Cir. 2008).

polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[52]

- "***Inactive mutants***" are modified PH20 polypeptides that "generally exhibit less than 20% … of the hyaluronidase activity of a wildtype or reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7."[53]

It then classifies mutants into tables of "active" and "inactive" mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).[54]

The common disclosure reports no examples of an "active mutant" modified PH20 with two or more replacements.[55] Notably, it reports no examples of an enzymatically active $PH20_{1-447}$ that incorporates: (i) a mutation that preserved

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[52] EX1001, 75:49-54; *see also id.* at 79:31-35 ("active mutants" "can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide …"); *id.* at 79:28-31.

[53] EX1001, 115:41-50. *See also id*. at 251:1-6 (mutants with <20% activity "were rescreened to confirm that the dead mutants are inactive" in Table 10).

[54] EX1001, 80:62-82:11, 228:7-9, 116:43-67, 251:29-32 ("reconfirmed inactive mutants are set forth in Table 10."); EX1003 ¶¶ 98, 100-101, 107.

[55] *E.g.*, EX1003, ¶¶ 141, 172.

activity in Tables 3 and 9 ("active mutants") plus (ii) a second mutation that eliminated activity in Tables 5 and 10 ("inactive mutants").

The specification also portrays "active" and "inactive" mutants as having distinct utilities requiring mutually exclusive properties.

- "Active mutants" are portrayed as being therapeutically useful ***because they possess hyaluronidase activity***. For example, the specification explains that ***due to*** having hyaluronidase activity, "the modified PH20 polypeptides can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents."[56]
- "Inactive mutants" are portrayed as being therapeutically useful ***because they lack hyaluronidase activity***. Their only identified utility is "as antigens in contraception vaccines," which is implausible (*see* § V.C) but ostensibly requires them to lack activity.[57]

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[56] EX1001, 174:41-47; *see also id*. at 4:33-36, 73:37-51, 174:41-188:6; EX1003, ¶ 108.

[57] EX1001, 72:63-65; *see also id.* at 188:8-9, 75:58-60, 188:6-27 (for "contraception" "the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.").

The specification does not portray "active mutants" as having contraceptive utility even though they may differ by only one amino acid from an inactive mutant; it proposes using them instead ***in combination*** with contraceptive agents.[58]

The claim language reinforces that each is limited to the "active mutant" embodiment.

First, every claim requires modified PH20 polypeptides with one of seven replacements at position 324 that yielded an "active mutant" as a single-replacement $PH20_{1-447}$ polypeptide (*i.e.*, E324D, E324N, E324R, E324H, E324M, E324A, or E324S). All seven mutants are identified as "Active Mutants" in Table 3 and have at least ~40% activity per Table 9.[59]

Second, claim 4 restricts the genus of active mutants in claim 1 (*i.e.*, those with hyaluronidase activity) to modified PH20 polypeptides that have at least 100% of the activity of unmodified PH20.[60]

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58 EX1001, 150:36-49; EX1003, ¶ 113; EX1060, 1711.

59 EX1001, 85 (Table 3), 231 (Table 9), 97:34-46; EX1003, ¶¶ 127-128.

60 Claim 3 requires mutants with increased resistance to or stability in denaturing conditions. The specification portrays increased stability as an additional attribute of an "active mutant." EX1001, 52:41-47, 126:67-127:19, 173:27-30, 289:18-290:45.

Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one amino acid modification," but can also "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity.***"[61] This aligns with the specification's prophetic methodology for discovering PH20 polypeptides with multiple changes, which selects "active mutants" with one substitution, randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity.[62] This also tracks the claims, which require one substitution and permit others.

Patentee may contend the claims should be read as encompassing both alternative embodiments (*i.e.*, "active" and "inactive" mutants). Reading the claims in that manner is incorrect. It also exacerbates the § 112 problems, as every claim still necessarily includes (and thus must describe and enable) the full sub-genus of "active mutants" in claim 1 defined by claim 4.[63]

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61 EX1001, 48:38-53; *see also id*. at 47:61-65, 76:7-10, 77:2-9, 81:3-82:11.

62 EX1001, 134:56-67; *see also id*. at 42:47-54.

63 EX1003, ¶ 135.

V. All Challenged Claims Are Unpatentable Under § 112 and None Are Entitled to Benefit to Any Pre-March 13, 2013 Application

Claims 1-35 are unpatentable because each lacks written description in and was not enabled by the common disclosure of the ’520 Patent and the ’731 Application in 2011.

As explained in § IV.D.1, the claim language defines enormous genera: between 10^{59} and 10^{112} distinct polypeptides. Their real-world scope is absurd—to practice the claims’ full scope requires a skilled artisan to make-and-test at least ~10^{59} mutants. Simply producing one molecule of each mutant—required to know if each is active or inactive or exhibits increased stability—which, in the case of the genera’s many multi-substituted mutants, would be would consume an aggregate mass (~3.93 x 10^{37} kg) that exceeds the mass of the Earth (~6 x 10^{24} kg).[64] Testing every polypeptide within the claims’ scope in search of “active mutants” is impossible—literally.

Relative to that broad scope, the ’520 Patent and the ’731 Application provide only a meager disclosure: ***singly***-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones. It nowhere demonstrates possession of the vast remainder of multiply-modified

[64] EX1003, ¶¶ 123, 189; *see also, e.g.*, EX1039, 136-37 (cell theoretically can make 10^{390} forms of a polypeptide with 300 amino acids).

polypeptides in the claims' scope, nor does it enable a skilled artisan to practice that full-range of mutant polypeptides without undue experimentation.

A. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.[65] "To fulfill the written description requirement, a patent owner 'must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent."[66] If the claims define a genus, the written description must "show that one has truly invented a genus …," "[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus."[67]

"[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the

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65 *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

66 *Idenix Pharm., LLC v. Gilead Scis., Inc.,* 941 F.3d 1149, 1163 (Fed. Cir. 2019).

67 *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1300 (Fed. Cir. 2014).

members of the genus so that one of skill in the art can visualize or recognize the members of the genus."[68] "One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent … [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus."[69]

A disclosure that fails to "provide sufficient blaze marks to direct a POSA to the specific subset" of a genus with the claimed function or characteristic does not satisfy § 112(a).[70] And "merely drawing a fence around the outer limits of a purported genus" is insufficient.[71] Instead, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."[72]

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68 *Idenix*, 941 F.3d at 1164.

69 *AbbVie*, 759 F.3d at 1299-1300.

70 *Idenix*, 941 F.3d at 1164.

71 *Ariad*, 598 F.3d at 1350-54.

72 *Ariad*, 598 F.3d at 1349.

Three cases are especially probative. First, in *AbbVie*, the Federal Circuit found a disclosure of 300 examples of IL-12 antibodies to not be representative of a functionally defined antibody genus:

> Although the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.[73]

It also criticized patentee's attempt to use a prophetic description for the remaining claim scope, portraying it as "only a research plan, leaving it to others to explore the unknown contours of the claimed genus" and a "trial and error approach."[74]

Second, *Idenix* addressed claims to methods of treatment with a broad genera of compounds defined by formulas analogous to the challenged claims here: "eighteen position-by-position formulas describing 'principal embodiments' of compounds that may treat HCV," each with "more than a dozen options" at each position (totaling "more than 7,000 unique configurations").[75] The court criticized the specification's failure to indicate which of the thousands of compounds would be effective, and found that "providing lists or examples of supposedly effective

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[73] *AbbVie*, 59 F.3d at 1300-1301.

[74] *Id.*

[75] *Idenix*, 941 F.3d at 1158-64.

nucleosides," without "explain[ing] what makes them effective, or why" deprives a skilled artisan "of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result" because they "fail to provide sufficient blaze marks to direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV."

Finally, the Board in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found.*, PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) considered claims that used "90% sequence homology" language to capture "a broad genus of amino acid sequence homologues" but (like here) imposed no restrictions on where particular amino acids replacements could be made, thus causing the claim "to cover, at minimum, thousands of amino acid sequences."[76] The Board found fatal the specification's failure to "explain what, if any, structural features exist (*e.g.*, remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification" and noted the homology limitation "serves to merely draw a fence around the outer

[76] *Boehringer*, at 16. The claims were directed to compositions and methods of using proteins. *Id.* at 6.

limits of a purported genus [which] is not an adequate substitute for describing a variety of materials constituting the genus" for purposes of section 112(a).[77]

The deficiencies of the claims here dwarf those in these three cases. They define much larger, much less predictable and much more diverse genera of modified PH20 polypeptides, and the common disclosure is far more limited. Because the common disclosure neither discloses a representative number of species within each immense claimed genus, nor identifies sufficient structural features common to the members of each claimed genus, it fails to demonstrate possession of the genera defined by the claims of the '520 Patent.

1. Claims 1-2, 6-15, and 25-26 Lack Written Description

a) The Claims Capture Massive and Diverse Genera of Enzymatically Active PH20 Polypeptides

The genera of modified PH20 polypeptides defined by the sequence identity language of claims 1-2, 6-15, and 25-26 is not only immense but is structurally and functionally diverse. They capture PH20 mutants with 2 substitutions, 3 substitutions and so on up to a number set by the sequence identity boundary (*i.e.*, 21 for the narrowest claims (*e.g.* claims 25 and 26) to 42 for the broadest (claim 1)). The optional substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the

[77] *Id.* at 35-36.

sequence), to any of 19 other amino acids, and arranged in any manner.[78] They thus capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with up to 42 substitutions that mix polar, charged, aliphatic, and aromatic amino acids together in any manner.[79]

Each claim also encompasses substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 37 alternative sequences that terminate at positions 430 to 474. The claims' sequence identity language also captures PH20 polypeptides that terminate at positions before 430. For example, claims referencing SEQ ID NO:32 that allow between 21 and 42 changes (and can be any mixture of deletions and substitutions) will capture a PH20 terminating at position 416 or below. But removing so many residues from the C-terminus of PH20 can render it inactive, and the disclosure does not describe or suggest that the claimed position 324 substitution renders such mutants active.[80] The claims, however, capture such polypeptides.

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78 EX1003, ¶ 119; EX1001, 60:61-61:1, 47:43-47, 47:56-58, 42:2-8.

79 EX1003, ¶¶ 119-20.

80 EX1003, ¶¶ 164-67.

b) The Claims Capture Modified PH20 Polypeptides the Common Disclosure Says to Avoid or Not Make

The claims' unconstrained sequence identity language capture three categories of PH20 mutants a skilled artisan would understand the disclosure to be saying to avoid. Each raises unique questions relative to the remainder of the genus and are thus "sub-genera" of PH20 mutants that are not representative of other "sub-genera" within the claimed genera. But instead of providing guidance that navigates this confusing landscape, the patent simply instructs the skilled artisan "to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein."[81] The common disclosure thus does not describe any of these sub-genera within the claims' scope.

(i) Multiply-Modified PH20 Mutants to Not Make

The common disclosure affirmatively addresses only six, specific modified PH20 polypeptides with more than one identified (*i.e.*, position and amino acid) substitution, but its guidance is to ***not make those polypeptides***:

> [W]here the modified PH20 polypeptide contains only two amino acid replacements, the amino acid replacements are ***not*** P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A or N333A/N358A. In a

[81] EX1001, 78:36-40; EX1003, ¶ 193.

> further example, where the modified PH20 polypeptide contains only three amino acid replacements, the amino acid replacements are ***not*** N47A/N131A/N219A.[82]

No explanation is provided why these particular combinations of replacements should be avoided, and nor any data testing their activity or other characteristics.[83] The substitutions are not included in Tables 5 and 10 (i.e., "inactive mutants") and N219A $PH20_{1-447}$ showed increased activity (129%).[84] Nothing in the claim language excludes these combinations.

(ii) Substitutions to Avoid in Active Mutants

The common disclosure indicates that active mutant modified PH20 polypeptides should not incorporate amino acid substitutions that rendered $PH20_{1-447}$ inactive, stating:

> ***To retain hyaluronidase activity***, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.[85]

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82 EX1001, 77:47-59 (emphases added).

83 EX1003, ¶¶ 146-47; EX1001, 49:30-35.

84 EX1001, 241 (Table 9).

85 EX1001, 80:15-17 (emphases added).

It identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10 that are made at other positions.[86] It does not limit this observation to single-replacement $PH20_{1-447}$ mutants, or suggest that any of these substitutions that render $PH20_{1-447}$ inactive should be included in enzymatically active, multiply-modified PH20 polypeptides (much less identify specific combinations including them).[87] Instead, by stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that the ***claimed*** enzymatically active multiply-modified PH20 polypeptides do not and should not contain them.[88] The sequence identity claim parameters, however, capture such mutants.

(iii) PH20 with Significant C-terminal Truncations Can Lose Activity

The common disclosure does not describe and provides no guidance concerning "active mutant" PH20 polypeptides having fewer than 447 residues,

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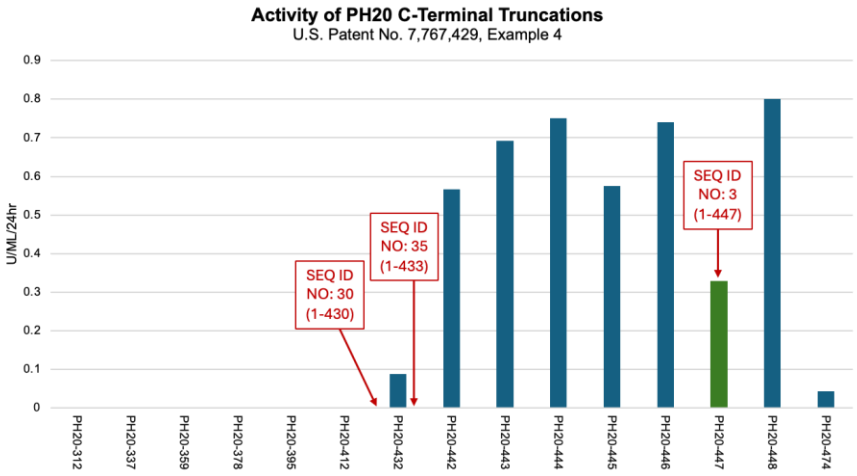
86 EX1001, 80:17-57 ("For example, generally modifications are not made at a position corresponding to position …").

87 EX1003, ¶¶ 151, 161-62, 169.

88 EX1003, ¶¶ 148-51, 162; EX1001, 80:15-57, 70:49-59.

particularly multiply-modified PH20 mutants terminating significantly before that position.[89]

But the common disclosure and the prior art report that wild-type PH20 polypeptides terminating at or below position 442 have ***significantly reduced or no*** hyaluronidase activity. For example, Patentee's '429 Patent reported that PH20 mutants terminating below position 432 residues lacked hyaluronidase activity, while those terminating between positions 432 and 448 had widely varying activities (below):[90]



Position (w/leader)	Mutant	U/ML/24hr	Normalized to PH20(1-447)
347	PH20-312	0	0.00
372	PH20-337	0	0.00
394	PH20-359	0	0.00
413	PH20-378	0	0.00
430	PH20-395	0	0.00
447	PH20-412	0	0.00
467	**PH20-432**	**0.089**	**27.05**
477	PH20-442	0.567	172.34
478	PH20-443	0.692	210.33
479	PH20-444	0.75	227.96
480	PH20-445	0.575	174.77
481	PH20-446	0.74	224.92
482	**PH20-447**	**0.329**	**100.00**
483	PH20-448	0.8	243.16
509	PH20-474	0.044	13.37

89 EX1003, ¶¶ 94, 97, 167-69; EX1001, 74:13-19.

90 EX1005, 87:52-88:24 ($PH20_{1-442}$ activity "decreased to approximately 10%"); EX1013, Figure 2, 430-32 ("[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA"); EX1003, ¶ 91.

The ’429 Patent also reported that “a very narrow range spanning … [437-447] … defined the minimally active domain” of human PH20, and elsewhere observed this “minimally active” human PH20 domain contains at least residues 1-429.[91]

The common disclosure reiterates these findings, stating that PH20 polypeptides must extend to at least position 429 to exhibit hyaluronidase activity:

> A mature PH20 polypeptide … containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue ***464*** of SEQ ID NO: 6 [position ***429*** without signal] … ***is the minimal sequence required for hyaluronidase activity***.[92]

In 2007, Chao reported that the C-terminal region of human hyaluronidases contains a unique domain (“Hyal-EGF”) linked to a characteristic pattern of sequences.[93] In PH20, the Hyal-EGF domain runs from positions 337-409.[94] In

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91 EX1005, 6:65-7:7 (“… sHASEGP from amino acids 36 to Cys 464 [429] … comprise the minimally active human sHASEGP hyaluronidase domain”); EX1003, ¶ 90.

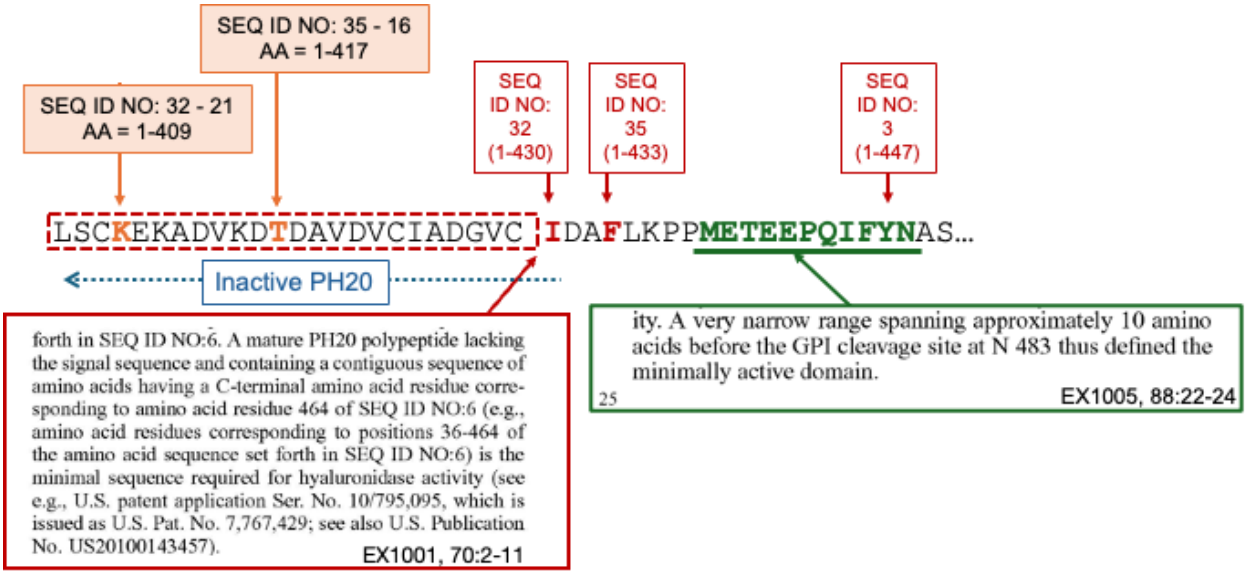
92 EX1001, 70:2-11 (emphases added); *also* EX1003, ¶ 93.

93 EX1006, 6912; EX1003, ¶¶ 84-86.

94 EX1004, ¶¶ 97-99; EX1003, ¶ 92.

2009, Zhang showed the Hyal-EGF domain was necessary for hyaluronidase activity.[95]

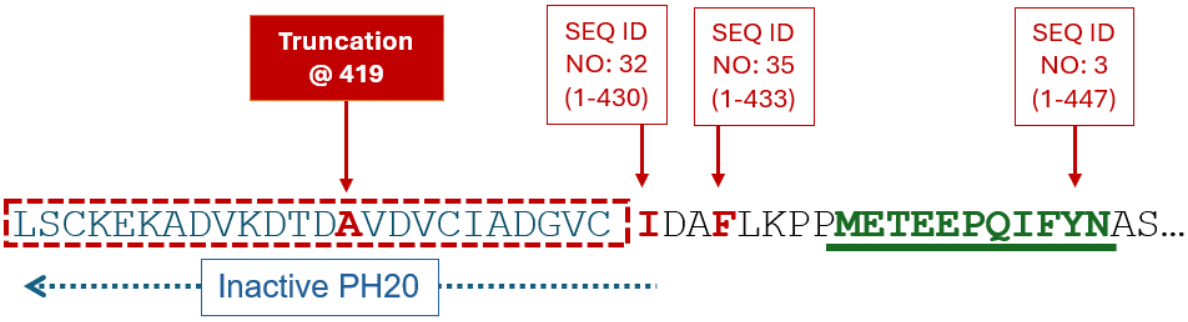
The C-terminus of PH20 is illustrated below, showing (i) the positions where SEQ ID NOS: **3** (447), **32** (430) and **35** (433) terminate, (ii) the "minimally active domain" at 437-447, and (iii) residues below position 429.[96] Positions resulting from deletion of 21 or 16 residues from SEQ ID NOS: 32 and 35 end before position 429.



95 EX1010, 9438; EX1003, ¶ 87.

96 EX1003, ¶ 153.

Consequently, a skilled artisan in 2011 would have believed that PH20 polypeptides that terminate before position 430 would be inactive (*e.g.*, at position 419, below).[97]



The common disclosure provides no examples of (or guidance concerning) PH20 mutants truncated below position 447 with one or more substitutions and that are enzymatically active. It thus ignores the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433.[98] The claims nonetheless capture modified PH20 polypeptides with truncations down to and beyond position 419.[99]

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97 EX1003, ¶¶ 92-93, 165-166.

98 EX1003, ¶¶ 92-93, 95, 97, 168.

99 EX1003, ¶¶ 164-66.

c) Empirical Test Results of Single-Replacement Modified PH20 Polypeptides Do Not Identify Multiply-Modified Enzymatically Active PH20 Polypeptides

The empirical results in the common disclosure provide no predictive guidance to a skilled artisan about the structural features of multiply-modified PH20 polypeptides within the claimed genera that are enzymatically active.

(i) The Data Concerning Single-Replacements Is Not Probative of Multiple-Replacement Mutants

The common disclosure reports results from testing a portion of a randomly generated library of ~6,743 single-replacement $PH20_{1-447}$ polypeptides.[100] These mutants were generated via a mutagenesis process which substituted one of ~15 amino acids into random positions in $PH20_{1-447}$ "such that each member contained a single amino change."[101] Approximately 5,917 were tested, while ~846 were uncharacterized.[102] More than half (~57%) of these mutants were classified as

[100] EX1001, 127:20-31, 194:65-67, 194:46-52.

[101] EX1001, 194:46-55.

[102] EX1003, ¶¶ 103-104. Inconsistent numbers of tested mutants and classifications of mutants are reported but not explained: (i) Table 3 lists 2,516 single-replacement $PH20_{1-447}$ mutants as "active mutants," but Table 9 identifies only 2,376 mutants that exhibit >40% hyaluronidase activity; (ii)

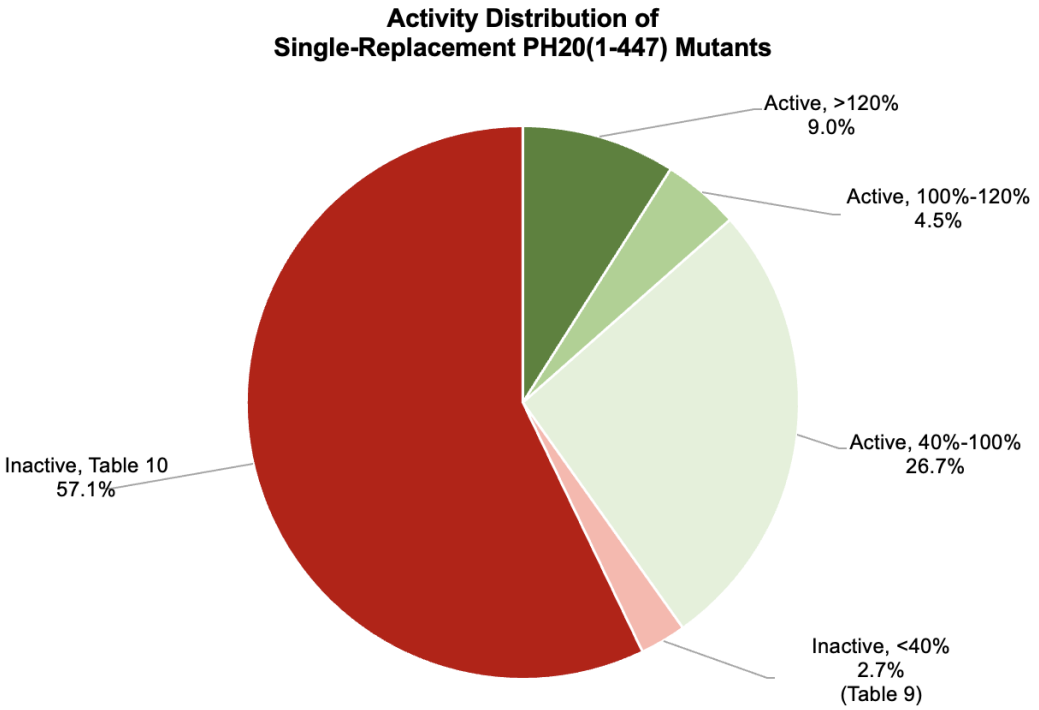
"inactive mutants," while ~30% (1335) were reported to have less activity than unmodified $PH20_{1-447}$ (20%-100%).[103] In other words, ~87% of the single-replacement $PH20_{1-447}$ polypeptides had ***less*** activity than unmodified $PH20_{1-447}$.[104]

Activity vs. Unmodified PH20	**Number**	**% of Tested (5916)**
Active Mutants (Table 9)		
>120%	532	9.0%
100%-120%	267	4.5%
40%-100%	1577	26.7%
Inactive Mutants (Table 9)		
<40%	160	2.7%
Inactive Mutants (Table 10)		
Table 10 'inactive mutants"	3,380	57.1%

Tables 5 and 10 list 3,368 and 3,380 $PH20_{1-447}$ "inactive mutants," respectively.

[103] EX1003, ¶ 105.

[104] *Id.*



The measured activity of single-replacement $PH20_{1-447}$ mutants shows no trends or correlations even for single-replacement $PH20_{1-447}$ polypeptides.[105] Instead, numerous examples show that even introducing different amino acids at the same position in $PH20_{1-447}$ resulted in (i) increased activity, (ii) decreased activity, or (iii) inactive mutants (below).[106]

[105] EX1003, ¶¶ 106, 142-43.

[106] Data from Tables 3, 5, 9, 10.

Position	Inactive	Decreased Activity	Increased Activity
008	P	L, M	I
067	R	L, Y	V
092	H	M, T	C, L, V
165	C	A, R, Y	D, F, N, S, V, W
426	K, S	E, G, N, Q, Y	P

The data on activities of tested single-replacement $PH20_{1-447}$ mutants is not analyzed or explained in the common disclosure—it is simply presented. There is no attempt to extrapolate its results to any combinations of substitutions in PH20 polypeptides, or to assess the impact of a single substitution on the protein's structure.[107] The quality of the data is also questionable: no control values or statistical assessments are provided.[108] All the data shows is that most of the tested single-substitution mutants impaired PH20's activity.[109]

The results from single substitutions provide no insights into PH20 polypeptides with multiple concurrent mutations, which together can cause complex and unpredictable effects on a protein's structure and resulting

[107] EX1003, ¶ 139.

[108] EX1003, ¶ 106.

[109] EX1003, ¶ 138.

function.[110] The patent's empirical test results thus provide no guidance to a skilled artisan about which of the many possible PH20 mutants with different sets of 2-42 substitutions will be enzymatically active.[111]

(ii) Purported Stability Data Is Not Reliable or Probative

The common disclosure reports results in Tables 11 and 12 from two runs of "stability" testing of ~409 single-replacement $PH20_{1-447}$ polypeptides.[112] Table 11 reports the hyaluronidase activity of single-replacement $PH20_{1-447}$ mutants tested at 4° C and 37° C, and in the presence of a "phenolic preservative" (m-cresol),[113] while Table 12 compares relative activities under pairs of these conditions.[114]

The data in Tables 11 and 12 provides no meaningful insights.[115] For example, unsurprisingly, single-replacement $PH20_{1-447}$ polypeptides showed higher activity at 37° C than at 4° C, given that PH20 exists at the former temperature in

[110] EX1003, ¶¶ 139, 142.

[111] EX1003, ¶¶ 140, 143.

[112] EX1001, 257:6-258:56.

[113] EX1001, 258:58-264:67 (Table 11).

[114] EX1001, 265:1-275:67 (Table 12).

[115] EX1003, ¶ 76.

humans.[116] And all that testing with m-cresol showed was that only a few mutants were able to resist its effects, with no explanation why.[117]

With one exception, there is no evidence the measured activity data was attributable to improved stability of PH20.[118] More directly, the common disclosure does not identify which ***combinations*** of substitutions improve stability.[119] It thus provides no probative insight regarding multiply-modified PH20 polypeptides with increased stability.[120]

The data is also largely meaningless, as many of their values fall within the range of activity observed for the positive control.[121] As the charts and table below show, the activity of unmodified $PH20_{1-447}$ varied by 97% and 87% in two rounds of testing.[122]

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116 EX1003, ¶ 73; EX1001, 171:11-20.

117 EX1003, ¶ 69.

118 EX1003, ¶ 69.

119 EX1003, ¶¶ 75-76.

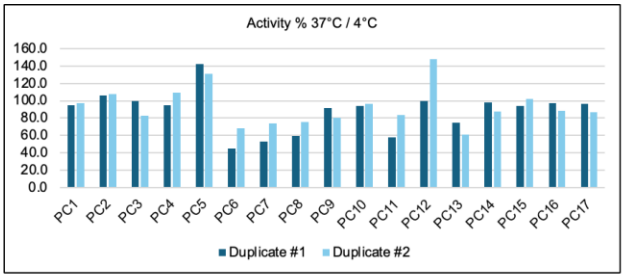
120 *Id*.

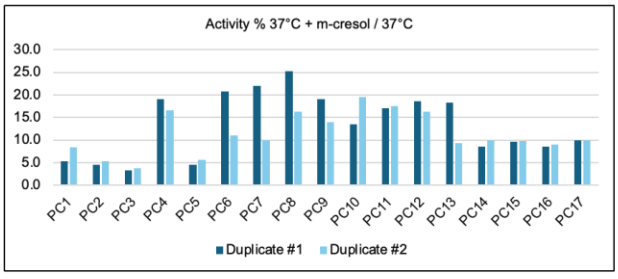
121 EX1003, ¶ 71; EX1001, 275 (Table 12).

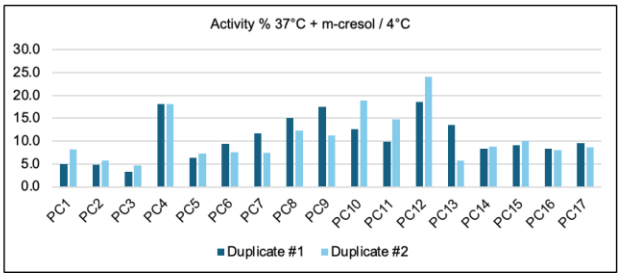
122 EX1003, ¶ 71, Appendix A-7, A-8.

Positive Control ("PC") (OHO)	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C+mcr/4°C
PC1	94.998	5.230	4.970	96.871	8.456	8.190
PC2	105.798	4.480	4.740	108.066	5.246	5.670
PC3	100.000	3.330	3.330	82.778	3.759	4.590
PC4	94.762	19.070	18.070	109.539	16.529	18.110
PC5	142.024	4.480	6.360	130.947	5.595	7.330
PC6	45.115	20.770	9.370	68.017	11.035	7.510
PC7	53.324	21.950	11.710	74.253	9.960	7.400
PC8	59.581	25.240	15.040	75.872	16.231	12.310
PC9	91.844	19.050	17.500	80.371	13.977	11.230
PC10	93.828	13.470	12.630	96.630	19.454	18.800
PC11	57.773	17.040	9.850	83.536	17.573	14.680
PC12	100.000	18.560	18.560	148.226	16.239	24.070
PC13	74.325	18.290	13.600	61.119	9.286	5.680
PC14	98.132	8.480	8.320	87.677	10.006	8.770
PC15	93.817	9.620	9.020	102.223	9.745	9.960
PC16	96.922	8.560	8.300	87.993	9.064	7.980
PC17	96.648	9.910	9.580	86.891	9.938	8.630

KEY
Coloration of Percent (%) Activity Values
n/a
>120
between 100 and 120
between 80 and 100
between 40 and 80
between 20 and 40
between 10 and 20
between 0 and < 10







	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C + m-cresol	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol	% Activity at 37°C+mcr/ 4°C
High	142.02	25.24	18.56	148.23	19.45	24.07
Low	45.12	3.33	3.33	61.12	3.76	4.59
Range	96.91	21.91	15.23	87.11	15.70	19.48
Average	88.17	13.38	10.64	93.00	11.30	10.64
Mean	94.76	13.47	9.58	87.68	9.96	8.63

As Dr. Hecht observes, this "significant variation raises serious doubts about how probative or instructive the values of individual tested mutants that fall within the range of variability observed for the control can possibly be."[123] The data not only fails to identify specific combinations of substitutions that yield PH20 mutants with increased resistance to or stability in denaturing conditions, it is unreliable.

d) The Common Disclosure's Research Plan Does Not Identify Multiply-Mutated Enzymatically Active PH20 Polypeptides

The common disclosure does not describe any multiply-modified PH20 polypeptides that are "active mutants." Instead, it simply presents ***the idea*** of multiply-modified PH20 polypeptides. First, it observes that "[a] modified PH20 polypeptide can have up to 150 amino acid replacements," "[t]ypically" contains between 1 and 50 amino acid replacements and "can include any one or more other

[123] EX1003, ¶¶ 70-72; *see also* EX1001, 277:7-17 (positive control also varied).

modifications**,** in addition to at least one amino acid replacement as described herein."[124] It also contends a modified PH20 polypeptide with "a sequence of amino acids that exhibits" between 68% and 99% sequence identity with any of unmodified Sequence ID Nos. 74-855 "***can*** exhibit altered, such as improved or increased, properties or activities compared to the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[125]

None of these statements identify ***any*** actual multiply-modified PH20 polypeptides (*i.e.*, particular sets of specific amino acid substitutions), much less provide results from testing any. They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides.

The common disclosure also describes no methods that produce any specific multiply-modified, enzymatically active PH20 polypeptides. What it provides instead is a prophetic research plan requiring "iterative" make-and-test experiments that ***might discover*** multiply-modified enzymatically active PH20 polypeptides:

> The method provided herein [] is ***iterative***. In one example, after the method is performed, any modified hyaluronan-degrading enzymes identified as exhibiting stability … ***can be modified or further modified*** to increase or optimize the

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[124] EX1001, 48:43-53.

[125] EX1001, 96:53-67 (emphasis added).

> stability. A secondary library ***can be*** created by introducing additional modifications in a first identified modified hyaluronan-degrading enzyme. … The secondary library ***can be*** tested using the assays and methods described herein.[126]

This prophetic research plan is effectively meaningless—it does not indicate that any active mutant multiply-modified PH20 polypeptides will be found, much less identify ***which*** multiply-modified PH20 polypeptides are active mutants.[127]

An alternative focus is then proposed: mutations can be "targeted near" "critical residues" which supposedly "can be identified because, when mutated, a normal activity of the protein is ablated or reduced."[128] But Tables 5 and 10 show that at least one substitution at each of 405 positions between positions 1 and 444 of $PH20_{1-447}$ resulted in an inactive mutant.[129] In other words, the common disclosure's guidance is to target locations "near" ~90% of the amino acids in

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[126] EX1001, 134:54-67 (emphases added); *see also id.* at 42:47-54, 127:66-128:4; EX1003, ¶¶ 173-177.

[127] EX1003, ¶¶ 173, 184-85, 190; EX1001, 44:1-3; *see generally id.*, 127:20-65, 128:7-129:49, 130:9-134:52.

[128] EX1001, 135:1-26; EX1003, ¶¶ 178-79.

[129] EX1003, ¶ 180, Appendix A-3.

$PH20_{1-447}$, which is no different than targeting every residue in the protein.[130] It is, like the first proposed "iterative" process, meaningless.

These prophetic research plans, based entirely on unfocused, iterative "make-and-test" experiments, provide no direction to the skilled artisan about which of the trillions and trillions of possible multiply-modified PH20 polypeptides are enzymatically active.[131] Instead, they require the skilled artisan to repeat the cycle of mutagenesis iteratively, screening and selecting until 10^{59} to 10^{112} modified PH20 polypeptides are produced and screened for activity.[132] That in no way demonstrates possession of the claimed genus.

The specification also incorrectly portrays the experimental readout—hyaluronidase activity—as a measure of "stability."[133] As Dr. Hecht explains, to assess a protein's stability directly one performs experiments that measure the energy associated with the protein's transition between its folded and unfolded

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130 EX1003, ¶ 180.

131 EX1003, ¶ 190.

132 EX1003, ¶¶ 175-77, 187-89; EX1001, 129:57-62, 129:50-130:7, 133:1-5, 133:17-22, 133:40-54.

133 EX1003, ¶¶ 67, 69, 179.

states.[134] Activity may or may not be influenced by stability but is not itself a measure of stability.[135]

e) The Common Disclosure Does Not Identify a Structure-Function Relationship for Multiply-Modified, Enzymatically Active PH20 Polypeptides

The common disclosure does not identify the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.[136] Instead, it simply lists single replacements to random amino acids at random positions that were classified as "active mutants" by a hyaluronidase assay; nothing is said about the effects (if any) of substitutions on the protein's structure.[137]

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134 EX1003, ¶¶ 63-66.

135 EX1003, ¶ 67.

136 EX1003, ¶¶ 139-40, 151.

137 EX1001, 228:7-35; EX1003, ¶¶ 139-40, 142.

The common disclosure also does not identify any ***sets*** of specific amino acid replacements that correlate to structural domains or motifs that positively or negatively influence hyaluronidase activity, much less ***predictably*** increase activity to defined thresholds.[138] Again, it simply reports activity data from testing randomly generated ***single***-replacement $PH20_{1-447}$ mutants.

The common disclosure's empirically identified examples of "active mutant" single-replacement $PH20_{1-447}$ mutants also do not ***by themselves*** identify any "structure-function" relationship between "active mutants" and the set of single-replacement modified $PH20_{1-447}$ polypeptides.[139] They certainly do not do so for the much larger genus of modified PH20 polypeptides of varying lengths and between 2 and 42 substitutions.[140]

Critically, the common disclosure ***does not even contend*** that a particular amino acid replacement at a particular position (*e.g.*, 324) that makes a $PH20_{1-447}$ an "active mutant" will make any other modified PH20 polypeptide with that same amino acid replacement (plus between 1 and 41 additional replacements or

[138] EX1003, ¶¶ 55, 142-43.

[139] EX1003, ¶¶ 61, 143, 157, 159.

[140] EX1003, ¶ 157.

truncations) an "active mutant."[141] Such an assertion would have no scientific credibility—the activity of a protein such as PH20 is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.[142] Thus, even the inventors did not view their compilation of test results as identifying a structure-function correlation for multiply-modified PH20 polypeptides.

The common disclosure, thus, does not identify to a skilled artisan ***any*** structural features shared by the many, diverse "active mutant" modified PH20 polypeptides within the scope of the claims,[143] and thus cannot satisfy the written description requirement of § 112(a) as a disclosure that links a functional property to a particular structure ***shared*** by the members of the genus.

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141 EX1003, ¶¶ 168, 192-93.

142 EX1003, ¶¶ 56-57.

143 EX1003, ¶ 157.

f) The Common Disclosure Does Not Describe a Representative Number of Multiply-Modified Enzymatically Active PH20 Polypeptides

The ~2,500 active mutant single-replacement $PH20_{1-447}$ polypeptides in the disclosure are not representative of the claimed genera or the various sub-genera within the claims.[144]

First, these single-replacement $PH20_{1-447}$ examples are not representative of the trillions and trillions of $PH20_{1-447}$ polypeptides with between ***2 and 42 substitutions*** at any of hundreds of positions within the protein.[145] The latter group of proteins is structurally distinct from single replacement PH20 polypeptides, both as to their sequences and as to the various secondary structures and structural motifs within the folded proteins that result when multiple amino acid substitutions are incorporated and from the distinct interactions they can cause with neighboring residues.[146] The effects of numerous substitutions on the PH20 protein's various secondary structures and structural motifs are not described or discussed in the common disclosure, and the magnitude of structural changes resulting from the

144 EX1003, ¶¶ 61, 143, 155, 159.

145 *See* § IV.D.1; EX1003, ¶¶ 61, 143, 159.

146 EX1003, ¶¶ 55-56, 58, 60, 156, 159.

concurrent substitutions encompassed by the claims was unknowable in 2011.[147] The overall activity of a protein with multiple substitutions also will not be due to one amino acid, but to the unique structure of each protein that reflects ***the totality*** of effects of those many substitutions.[148]

More specifically, introducing a first amino acid substitution often affects the neighbors of that original/replaced amino acid by, for example, (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, and/or (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).[149] Introducing a second substitution in that region may reverse those interactions (or not) with each neighboring residue, and a third substitution may do the same, with up to 21 rounds permitted by even the narrowest claims, each potentially impacting each interaction.[150] The data associated with a single amino acid substitution thus cannot be representative of the properties of any of these downstream, multiply-substituted mutants, which will have an unknowable

147 EX1003, ¶¶ 157-58, 228.

148 EX1003, ¶¶ 61, 141.

149 EX1003, ¶¶ 56-58.

150 EX1003, ¶¶ 58-60, 142.

combination of substitutions that each uniquely impact the properties of the mutated protein.[151]

Enzymatically active single-replacement $PH20_{1-447}$ polypeptides also are not representative of enzymatically active, multiply modified PH20 polypeptides that incorporate changes that alone render PH20 proteins inactive (*e.g.*, truncations terminating below position 429, or single substitutions that render $PH20_{1-447}$ inactive).[152] That is because an ***active*** single-replacement $PH20_{1-447}$ polypeptide does not also contain the distinct structural features that render the latter types of PH20 polypeptides enzymatically ***inactive***. For example, an enzymatically active $PH20_{1-447}$ protein with a single amino acid substitution (*e.g.*, E324D) would not be considered representative of a PH20 that combines that E324D substitution with truncations at the C terminus ending at positions between 409 to 433 because the common disclosure would have led a skilled artisan to expect that PH20 proteins terminating at those positions would be inactive.[153] A skilled artisan could not have predicted—based on the examples in the common specification, all of which are limited to single-replacement $PH20_{1-447}$ polypeptides—whether enzymatic

[151] EX1003, ¶¶ 143, 159.

[152] EX1003, ¶¶ 161-64.

[153] EX1003, ¶¶ 167-69.

activity could be restored to such severely truncated PH20 mutants, much less the precise additional changes that would do so.[154]

The common disclosure thus provides a very narrow set of working examples relative to the diversity of modified PH20 polypeptides being claimed.[155] The examples are restricted to ***one type of change*** (a single amino acid replacement) in ***one type of PH20 polypeptide*** (SEQ ID NO: 3).[156] By contrast, the claims encompass changes in 37 different unmodified PH20 sequences, and include, in addition to one identified replacement at position 324, anywhere from 1 to 41 (claim 1) to 20 (claims 25-26) additional changes.[157] A simple illustration demonstrates how ***non-representative*** the examples are: all of the examples of single-replacement $PH20_{1\text{-}447}$ mutants fit into one box of the array below (claim 2).

[154] EX1003, ¶ 168.

[155] EX1003, ¶ 155.

[156] EX1003, ¶¶ 97, 99, 103.

[157] EX1003, ¶¶ 115-20.

	Number of Changes																					
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3																							
7																							
32																							
33																							
34																							
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Unlike claim 2, which requires 95% sequence identity, claim 1 permits 91% sequence identity, thus capturing an even ***larger*** genus (up to 42 permitted changes) than depicted above.

Consequently, a skilled artisan would not have viewed the Patents' examples of individual single amino acid replacements in $PH20_{1-447}$ as being ***representative*** of the diversity of modified PH20 polypeptides encompassed by the claims.[158]

[158] EX1003, ¶ 143.

g) The Claims Capture Multiply-Modified PH20 Polypeptides the Disclosure Excludes from the Class of Enzymatically Active PH20 Proteins

Patentee's position on the breadth of the claims is unknown. However, by their literal language, they capture several sub-genera of "active mutant" modified PH20 polypeptides that the common disclosure says caused single-replacement $PH20_{1-447}$ mutants to be inactive (*i.e.*, those with replacements in Tables 5/10 or in PH20 sequences terminating before position 429). Likewise, the claim language captures modified PH20 polypeptides with the six combinations of replacements the common disclosure explicitly says to not make: P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, N333A/N358A and N47A/N131A/N219A.[159] The claims thus improperly capture multiply-modified PH20 polypeptides the common disclosure affirmatively excludes from the genus of enzymatically active PH20 polypeptides.

The common disclosure provides no exemplification of multiply-modified species of PH20 polypeptides that disregard these restrictions in the common disclosure.[160] There is no explanation of the types of substitutions that might be made to restore activity that, under the logic of the common disclosure, will result

[159] *See* § V.A.2.a; EX1001, 77:47-59.

[160] EX1003, ¶ 161.

in enzymatically inactive PH20 polypeptides or which the specification teaches ***not*** to make.[161] Yet the claims encompass such proteins.

The claims thus independently violate the written description requirement for the reasons articulated by the Federal Circuit in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998)—if a disclosure "unambiguously limited" the invention, but the claims circumvent that limitation, those claims are "broader than the supporting disclosure" and are unpatentable.

2. Dependent Claims 3-5 and 16 Lack Written Description

a) Claims 3 and 4

Claims 3 and 4 specify additional functional properties of the modified PH20 polypeptides in the genus defined by claim 1: either (i) increased hyaluronidase activity (claim 4) or (ii) increased stability (claim 3) relative to unmodified $PH20_{1-447}$.

The reasons provided in § V.A.1 explaining why the claims generally lack written description apply with full force to claims 3 and 4.

In addition, the common disclosure's recitation of a ***desired*** level of stability or hyaluronidase activity in claims 3 and 4 does not identify ***which*** of the many trillions of PH20 polypeptides having 91% or 95% sequence identity with SEQ ID

[161] EX1003, ¶ 168.

NOS: 3, 7, or 32-66 and one of seven replacements at position 324 will exhibit either of those functional properties.[162]

First, the identification of three $PH20_{1-447}$ mutations at position 324 that exhibited similar or increased activity (E324D, E324N, E324R) as unmodified $PH20_{1-447}$ is not representative of each claim's genus of PH20 polypeptides having 1 to 41 additional substitutions and/or truncations; indeed, four of the seven singly-substituted position 324 mutants showed ***reduced*** activity (*i.e.*, E324A, E324H, E324M, E324S).[163] Regarding "stability," only one position 324 mutant (E324N) was tested, and it showed activities indistinguishable from unmodified $PH20_{1-447}$.[164]

TABLE 12-continued

	Percent (%) Activity					
	duplicate 1			duplicate 2		
	% activity at 37° C./4° C.	% activity 37° C. + m-cresol/37° C.	% activity 37° C. + m-cresol/4° C.	% activity at 37° C./4° C.	% activity 37° C. + m-cresol/37° C.	% activity 37° C. + m-cresol/4° C.
N321S	102.489	8.29	8.49	108.732	4.534	4.93
→ E324N	104.618	7.72	8.08	131.265	9.124	11.98
T325E	124.837	14.44	18.02	106.457	10.577	11.26

[162] EX1003, ¶¶ 185, 191-92.

[163] EX1001, 231 (Table 9); EX1003, ¶¶ 191-92.

[164] EX1001, 271 (Table 12); EX1003, ¶ 71; *see* § IV.A.1.c.ii.

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides (if any) exhibiting increased activity or stability.[165] The mere presence of a single substitution at position 324 in a modified PH20 certainly does not demonstrate possession of any multiply-modified PH20 polypeptide with increased activity or stability having that position 324 substitution, and the common disclosure does not contend otherwise.[166]

The common disclosure does not describe any multiply-modified PH20 polypeptides having the claimed substitutions at position 324, much less those with 1 to 41 additional substitutions, and that exhibit increased enzymatic activity or increased stability.[167] Indeed, the common specification does not identify any multiply-modified PH20 polypeptides with any level of hyaluronidase activity.[168] Similarly, even if the data reported in Tables 11 and 12 was not flawed and unreliable as a measure of "stability" (as discussed above, it is), it too is limited to

[165] EX1003, ¶¶ 157, 185, 190.

[166] EX1003, ¶¶ 143, 168, 185.

[167] EX1003, ¶¶ 140, 190-93.

[168] EX1003, ¶¶ 130, 172.

singly-substituted PH20 polypeptides, and, provides no "stability" data for multiply-modified PH20 polypeptides.[169]

Claims 3 and 4 lack written description in the common disclosure.

b) Claims 5 and 16

Claims 5 and 16 require an additional functional property: that the modified PH20 polypeptide be "soluble." Each lacks written description support (i) for the same reasons identified for claim 1, and (ii) because they encompass modified PH20 polypeptides that the common disclosure suggests would be insoluble.

The common disclosure explains that "a soluble PH20 lacks all or a portion of a glycophosphatidyl anchor (GPI) attachment sequence,"[170] which was known to be hydrophobic.[171] Citing prior art, it identifies the first residue of the GPI sequence in human PH20 as position 456 (position 491 in SEQ ID NO: 6).[172] It

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169 EX1001, Tables 11, 12.

170 EX1001, 46:28-30, 72:11-12, 74:30-42.

171 EX1001, 72:35-47; EX1005, 86:18-22.

172 EX1001, 72:35-47; *also* EX1005, 2:56-61 ("Attempts to make human PH20 DNA constructs that would not introduce a lipid anchor into the polypeptide resulted in either a catalytically inactive enzyme, or an insoluble enzyme") (citing EX1011).

also states that a soluble PH20 "is a polypeptide that is truncated after amino acid 482 of … SEQ ID NO: 6" (*i.e.*, 447 in SEQ ID NO:3)."[173] It thus suggests that human PH20 sequences that terminate below position 448 are soluble and those that terminate above position 456 are insoluble.[174]

Claims 5 and 16 encompass PH20 polypeptides based on SEQ ID NOS:59-66, which terminate between positions at 457 to 464 respectively (*i.e.*, beyond position 456), and does not restrict where in the PH20 polypeptide changes are made, other than the replacement at position 324. Consequently, claims 5 and 16 capture modified PH20 polypeptides that are C-terminally truncated but, per the common disclosure, ***are not*** "soluble modified PH20 polypeptide[s]" because each contains "all or a portion of" the GPI attachment sequence.[175]

Patentee may contend that some unidentified number of modified PH20 polypeptides based on SEQ ID NOS: 59-66 ***may*** be soluble, citing the common disclosure as suggesting that between 1-10 residues within the GPI anchor "can be retained, provided the polypeptide is soluble."[176] But the common disclosure does

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173 EX1001, 75:20-22; EX1005, 3:57-62.

174 EX1003, ¶¶ 89-90.

175 EX1001, 46:55-61.

176 EX1001, 74:23-29.

not identify ***which*** modified PH20 polypeptides terminating above position 448 (and especially terminating between 457 and 464) ***are*** soluble, provides no examples of such soluble PH20 mutants, and provides no reason to expect that many modified PH20 polypeptides within the claim's scope are soluble.

Thus, claims 5 and 16 are unpatentable for lack of written description for this additional, independent reason.

3. Dependent Claims 17-24 and 27-35 Lack Written Description

The remaining dependent claims (17-24 and 27-35) do not alter the number of PH20 polypeptides in the genus of claim 1.[177] They instead specify additional features (claims 17-23, 34-35), or pharmaceutical compositions, or methods of treatment that reference the genus of claim 1. They lack written description for the same reasons explained in § V.A.1.[178]

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[177] Claim 22 omits reference SEQ ID NO:7.

[178] *Idenix*, 941 F.3d at 1155, 1165 (method of treatment claims involving immense genus of modified proteins invalid for lack of written description and non-enablement); *Boehringer*, PGR2020-00076, Paper 42, at 40-41 (methods of treatment claims found to lack written description because specification did not provide an adequate written description of compositions being administered).

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

"If a patent claims an entire class of … compositions of matter, the patent's specification must enable a person skilled in the art to make and use the ***entire*** class," *i.e.*, "the ***full scope*** of the invention" and so the "more one claims, the more one must enable."[179] "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."[180] "Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation."[181]

Although not required, enablement may be assessed using the *Wands* factors, which consider: "(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the

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179 *Amgen*, 598 U.S. at 610 (emphases added).

180 *Idenix*, 941 F.3d at 1159.

181 *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention."[182]

Where the scope of the claims is large, there are few working examples disclosed in the patent, and the only guidance to practice "the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims' functional limitations—the asserted claims are not enabled."[183]

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the 10^{59}+ PH20 polypeptides having multiple amino acid replacements and/or truncations within the scope of the claims are "active mutant" PH20 polypeptides.[184]

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182 *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

183 *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, T., sitting by designation) *aff'd* 81 F.4th 1362 (Fed. Cir. 2023).

184 EX1003, ¶¶ 170-71, 190.

1. Claims 1-2, 6-15, 22, and 25-26 Are Not Enabled

The facts of this case are a textbook example of claims that are not enabled under the reasoning articulated by the Supreme Court in *Amgen*. An analysis of the common disclosure under the Federal Circuit's framework for assessing undue experimentation using the factors in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) compels the same conclusion.

a) Extreme Scope of the Claims

As explained in § IV.D.1, each of claims 1-2, 6-15, 22, and 25-26 define an immense and diverse genus of between 10^{59} and 10^{112} enzymatically active modified PH20 polypeptides. Practicing that full genus, however, raises substantial scientific questions left unanswered by the common disclosure:

(i) The claims encompass many modified PH20 polypeptides that terminate below position 429.[185] The common disclosure and the prior art, however, report that unmodified human PH20 must include residues through position 429 to have hyaluronidase activity.[186]

(ii) Several claims (1-2, 6-10, 15, 22) encompass modified PH20 polypeptides that, per the common disclosure's guidance, would be

[185] EX1003, ¶¶ 154, 164.

[186] EX1001, 70:2-11; EX1003, ¶¶ 93, 152-53.

expected to be insoluble because they include all or some of the GPI anchor sequence.[187]

(iii) The mathematical "sequence identity" boundaries set by the claim language cause the claims to capture (without restriction) modified PH20 polypeptides with 2 to 42 amino acid replacements that the common disclosure instructs "are less tolerant to change or required for hyaluronidase activity"[188] or which the common disclosure affirmatively says to not make.[189]

In other words, the claims capture massive genera of modified PH20 polypeptides, most of which would have unknowable properties absent individual production and testing.[190]

Claims that capture a massive and diverse genus of proteins have routinely been found non-enabled. For example, the claims in *Amgen* covered "millions" of different, untested antibodies,[191] while in *Idenix*, a skilled artisan would

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187 EX1001, 46:28-30, 72:11-12, 74:23-29, 75:20-22; EX1005, 2:56-61, 3:57-62.

188 EX1001, 80:15-17.

189 EX1001, 77:47-59.

190 EX1003, ¶ 158.

191 598 U.S. at 603.

"understand that 'billions and billions' of compounds literally meet the structural limitations of the claim."[192] In both cases, the enormous claim scope was found non-enabled after being contrasted to the limited working examples in the patent, the existence of unpredictability, and the quantity of experimentation needed to practice the full scope of the claims (*Wands* Factors 1, 3, 4, and 7). And, as the *Idenix* court observed, one cannot rely on the knowledge and efforts of a skilled artisan to try to "fill the gaps in the specification" regarding which of the "many, many thousands" of possible compounds should be selected for screening, and which in this case is impossible.[193]

b) Limited Working Examples and Only a Research Plan for Discovering Active Mutant PH20 Polypeptides

The common disclosure provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement $PH20_{1-447}$ polypeptides, of which ~2500 were "active mutants."[194] Those examples are a tiny fraction of the 10^{59} to 10^{112} modified PH20 polypeptides covered by the claims, and provide no guidance that would help a skilled artisan navigate the "trial-and-error" methodology the common disclosure describes using to make modified PH20

192 941 F.3d at 1157.

193 *Id.* at 1159.

194 EX1003, ¶ 103.

polypeptides; indeed, none incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.[195]

The common disclosure provides no credible guidance on the full scope of the genus comprising multiple combinations of changes to PH20 polypeptides.[196] Instead, it describes an explicitly prophetic and "iterative" process for ***discovering*** active mutant PH20 polypeptides. *See* § V.A.1.d.

The purely prospective research plan in the common disclosure demands that a skilled artisan engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of ***randomized*** mutations (up to 41 rounds per starting molecule under the broadest claims) to ***discover*** which of the 10^{59}+ possible modified PH20 polypeptides having 2 to 41 replacements to any of 19 other amino acids in any of 35 starting PH20 sequences might possess hyaluronidase activity.[197]

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195 EX1003, ¶¶ 155, 159, 167.

196 EX1003, ¶¶ 131, 139.

197 EX1003, ¶¶ 188-90; *see also* EX1018, 382 ("combinatorial randomization of only five residues generates a library of 205 possibilities (3.2×10^6 mutants), too large a number for manual screening"). Chica also credited a supposed "ground-breaking" advancement in predictive molecular modeling techniques.

Second, it provides no meaningful guidance in producing "active mutant" modified PH20 polypeptides:

(i) it does not identify ***any*** specific combination of two or more replacements within any PH20 polypeptide that yield "active mutants";

(ii) it provides no data from testing ***any*** PH20 polypeptide with two or more substitutions; and

(iii) it does not identify any regions or residues that are "associated with the activity and/or stability of the molecule" or "'critical residues involved in structural folding or other activities' of the molecule" when two or more concurrent replacements have been made.[198]

From the common disclosure and their knowledge in 2011, a skilled artisan could not predict whether a particular multiply-modified PH20 polypeptide will be enzymatically active without making and testing each one.[199]

EX1018, 384, 382. That supposed advancement, however, was later shown to be false. EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

[198] EX1003, ¶¶ 144, 158, 172, 184-85.

[199] EX1003, ¶ 190.

Regardless whether individual rounds of "iterative" production and testing might be considered "routine," the process described in the common disclosure is indistinguishable from the "***iterative, trial-and-error process[es]***" that have consistently been found to not enable broad genus claims to modified proteins.[200] Simply put, the common disclosure's prophetic, iterative and labor-intensive process requires making and screening an immense number of modified PH20 polypeptides, before which the skilled artisan will not know which multiply-modified PH20 polypeptides are within the claims' scope.[201]

c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable

Like any protein, the activity of PH20 can be unpredictably influenced by changes to its amino acid sequence.[202] Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary

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200 *Idenix*, 941 F.3d at 1161-63 (emphasis added); *see also Amgen,* 598 U.S. at 612-15; *Wyeth*, 720 F.3d at 1384-86; *Baxalta*, 597 F. Supp. 3d at 616-19; *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 n.2 (Fed. Cir. 2020).

201 EX1003, ¶¶ 172, 183-85, 189.

202 EX1003, ¶ 61.

structures or structural motifs within the protein that are important to its biological activity (*e.g.*, catalysis, ligand binding, etc.) and/or stability.[203]

As explained in § VI, below, by 2011, skilled artisans could have assessed whether certain ***single*** amino acid substitutions at certain positions would be tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.[204] That person, using a rational design approach, would have performed such an assessment by, *inter alia*, analyzing evolutionarily non-conserved positions and evaluating specific changed residues using a PH20 protein structure model using experimental evidence available before 2011 that is not disclosed in or referenced by the common disclosure.[205]

By contrast, the skilled artisan could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011.[206] Introducing ***multiple*** concurrent changes into a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity and/or stability,

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203 *Id.*

204 EX1003, ¶ 194.

205 EX1003, ¶¶ 20, 49.

206 EX1003, ¶¶ 158, 228.

and can even introduce new ones into the protein.[207] Replacing multiple amino acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.[208]

The cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure in 2011. For example, the further away the modeled amino acid sequence gets from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model became.[209] In addition, depending on the structural template used to produce the model, regions of the protein not supported by a corresponding structure cannot be reliably used to assess particular changes.[210] And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.[211]

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207 EX1003, ¶¶ 59-60, 185.

208 EX1003, ¶¶ 55, 58, 61.

209 EX1003, ¶¶ 158, 190, 228; EX1004, ¶¶ 173-174.

210 EX1003, ¶¶ 158, 228; EX1004, ¶¶ 163-165; EX1012, 4, 8.

211 EX1003, ¶ 51, 190; EX1059, 1225-26; EX1018, 378.

Consequently, a skilled artisan could not have used conventional rational design techniques to identify, much less predict the outcome of attempts to make, the enormous number of PH20 polypeptide sequences that incorporate the myriad possible combinations of between 2 and up to 42 substitutions the claims encompass.[212] Stated another way, practicing the full scope of the claims would have been well beyond the ability of the skilled artisan's ability to reasonably predict which multiply-modified PH20 polypeptides would be enzymatically active, and, even if possible, doing so would have taken an extreme amount of time and effort even for a small handful of the vast universe of multiply-modified polypeptides within the claims.[213]

d) Other Wands Factors and Conclusion

The remaining *Wands* factors either support the conclusion that practicing the full scope of the claims would require undue experimentation or are neutral.

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed.[214]

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212 EX1003, ¶¶ 61, 158, 228.

213 EX1003, ¶¶ 158, 190.

214 EX1003, ¶¶ 158, 228.

Likewise, while there was significant knowledge in the public art about hyaluronidases, there was no solved structure of the PH20 protein, experimental reports generally reported on ***loss of activity*** from mutations, and did not predictably teach how to introduce changes that ***enhanced*** stability or activity. Indeed, the non-enabled patent disclosure at issue in *Amgen* dates to the same 2011 timeframe as the common disclosure.

Practicing the full scope of claims 1-2, 6-15, 22, and 25-26 thus would have required a skilled artisan to engage in undue experimentation, which renders those claims non-enabled.

2. Dependent Claims 3-5, 16-21-24 and 27-35 Are Not Enabled

a) Claims 3 and 4

Claims 3 and 4 require the modified PH20 polypeptides to have increased activity (*i.e.*, >100% of unmodified PH20) or increased resistance to or stability in denaturing conditions.

The reasons why claims 1-2, 6-15, 22, and 25-26 are not enabled (*see* § V.B.1) establish why claims 3 and 4 are also not enabled. Specifically, a skilled artisan could not have predicted which of the trillions of PH20 polypeptides having up to 41 changes beyond a required change at position 324 would exhibit increased

activity or stability compared to an unmodified PH20.[215] Instead, a skilled artisan would need to make-and-test each molecule in order to practice the "full scope" of the claims.[216]

b) Claims 5 and 16

Because claims 5 and 16 encompass a substantial portion of the genus defined by claim 1, they are not enabled for the same reasons.

Additionally, as explained in § V.A.2.b, the common disclosure suggests that PH20 polypeptides (modified or unmodified) that extend past position 456 would be "insoluble." Based on it and published literature, a skilled artisan would have expected the presence of the hydrophobic GPI sequence in the PH20 protein could cause aggregation, loss of activity, and/or reduced expression.[217] The common disclosure reinforces that these problems can occur, but provides no guidance as to how solve them and no examples of modified PH20 polypeptides extending past position 456 that are soluble. Claims 5 and 16 are thus not enabled.

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215 EX1003, ¶¶ 185, 190.

216 *Id.*

217 EX1003, ¶¶ 89-90, 196; EX1001, 51:2-4, 72:35-47; *also* EX1005, 2:56-61.

c) Claims 17-24, 27-35

The remaining claims employ the genus definition used in claim 1 and recite either further modifications to the modified polypeptides, pharmaceutical compositions, or methods of treatment using the claimed genus. These claims do not add requirements that limit the numbers of polypeptides in the claim 1 genus.[218] They are therefore not enabled for the same reasons.[219]

C. Inactive PH20 Polypeptides Are Not Useful and Do Not Remedy the § 112(a) Deficiencies of the Claims

Patentee may contend the claims do not require the modified PH20 polypeptides to be "active mutants." Such a contention, even if accepted, does not solve the written description and enablement problems of the claims.

First, it ignores that at least ***a portion*** of the claimed genus ***does*** require the modified PH20 polypeptides to be an "active mutant." *See* § V.B.2.a. Because dependent claim 4 requires the modified PH20 polypeptides to exhibit increased hyaluronidase activity, parent claim 1 necessarily encompasses a sub-genus comprised of "active mutant" modified PH20 polypeptides. A failure to enable or

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[218] Claim 22 limits the genus by removing SEQ ID NO:7, but defines an immense genus otherwise identical to claim 1.

[219] *See, e.g.*, *Idenix*, 941 F.3d at 1155, 1165.

describe a subgenus within the scope of the claims demonstrates that the claim ***as a whole*** is unpatentable for lack of written description and non-enablement.[220]

Second, the common disclosure fails to provide any correlation between changes to PH20 polypeptides and ***either*** active or inactive mutants.[221] Rather, it leaves to the skilled artisan the burdensome task of making and testing, through trial-and-error iteration, each of the 10^{59}+ candidate polypeptides within the claims' scope to determine which exhibit hyaluronidase activity and which are inactive mutants.[222]

Third, the only putative utility identified for "inactive" polypeptides is as "antigens in contraception vaccines."[223] This assertion is not scientifically credible, but regardless, the common disclosure provides no guidance about which

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220 *ABS Glob., Inc. v. Inguran*, 914 F.3d 1054, 1070, 1074 (7th Cir. 2019) ("If the specification failed to enable [a limitation] in the dependent claim, then [] the full scope of the invention is also not enabled in the independent claim, and *both* claims are invalid for non-enablement") (citing *Alcon Research, Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1367-68 (Fed. Cir. 2012)).

221 EX1003, ¶ 143.

222 EX1003, ¶¶ 173-74, 182-84.

223 EX1001, 75:58-60, 188:6-27.

epitopes on the PH20 protein must be preserved in an "inactive mutant" (if any) to induce contraceptive antibody production in a human subject.[224] Notably, while the specification cites two studies in guinea pigs,[225] it ignores numerous publications before 2011 that showed that immunizing mammals with PH20 did ***not*** cause contraception.[226] Moreover, Patentee's own clinical studies of the unmodified $PH20_{1-447}$ protein reported in 2018 that, despite producing anti-PH20 antibodies, those anti-PH20 antibodies ***did not affect fertility*** in humans:

> Although some antisperm antibodies are associated with decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex.[227]

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224 EX1003, ¶ 113.

225 EX1001, 188:6-27; EX1022, 1142-43; EX1023, 1133-34.

226 *See* EX1019, 325, 331-33 ("recombinant mPH20 is not a useful antigen for inclusion in immunocontraceptive vaccines that target mice"); EX1020, 179-81 ("immunization [of rabbits] with reproductive antigens … are unlikely to result in reduced fertility …"); EX1021, 30310, 30314 ("PH-20 is not essential for fertilization, at least in the mouse …").

227 EX1024, 87-88; *see also* EX1061, 1154; EX1003, ¶¶ 110-11.

Notably, Patentee reported this clinical result before filing the application that issued as the '520 Patent.

Even if one considers the unlikely possibility than some epitope on human PH20 might induce contraceptive effects in a human, a skilled artisan could not have reasonably predicted from the common disclosure whether any "inactive mutant" modified PH20 polypeptides would preserve that epitope or induce antibody production that would confer (contrary to Patentee's clinical evidence) contraceptive effects in humans.[228] Indeed, a skilled artisan would have expected the vast majority of "inactive mutant" PH20 polypeptides would have no utility at all.[229] Consequently, a skilled artisan would not have accepted the common disclosure's assertion that "inactive mutants" are useful as contraceptive vaccines, particularly in humans.[230]

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228 EX1003, ¶¶ 112-13.

229 *Id.*; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App'x. 26, 30 (Fed. Cir. 2007).

230 EX1003, ¶¶ 112-13; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

Finally, and most significantly, the common disclosure does not identify a single inactive PH20 mutant (with any number of substitutions) that was shown to have contraceptive effect.[231] Therefore, at most, the common disclosure presents only a "research proposal" to discover such "inactive mutants."[232] It does not demonstrate possession of or enable the immense and diverse genus of PH20 polypeptides claimed, regardless of whether the claims are appropriately limited to "active mutants" or, instead, include "inactive mutants."

D. The Original Claims of the '731 Application Do Not Cure the Written Description and Enablement Deficiencies

The specifications of the pre-AIA '731 Application and AIA '520 Patent are substantially identical, and neither supports the challenged claims as § 112(a) requires by either. The claims are both PGR eligible and unpatentable under § 112(a).

The original claims of the '731 Application provide no additional guidance demonstrating written description or enablement of the claimed genera of multiply-modified PH20 polypeptides. Those original claims claimed equivalently broad

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231 EX1003, ¶ 113.

232 *See Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("[t]he utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research").

genera via sequence identity language (*e.g.*, 85% to SEQ ID NOS: 3, 7 or 32-66) (claims 1-3) or having up to "75 or more amino acid replacements" (claim 4). Dependent claims listed single positions (claim 12) or replacements (claims 13-16) in those polypeptides. And, while certain claims contemplated 2-3 particular combinations of amino acid replacements (from dozens listed), others encompassed substitutions at unspecified locations.[233] The original claims do not provide § 112 support for the challenged claims.[234]

VI. Challenged Claims 1-2 and 5-35 Are Unpatentable Under § 103

Claims 1-2, 6-15, 22, and 25-26 each define genera that encompass one or more of three specific modified PH20 polypeptides: E324D $PH20_{1-447}$, E324N $PH20_{1-447}$, and E324R $PH20_{1-447}$. *See* § IV.D.2. Because these mutants would have been obvious from the '429 Patent in view of Chao and the knowledge of a skilled artisan, each of those claims is unpatentable. Claims 5, 16-24, and 27-35

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[233] EX1026, at 335.

[234] *See, e.g.*, *Ariad Pharms.*, 598 F.3d at 1349 ("original claim language" does not "necessarily disclose[] the subject matter that it claims"); *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993) (original claim amounted to no more than a "wish" or "plan" for obtaining the claimed DNA and "attempt[ed] to preempt the future before it has arrived").

are also obvious, as each recites attributes met by E324D, E324N, or E324R $PH20_{1-447}$, or is suggested by the '429 Patent alone or with other prior art.

A. The Prior Art

The '429 Patent (EX1005) is owned by Patentee, was originally filed in 2003, and issued on Aug. 3, 2010.

Chao (EX1006) was published in "Biochemistry" in 2007. Chao is not discussed in the common disclosure of the '520 Patent and '731 Application and was not cited during examination.

Knowledge of the skilled artisan relevant to obviousness is described in the testimony of Drs. Hecht (EX1003) and Park (EX1004), and is also documented in the prior art, including Patentee's earlier-published application, WO297 (EX1007).

B. Because E324D, E324N, and E324R $PH20_{1-447}$ Would Have Been Obvious, Claims 1-2, 6-15, and 25-26 Are Unpatentable

Patentee's '429 Patent would have motivated a skilled artisan to produce modified $PH20_{1-447}$ polypeptides having a single amino acid substitution in non-essential regions of the protein. Guided by her familiarity with rational protein design and the teachings of the '429 Patent and Chao, the artisan would have readily identified single amino acid substitutions in non-essential regions of $PH20_{1-447}$ that would have been tolerated (*i.e.*, a $PH20_{1-447}$ with that single substitution would retain its enzymatic activity). E324D $PH20_{1-447}$, E324N $PH20_{1-447}$, and

E324R $PH20_{1-447}$ are three such examples. Because claims 1-2, 6-15 and 25-26 encompass at least one of these obvious variants of $PH20_{1-447}$, each is unpatentable.

1. Patentee's '429 Patent Motivates a Skilled Artisan to Make Single Amino Acid Substitutions in Non-Essential Regions of $PH20_{1-447}$

Patentee's '429 Patent, filed in 2003, describes its invention as soluble PH20 hyaluronidase glycoproteins ("sHASEGPs") that are enzymatically active at neutral pH.[235] It exemplifies and claims one such "sHASEGP" that terminates at position 447 (positions 36-482 of SEQ ID NO: 1).[236]

The '429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, in pharmaceutical compositions, and combined with other therapeutic agents (*e.g.*, antibodies, chemotherapeutics), and illustrates administering such combinations subcutaneously to treat cancer and hyaluronidase disorders.[237] $PH20_{1-447}$ was approved by the FDA as Hylenex® in 2005.[238] The '429 Patent's teachings combined with the status of $PH20_{1-447}$ as an approved

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235 EX1005, 6:4-10, 10:30-59.

236 EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

237 EX1005, 8:25-9:4, 54:40-65, 56:34-57:36, 60:38-61:4, 63:41-61, 74:10-29, 76:19-77:36, 99:28-100:47.

238 EX1049, 1.

human therapeutic before 2011 would have induced a skilled artisan to focus on this particular PH20 polypeptide.[239]

Patentee's '429 Patent defines sHASEGPs as including wild-type $PH20_{1-447}$ and "equivalent" proteins "with amino acid substitutions that do not substantially alter activity" of the protein.[240] It explains:

> Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity …[241]

The '429 Patent also explains that single amino acid substitutions can include "conservative" substitutions in Table 1, but that "[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions."[242]

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239 EX1003, ¶ 195.

240 EX1005, 9:65-10:13; *see also id.* at 18:64-19:6 ("equivalent" proteins).

241 EX1005, 16:14-22.

242 EX1005, 16:24-36.

The ’429 Patent thus teaches making a ***particular*** type of modification (a single amino acid substitution) in ***particular*** locations (non-essential regions of PH20) in a ***particular*** PH20 sequence ($PH20_{1-447}$) to yield equivalents of $PH20_{1-447}$ (*i.e.*, those that do not substantially alter the activity or function of $PH20_{1-447}$).[243]

The ’429 Patent also motivates skilled artisans to undertake this effort to design and produce such single-amino acid substituted $PH20_{1-447}$ proteins because it assures them their efforts will be successful.[244] As it states, skilled artisans recognized that such “single amino acid substitutions in non-essential regions” of $PH20_{1-447}$ “do not substantially alter biological activity” of $PH20_{1-447}$. As such, a skilled artisan would have expected a $PH20_{1-447}$ mutant with a single amino acid substitution in a non-essential region to have the same utility, therapeutic applications, and other characteristics that the ’429 Patent identifies for wild-type $PH20_{1-447}$ and other sHASEGPs.[245]

2. Chao Provides Information Useful for Engineering the Changes to $PH20_{1-447}$ that the ’429 Patent Suggests

In 2011, a skilled artisan looking to implement the ’429 Patent’s suggestion to make a single-amino acid modification in a non-essential region of $PH20_{1-447}$

[243] EX1003, ¶¶ 206-208; EX1004, ¶ 32.

[244] EX1003, ¶¶ 207-208.

[245] EX1003, ¶¶ 199-202, 207, 222.

would have recognized such changes could best be accomplished using rational design, which here involves determining (i) which regions are non-essential in PH20, and (ii) which single amino acids to substitute into positions in those non-essential regions.[246]

The '429 Patent was written eight years before 2011. Given that, a skilled artisan would have looked for additional published insights into the structure of human hyaluronidase enzymes like PH20.[247] That would have led the person directly to Chao (EX1006), which reported an experimentally determined structure for human HYAL1, and provided new insights into the shared characteristics of human hyaluronidase enzymes.[248]

First, by superimposing the HYAL1 and bee venom hyaluronidase structures, Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues in it that interact with HA.[249]

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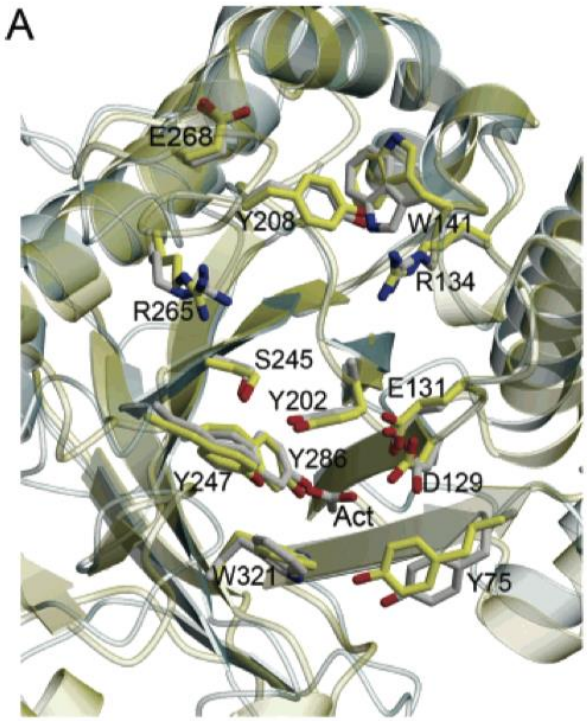
246 EX1003, ¶¶ 213-14.

247 EX1003, ¶¶ 86, 209; EX1004, ¶ 88.

248 EX1003, ¶¶ 86, 209-11; EX1004, ¶ 88; EX1006, 6912-17.

249 EX1006, 6917 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1004, ¶¶ 89-91; EX1003, ¶¶ 81-82.



The ’429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20,[250] and taught that hyaluronidase domains share similarity among and between species, including residues necessary for enzymatic activity.[251]

Second, using an alignment of five human hyaluronidases, Chao identified predicted secondary structures (*e.g.*, β-sheets, α-helices) (Figure 3, below), as well as invariant conserved positions (blue), residues involved in catalysis (red),

[250] EX1005, 4:12-22, 86:49-53, 88:14-24.

[251] EX1005, 2:6-67, 4:11-22.

conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).[252]

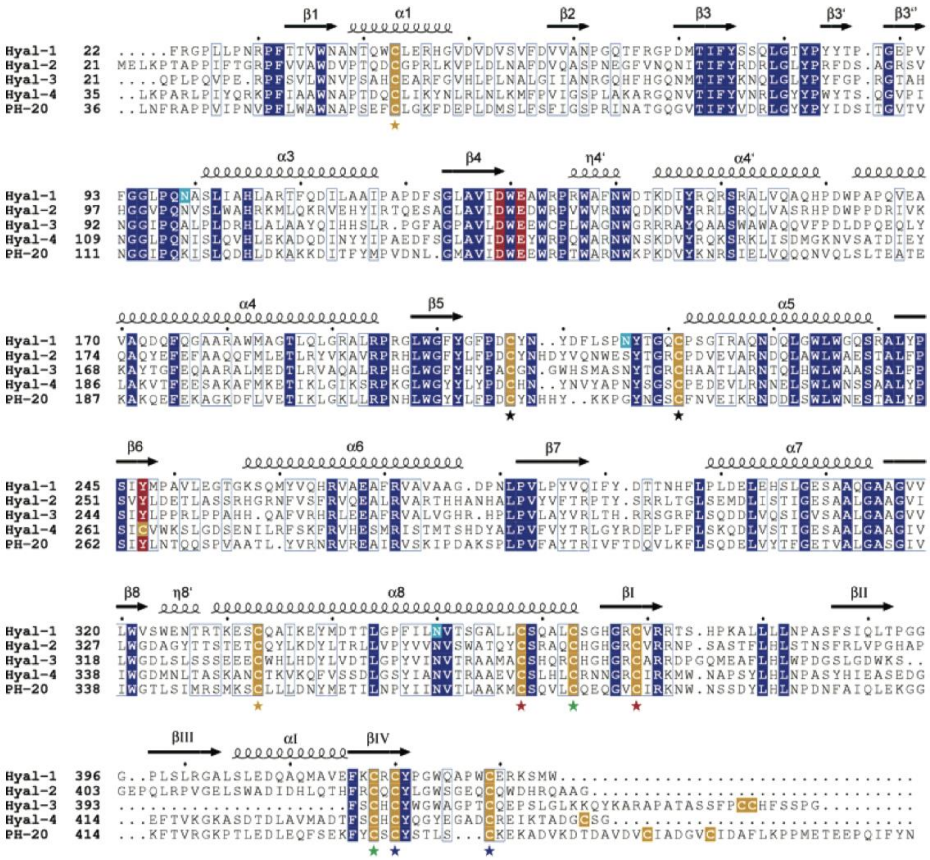


FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative replacements are blocked in blue. Pairs of cysteine residues that form disulfide bonds are indicated by stars with matching colors. Secondary structure units are labeled as in Figure 2B.

Third, Chao reported the presence of "a novel, EGF-like domain" in the C-terminal region of human hyaluronidases that was "closely associated" with the

252 EX1006, 6916; EX1003, ¶ 83; EX1004, ¶ 92.

catalytic domain (discussed above, § V.A.1.b.iii), and identified a characteristic pattern for the Hyal-EGF domain in PH20 at positions 337-409.[253]

3. A Skilled Artisan Would Have Identified Position 324 as Being in a Non-Essential Region of $PH20_{1-447}$ in 2011

To implement the '429 Patent's suggestion to produce modified $PH20_{1-447}$ polypeptides with single amino acid substitutions in non-essential regions that retain hyaluronidase activity, the skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011.[254] The person would have done that using conventional sequence alignment tools in conjunction with the information in the '429 Patent and in Chao, as well as information publicly known in 2011.[255]

A multiple-sequence alignment identifies non-essential regions in PH20—they are the sequences between essential residues and are positions at which variations occur at a frequency above ~5% (illustrated using Chao below).[256]

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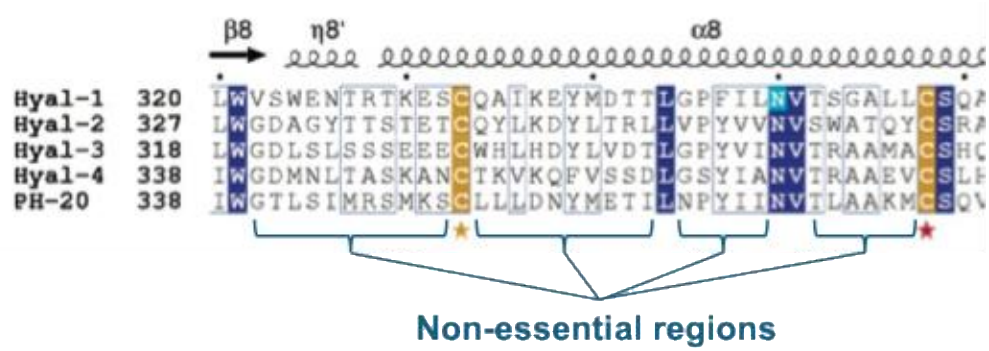
253 EX1006, 6911; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84-85.

254 EX1003, ¶¶ 212-214; EX1004, ¶¶ 22, 25-30, Appendix D-3.

255 EX1003, ¶¶ 20-21, 213-215; EX1004, ¶¶ 22-24; EX1017, 224-26.

256 EX1004, ¶¶ 31-32, Appendix D-2; EX1003, ¶ 215; EX1006, 6916.

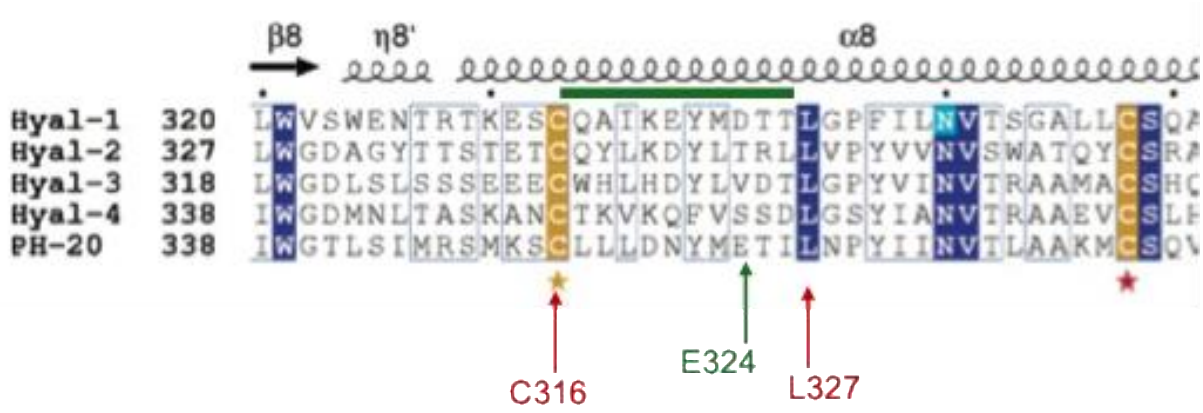


Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps. He first identified 88 homologous hyaluronidase protein sequences that had been published by December 29, 2011.[257] Dr. Park then prepared a multiple-sequence alignment of the 88 homologous proteins, similar to what Chao did with the five human hyaluronidases, and from that alignment identified essential (Appendix D-3) and non-essential (Appendix D-2) residues.[258]

[257] EX1004, ¶¶ 27, 155-158; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

[258] EX1004, ¶¶ 28-32, 159-160, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

Position 324 is within a non-essential region of $PH20_{1-447}$, which is shown by Dr. Park's analysis, and also by Chao's Figure 3; both report the same bounding essential residues (*i.e.*, C316 and L327) (below).[259]



Following the guidance and information in the '429 Patent and Chao, and assessing information publicly available in December 2011 using conventional sequence analysis tools, a skilled artisan would have readily identified position 324 as a position within a non-essential region $PH20_{1-447}$.[260]

4. A Skilled Artisan Would Have Viewed Aspartic Acid, Asparagine, or Arginine as Obvious Single Amino Acid Substitutions for Glutamic Acid at Position 324 of $PH20_{1-447}$

The multiple-sequence alignment reveals a second powerful insight: it identifies ***which*** amino acids have been tolerated at specific positions in the amino

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[259] EX1003, ¶ 217; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.

[260] EX1003, ¶ 220; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

acid sequence of homologous, stable and active, naturally occurring hyaluronidase enzymes.[261] This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms those variations in the sequences of a protein that do not yield stable and active forms of the protein.[262]

Using a multiple-sequence alignment, a skilled artisan can readily compile a list of amino acids tolerated at positions within non-essential regions of PH20.[263] Dr. Park did this: using his multiple-sequence alignment of the 88 hyaluronidase proteins known by December 2011, he identified the different amino acids that occur at positions corresponding to position 324 in PH20 in homologous hyaluronidases, and how many proteins contain each residue (below).[264]

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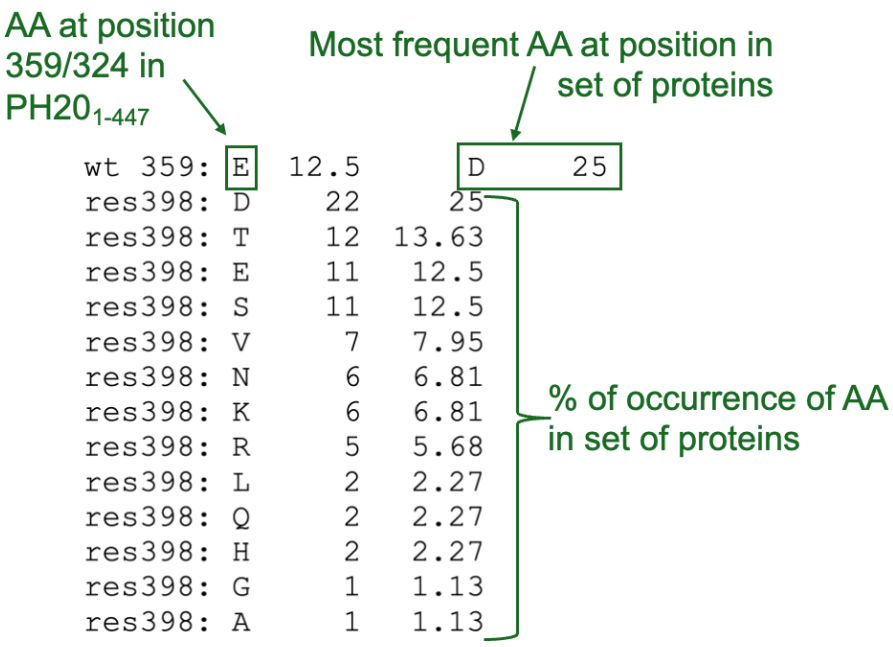
261 EX1003, ¶¶ 20, 49, 214, 218, 220; EX1004, ¶¶ 21-22.

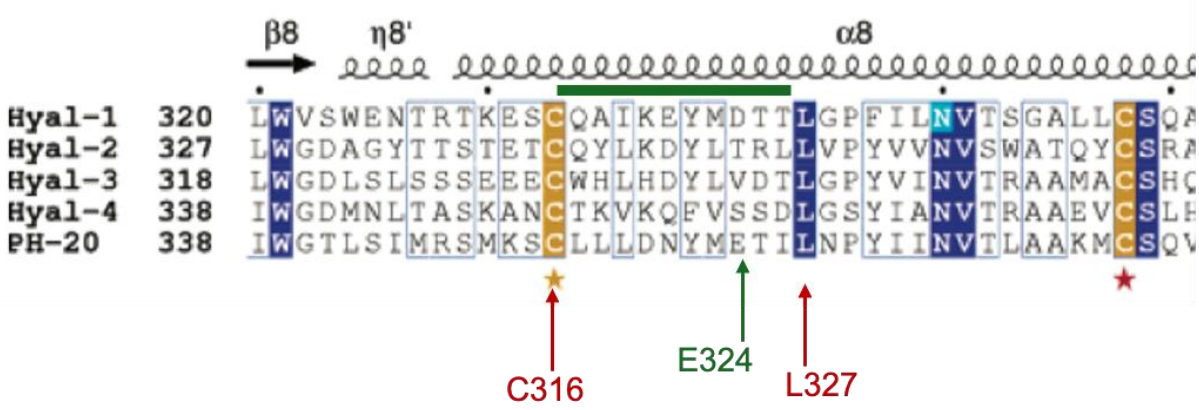
262 EX1003, ¶¶ 20, 214; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 ("Evolution provides a tremendously useful model for protein design. … By considering the common features of the sequences of these proteins, it is possible to deduce the key elements that determine protein structure and function—even in absence of any explicit structural information."); EX1014, 351.

263 EX1003, ¶¶ 218, 220; EX1004, ¶¶ 21-22.

264 EX1004, ¶¶ 30-32, 41-43, 106, 113, Appendix D-1; EX1003, ¶ 218.



Glutamic acid (E) occurs in 12.5% of the homologous proteins (including PH20). Aspartic acid (D) is the most prevalent amino acid at this position (*i.e.*, 22 hyaluronidase proteins (25%), including human HYAL1 protein as shown in Chao, below).[265] Asparagine (N) and arginine (R) appear in many homologous proteins (*i.e.*, 6 and 5, respectively).



[265] EX1006, 6916, Fig. 3.

When considering options for single amino acid substitutions in non-essential regions of $PH20_{1-447}$ pursuant to the guidance in the '429 Patent, skilled artisans would have considered position 324 and the amino acids that are tolerated at this position. That would have led the skilled artisan to select aspartic acid (D), asparagine (N), or arginine (R) as obvious choices for position 324 in $PH20_{1-447}$.[266]

First, each of the three amino acids is found in many homologous, enzymatically active hyaluronidase proteins at positions corresponding to 324 in PH20, which would have led a skilled artisan to expect that each would be tolerated as a single amino acid substitution at position 324 in $PH20_{1-447}$.[267]

Second, many different amino acids occur in homologous hyaluronidase enzymes corresponding to position 324 in PH20: there are 13 different amino acids found at that position in the 88 proteins.[268] Those amino acids also have widely varying characteristics (*e.g.*, polar, non-polar, charged, neutral, and of varying size).[269] This would have suggested to the skilled artisan that many different amino acids can be tolerated at position 324 in PH20, including amino acids with

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266 EX1003, ¶¶ 214, 218-22; EX1004, ¶¶ 41-42, 106.

267 EX1003, ¶¶ 218-220; EX1004, ¶¶ 43, 106, 113.

268 EX1004, ¶ 106.

269 EX1003, ¶ 219; EX1004, ¶ 106.

low helix propensity.[270] Moreover, as aspartic acid, asparagine, and arginine are (like glutamic acid) hydrophilic, a skilled artisan would have expected each to be tolerated in the environment around position 324 in PH20.[271]

Third, the ’429 Patent expressly identifies aspartic acid as a conservative amino acid substitution for glutamic acid in its Table 1.[272] A skilled artisan would have understood the ’429 Patent to be specifically suggesting replacing glutamic acid residues in non-essential positions in PH20 (such as at position 324) with aspartic acid residues.[273]

For all these reasons, a skilled person would have found aspartic acid, asparagine, and arginine to be obvious choices for a single amino acid substitution for glutamic acid at position 324 in $PH20_{1-447}$.[274]

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270 EX1004, ¶¶ 21, 106, 109; EX1003, ¶¶ 232-233.

271 EX1003, ¶ 220; EX1004, ¶¶ 32, 110, 116, 124, 132.

272 EX1005, 16:7-36.

273 EX1003, ¶¶ 208, 220.

274 EX1003, ¶¶ 217-220.

5. A Skilled Artisan Would Have Reasonably Expected the E324D, E324N, and E324R Substitutions in $PH20_{1-447}$ to Yield Enzymatically Active PH20 Proteins

a) Patent Owner Cannot Contradict Its Past Representations to the PTO

Replacing the glutamic acid at position 324 with aspartic acid, asparagine, or arginine yields a $PH20_{1-447}$ with a single amino acid substitution in a non-essential region of the polypeptide.[275] In its '429 Patent, Patentee stated:

> Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.[276]

Patentee also secured claims in the '429 patent to modified $PH20_{1-447}$ proteins with at least one substitution (*e.g.*, claim 1), despite not providing examples of PH20 proteins with any substitutions. Patentee, thus, made and relied on its statements that a skilled artisan would have expected ***any*** single amino acid substitution in ***any*** non-essential position of $PH20_{1-447}$ to not substantially affect the activity of the enzyme, and particularly ones in Table 1. Patentee should not be permitted to now contend a skilled artisan would not have reasonably expected that

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[275] *See* § VI.B.3; EX1003, ¶¶ 217-218; EX1004, ¶ 32.

[276] EX1005, 16:17-20.

the E324D, E324N, or E324R substitutions in $PH20_{1-447}$ would yield an enzyme with substantially the same activity as unmodified $PH20_{1-447}$.

b) Skilled Artisans Would Reasonably Expect E324D, E324N, and E324R to be Tolerated in $PH20_{1-447}$

Independently, a skilled artisan would have reasonably expected the E324D, E324N, and E324R substitutions to not substantially alter the biological activity (hyaluronidase activity) of $PH20_{1-447}$. Both experts noted that many naturally occurring homologous hyaluronidase proteins contain aspartic acid, asparagine, or arginine at positions corresponding to position 324 in PH20 (including aspartic acid in human HYAL1 (Chao)), which suggests each would be tolerated at position 324 in PH20.[277] Aspartic acid, asparagine, and arginine also are hydrophilic (like glutamic acid) and would be expected to be compatible with the environment of position 324.[278] A skilled artisan thus would have reasonably expected the E324D, E324N, and E324R substitutions would be tolerated in $PH20_{1-447}$.[279]

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277 EX1003, ¶ 218; EX1004, ¶¶ 106, 113.

278 EX1003, ¶ 220; EX1004, ¶ 110, 116, 124, 132; EX1077, 1325; EX1076, 1650-52; EX1078, 2-3.

279 EX1003, ¶¶ 221-222.

c) A PH20 Structural Model Confirms that $PH20_{1-447}$ Would Tolerate Aspartic Acid, Asparagine, and Arginine at 324

Dr. Park assessed whether single amino acid substitutions in $PH20_{1-447}$ would be tolerated, including E324D, E324N, and E324R, using a PH20 protein structural model generated by SWISS-MODEL using Chao's HYAL1 structure as the template, as would have been done in 2011 by a skilled artisan.[280]

Dr. Park explains that his PH20 model was reliable in the region of position 324 of PH20 based on QMEAN values,[281] and would be very similar to a PH20 model generated by SWISS-MODEL in 2011 (*e.g.*, it used 165 conserved positions in the backbone of the two proteins).[282]

Dr. Park also devised a consistent, objective methodology for assessing substitutions using the $PH20_{1-447}$ model.[283] Factors he considered included, *inter*

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[280] EX1004, ¶¶ 39-40, 161-62; EX1003, ¶¶ 225, 227; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

[281] EX1004, ¶¶ 163-65 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

[282] EX1004, ¶¶ 166-67, 171; EX1038, 3382-4; EX1017, 229-230; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

[283] EX1004, ¶¶ 102-103; *see generally id.* at § IV.C (description of Dr. Park's methodology).

alia, the number of neighboring residues at position 324 (*i.e.*, those within 5 Å), the various possible interactions between neighbors (*e.g.*, hydrophobic, charged, van der Walls, steric, etc.), and solvent accessibility.[284] Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*, hydrophobic-hydrophilic, effects on secondary structures, size related issues such as steric clashes or creation/filling of "holes" in the structure).[285]

Dr. Park assessed the environment of position 324 visually by comparing the wild-type with the version incorporating substituted amino acids at position 324 using functionality within the viewer (PyMol) and as a modeled sequence generated from the $PH20_{1-447}$ sequence incorporating the single substitution in SWISS-MODEL.[286] These technologies were available in 2011.[287] He used his methodology to assess substitutions representing diverse interactions, and

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[284] EX1004, ¶¶ 44-47, 53-60, 65-85, Appendix D-5; EX1035, 1408, Table 2; EX1043, 2, Table 1.

[285] EX1004, ¶¶ 62-63, 85.

[286] EX1004, ¶¶ 61, 107, 112, 120, 128, 136, 176-78; EX1003, ¶¶ 22, 49, 225, 227.

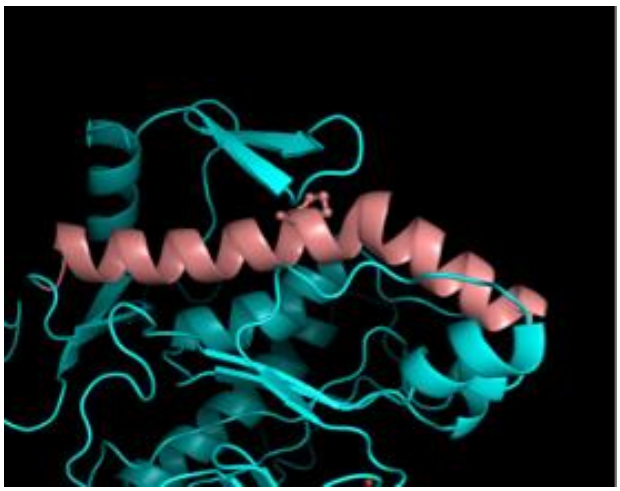
[287] EX1004, ¶¶ 161, 166-67, 175, 177-79; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4.

confirmed it provided a consistent, objective and unbiased evaluation of substitutions.[288]

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed (below).[289]

Score	***Expected Impact***	***Expected Toleration***
1	Significantly Destabilized	Likely Not Tolerated
2	Neutral or Minor Impacts	Tolerated
3	Improved Stability	Tolerated

Initially, Dr. Park's model shows there is a "kink" in the α8 helix structure of PH20 near position 324, which is due to the proline at position 329 (below).[290]



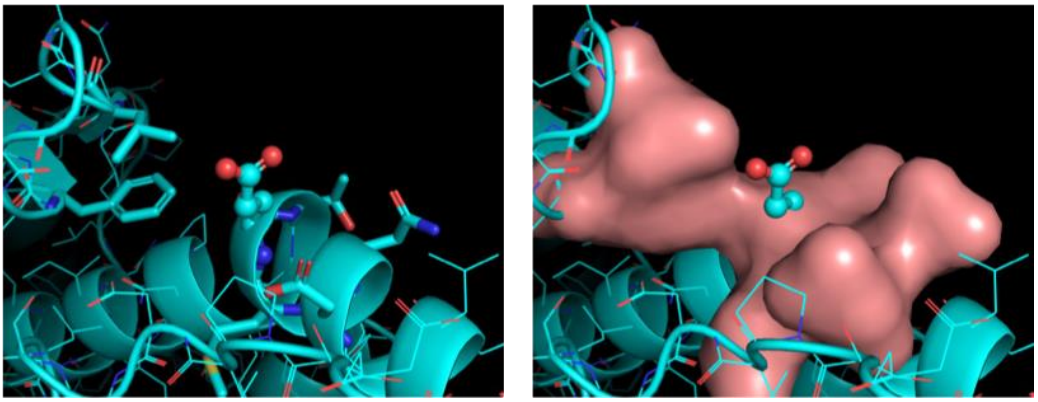
[288] EX1004, ¶¶ 102-103.

[289] EX1004, ¶¶ 85-87.

[290] EX1004, ¶ 109; EX1003, ¶ 231.

Proline residues were known to disrupt α-helix structures, and the disruption caused by P329 makes position 324 more accommodating of residues with a low helix propensity, as shown by the diverse amino acids found at this position in homologous proteins.[291]

Dr. Park's model also shows that the glutamic acid at position 324 in the wild-type PH20 is solvent exposed (below).[292] Because aspartic acid, asparagine, and arginine are hydrophilic amino acids, a skilled artisan would have viewed each as being compatible with this solvent-exposed environment.[293]



Dr. Park's model also shows that the position 324 residue in PH20 functions to sterically shield the phenylalanine (F) residue at position 380 from solvent.[294]

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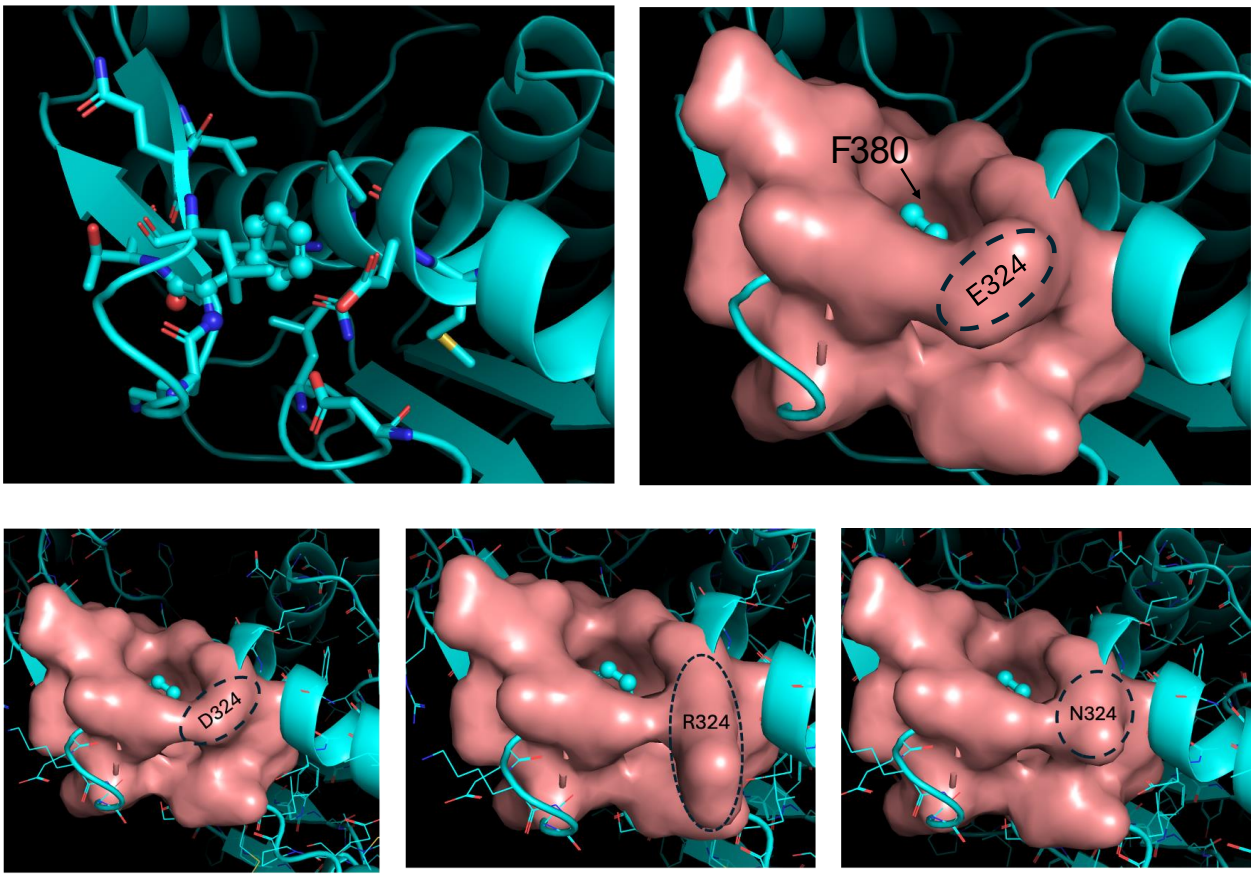
[291] EX1003, ¶ 232; EX1004, ¶¶ 106, 109.

[292] EX1004, ¶ 110.

[293] EX1004, ¶¶ 110, 116, 124, 132; EX1003, ¶¶ 230, 233.

[294] EX1004, ¶ 111; EX1003, ¶ 233.

Modeling of the E324D, E324N, and E324R mutants shows that each substitution yields a PH20 structure that comparably shields F380 from solvent via steric effects.[295] The comparable roles of E324 and the three substitutions are illustrated below, and reinforces that each substitution would be expected to be tolerated in $PH20_{1-447}$ as a single amino acid substitution.[296]



[295] EX1004, ¶¶ 117, 125, 134; EX1003, ¶¶ 233-234.

[296] EX1004, ¶¶ 117, 121, 125, 129, 134, 137; EX1003, ¶¶ 233-234, 236.

Dr. Park also found that substitutions at position 324 could introduce additional beneficial interactions in PH20. For example, the E324N substitution could avoid a repulsion of negative charges between positions 324 and 320 and introduce hydrogen bonding between those residues.[297] Additionally, the E324R substitution can introduce a salt bridge and stabilizing hydrogen bond interactions between positions 324 and 320.[298]

After analyzing each of the three single substitutions in PH20, Dr. Park assigned a score of 2 for the E324D and E324N substitutions in $PH20_{1-447}$ and a score of 3 for the E324R substitution, indicating that each would not be expected to significantly reduce the stability of the protein.[299]

Dr. Park's visualization-based assessment is a technique that was prevalent in 2011.[300] Similarly, his technique of assessing interactions between neighbors

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297 EX1004, ¶ 126.

298 EX1004, ¶ 133.

299 EX1004, ¶¶ 121, 129, 137, Appendix C.

300 EX1017, 228 ("… a structural biologist's intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field.

and assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications.[301]

Dr. Hecht reviewed Dr. Park's analysis and conclusions concerning the three single substitutions and agreed with each.[302] Through his own assessment of Dr. Park's PH20 models, Dr. Hecht concluded that aspartic acid, asparagine, and arginine each would have likely been tolerated at position 324 as a single substitution in $PH20_{1-447}$, as noted above.[303]

The common disclosure defines an "active mutant" as a modified PH20 polypeptide with at least ~40% of the activity of unmodified $PH20_{1-447}$.[304] Drs. Hecht and Park each independently concluded that the E324D, E324N, and E324R substitutions would have been tolerated by $PH20_{1-447}$, meaning each would exhibit comparable hyaluronidase activity to unmodified $PH20_{1-447}$ (*i.e.*, activity well

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Visualization of the known reference structure is a key component of this."); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 22, 49, 225, 227.

301 EX1004, ¶¶ 48-52; EX1031, 459, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 227.

302 EX1003, ¶ 229.

303 EX1003, ¶¶ 230-234.

304 EX1001, 75:49-54; *also id.* at 79:31-35.

above 40%).[305] A skilled artisan considering the E324D, E324N, and E324R substitutions in $PH20_{1-447}$ would have reasonably expected that both would exhibit at least 40% of the activity of unmodified $PH20_{1-447}$.[306]

Based on the '429 Patent, Chao, and information available in 2011, the E324D, E324N, and E324R $PH20_{1-447}$ mutant polypeptides would have been obvious to a skilled artisan in 2011. And because claims 1-2, 6-15, and 25-26 each encompass one or more of these single-replacement mutants, each claim is unpatentable.

C. Dependent Claims 5, 16-24, and 27-35 Are Obvious

For the reasons below, each of claims 1-2, 6-15, and 25-26 defines subject matter that would have been obvious to a skilled artisan.

1. Claims 5 and 16

Claims 5 and 16 require the modified PH20 polypeptide to be "a soluble PH20 polypeptide" and, in the case of claim 16, "C-terminally truncated."

The '429 Patent indicates that $PH20_{1-447}$ exists as a soluble form of the PH20 protein because it omits the C-terminal residues above position 448 (483)

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[305] EX1003, ¶¶ 229-234, 236; EX1004, ¶¶ 121, 129, 137.

[306] EX1003, ¶ 236.

containing the GPI anchor sequence.[307] A skilled artisan would have expected that changing glutamic acid (E) to aspartic acid, asparagine, or arginine at position 324 would not affect the solubility of $PH20_{1-447}$ as it would not meaningfully alter the overall structure of the protein.[308]

2. Claims 17-19

Claims 17-19 require the modified PH20 polypeptide to "comprise[] one or more post-translational modifications" including glycosylation (claims 17-18) and be a "glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues" (19).

The '429 Patent teaches (i) that human PH20 must be glycosylated to exhibit activity, and (ii) expression of $PH20_{1-447}$ in mammalian (CHO) host cells that yield active forms of $PH20_{1-447}$.[309] It further teaches that "N- and O-linked glycans are attached to polypeptides through asparagine-N-acetyl-D-glucosamine … linkages," and claims PH20 polypeptides (including $PH20_{1-447}$) having asparagine-linked sugar moieties.[310] Frost reports that the recombinant production of $PH20_{1-447}$ in

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307 EX1005, 3:57-62; 87:52-88:24.

308 EX1003, ¶¶ 196, 203, 222.

309 EX1005, 95:13-30; 40:41-51, 89:53-91:67; 88:5-9.

310 EX1005, 3:27-35, claims 1, 6.

CHO cells "resulted in a 447 amino acid 61 kDA glycoprotein with a properly processed amino terminus and 6 N-linked glycosylation sites."[311]

Based on the '429 Patent and knowledge in the art, a skilled artisan would have found it obvious to produce E324D, E324N, or E324R $PH20_{1-447}$ in a CHO cell, and that doing so causes six N-linked glycosylation sites to be glycosylated.[312]

3. Claims 24, 27-33

Claim 24 specifies a pharmaceutical composition comprising any modified PH20 polypeptide in the genus of claim 1. Claims 27-30 add a "therapeutically active agent formulated in the same composition or in a separate composition" (27), and that the active agent may be a "drug" (28) or "chemotherapeutic agent" (29) or "antibody" (30).

Claims 31-33 concern methods of treating "hyaluronan-associated disease" (30) such as cancer (31) or a "solid tumor" by administering any of the modified PH20 polypeptides captured by claim 1.

The '429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*, $PH20_{1-447}$), alone or in combination with other therapeutic agents including

311 EX1013, 432.

312 EX1003, ¶¶ 197-98, 203-04.

antibodies, small molecule drugs, chemotherapeutics, and agents used in treating cancer and hyaluronan-associated disease.[313] It similarly describes and claims methods of administering them subcutaneously via formulations that combine an enzymatically active hyaluronidase protein with another therapeutic agent, which together enable "spreading" of the therapeutic agent after injection.[314]

A skilled artisan would have appreciated that a single-replacement $PH20_{1-447}$ polypeptide with comparable hyaluronidase activity to $PH20_{1-447}$ (such as the E324D mutant) would be equivalently useful in the therapeutic compositions, methods of administration, and methods of treatment described in the '429 Patent for $PH20_{1-447}$.[315] Indeed, in the '429 Patent, Patentee secured claims encompassing pharmaceutical compositions containing certain modified PH20 polypeptides and chemotherapeutic agents despite the absence of any exemplification.[316] Claims 24 and 27-33 also impose no restrictions on the makeup of the pharmaceutical

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313 EX1005, 8:60-9:4, 54:40-55:35, 56:28-57:21, 55:61-56:9, 56:66-57:21, 63:41-44, 73:4-74:29, claims 14, 29, 33.

314 EX1005, 8:25-38, 56:28-56, 57:22-36, 58:59-59:12, 63:40-64:4, 76:18-77:37, claim 27.

315 EX1003, ¶¶ 199-202, 207, 221-22, 236.

316 EX1005, claims 29, 30, 50.

composition. A skilled artisan would have found such compositions and methods of administration/treatment to have been obvious from the '429 Patent.[317]

4. Claims 20-23, 34-35

Claims 20-21 and 34-35 concern conjugation of a modified PH20 polypeptide to (i) a polymer (claim 20) that may be polyethylene glycol (claim 21), (ii) a moiety such as a toxin, drug, label, or multimerization domain (claim 34) or (iii) an Fc domain (claim 35). Claim 22 specifies the modified PH20 polypeptide further comprises a heterologous signal sequence, while claim 23 specifies a chimeric peptide comprising the modified PH20 polypeptides of claim 1.

A skilled artisan would have found these further modifications to the E324D, E324N, or E324R $PH20_{1-447}$ mutants obvious from the '429 Patent.[318] The '429 Patent teaches $PH20_{1-447}$ proteins with mutations ("sHASEPGs") can be (i) "modif[ied]" "with polymers such as polyethylene glycol";[319] (ii) conjugated to "one or more targeting agents" (*e.g.*, any moiety that specifically binds to a

317 EX1003, ¶¶ 199-202, 207.

318 EX1003, ¶¶ 203, 205.

319 EX1005, 3:64-4:1, 4:45-53, 26:20-28:4.

receptor);[320] (iii) attached to a label;[321] and (iv) incorporated into fusion (*i.e.*, "chimeric") proteins.[322] It also teaches expression of modified PH20 polypeptides that incorporate a heterologous signal sequence.[323]

D. There Is No Nexus Between the Claims and Any Evidence of Putative Secondary Indicia

Well-established law holds that evidence of secondary indicia cannot support non-obviousness if it does not have nexus to the claims. A key question in a nexus analysis is whether such evidence is commensurate with the scope of the claims. The answer here is a definitive no.

Patentee is likely to dispute that the E324D, E324N, and E324R $PH20_{1-447}$ substitutions are obvious. For example, Patentee may contend the E324R variant has unexpectedly high hyaluronidase activity as a single substitution mutant. Demonstrating that result for one mutant out of the ~10^{59} and 10^{112} modified PH20 polypeptides encompassed by the claims, however, utterly fails to establish a nexus between that evidence and the claims. Such an argument also is inapplicable to the

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320 EX1005, 18:33-52.

321 EX1005, 38:40-49, 40:15-21.

322 EX1005, 18:33-52, 47:10-22, 51:25-30.

323 EX1005, 34:33-37; 88:28-90:15 ("Kappa leader sequence" used in expression of PH20 polypeptides).

E324D and E324N mutants, which exhibit only modestly increased activity (*i.e.*, ~115% and 101% of unmodified PH20).[324] As explained in § V.A.1, the single-substitution E324D, E324N, and E324R $PH20_{1-447}$ mutants are not representative of the numerous, structurally different proteins encompassed by the claims, particularly those expected to be inactive. No evidence or explanation is provided in the common disclosure that resolves this confusion.

If Patentee advances evidence or arguments concerning nexus, consideration of that issue should be deferred until after institution, and Petitioner reserves its right to contest such evidence.

VII. The Board Should Not Exercise Its Discretion Under § 324(a) or § 325(d)

No litigation involving the '520 Patent is pending, making discretionary denial unwarranted under the factors in *Apple Inc. v. Fintiv, Inc.,* IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020).

The examination record also does not warrant the Board exercising its discretion to not institute. As explained in § IV.C, no obviousness rejections were raised during prosecution.[325] The present obviousness grounds also rely on Chao (EX1006), which was not cited or considered during examination, and are

[324] EX1001, Table 9, column 231.

[325] EX1002, 481-86.

supported by evidence not available to the Examiner (*e.g.*, expert testimony of Drs. Hecht and Park).

Also, while certain indefiniteness and improper dependency rejections were imposed and overcome by claim amendments,[326] the Examiner erred by not rejecting the claims for lack of written description and non-enablement. *See* §§ V.A and V.B.

There is no proper basis for the Board to exercise its discretion to not institute trial.

VIII. CONCLUSION

For the foregoing reasons, the challenged claims are unpatentable.

Dated: January 17, 2025

Respectfully Submitted,

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[326] EX1002, 481-83, 563-64.

EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,110,520
1002	File History of U.S. Patent No. 12,110,520
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Brandon & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '520 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," Methods in Enzymology, 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," Protein Eng'g & Design, Ch. 10, 223-237 (2010)
1018	Chica et al., "Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design," Curr. Opin. Biotechnol., (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," Reprod., 127:325-334 (2004)
1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," Am. J. Reprod. Immunol., (3):174-82 (2002)
1021	Baba et al., "Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg," J. Biol. Chem., 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," Biol Reprod., 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 56(5):1133-41 (1997)
1024	Rosengren et al., "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects," BioDrugs, 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	[Reserved]
1028	[Reserved]
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," FEBS Letters, 3:545-548 (1993)

No.	Exhibit Description
1030	Sills, "Retraction," Science, 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," J. Mol. Biol., 353:459-473 (2005)
1032	Wang & Moult, "SNPs, Protein Structure, and Disease," Hum. Mutation, 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," Structure, 8:1025-1035 (2000)
1034	"Negative Results," Nature: Editorials, 453:258 (2008)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," Protein Sci., 12:1406-1417 (2003)
1036	Hayden, "Chemistry: Designer Debacle," Nature, 453:275-278 (2008)
1037	Benkert et al., "Toward the Estimation of the Absolute Quality of Individual Protein Structure Models," Bioinformatics, 27:343-350 (2010)
1038	Schwede et al., "SWISS-MODEL: An Automated Protein Homology-Modeling Server," Nucleic Acids Rsch., 31:3381-3385 (2003)
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007).
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," PNAS, 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," PNAS, 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," Nature Comm., 14 (2023)
1043	Sievers et al., "Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega," Molecular Sys. Biology, 7.1 (2011)
1044	Mihel, "PSAIA – Protein Structure and Interaction Analyzer," BMC Structural Biology, 8:21 (2008)

No.	Exhibit Description
1045	Redline Comparison of the ’731 and ’520 Specifications
1046	Beasley & Hecht, “Protein Design: The Choice of *de Novo* Sequences,” J. Biological Chemistry, 272:2031-2034 (1997)
1047	Xiong et al., “Periodicity of Polar and Nonpolar Amino Acids is the Major Determinant of Secondary Structure in Self-Assembling Oligomeric Peptides,” PNAS, 92: 6349-6353 (1995)
1048	Hayden, “Key Protein-Design Papers Challenged,” Nature, 461:859 (2009)
1049	KEGG, *DRUG: Hyaluronidase (human recombinant)*, available at: https://www.genome.jp/entry/D06604
1050	Pace & Scholtz, “A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins,” Biophysical J. 75:422-427 (1998)
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
1057	Ph20_pre2011.aln-clustal_num
1058	Ph20_pre2011 Alignment html
1059	Leisola & Turunen, “Protein Engineering: Opportunities and Challenges,” Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	Hecht et al., “De Novo Proteins from Designed Combinatorial Libraries,” Protein Sci., 13:1711-1723 (2004)
1061	Rosengren et al., “Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration,” AAPS J., 17:1144-1156 (2015)
1062	[Reserved]
1063	[Reserved]

No.	Exhibit Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with E324D Mutation
1071	Swiss Model Printout of PH20 Model with E324N Mutation
1072	Swiss Model Printout of PH20 Model with E324R Mutation
1073	Swiss Model Printout of PH20 Model with E324A Mutation
1074	Swiss Model Printout of PH20 Model with E324H Mutation
1075	Swiss Model Printout of PH20 Model with E324S Mutation

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,635 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

Dated: January 17, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 17th day of January, 2025, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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Paper No. 1
Filed: December 27, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00009
U.S. Patent No. 12,123,035

PETITION FOR POST GRANT REVIEW

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Statutes

I. Introduction

Petitioner Merck Sharp & Dohme LLC ("Merck") requests post grant review of claims 1-34 of U.S. Patent No. 12,123,035 ("'035 Patent").

The '035 Patent claims are unpatentable for three independent reasons.

The first two are linked to the extreme breadth of the claims, which, due to their unconstrained language, encompass between 10^{59} and 10^{112} different enzymatically active human hyaluronidase ("PH20") polypeptides. Each defines a genus of PH20 polypeptides that (i) ***must have one*** amino acid substitution at position 312, and (ii) ***may have*** between 20 and 41 additional substitutions at ***any*** of 430+ positions, and to ***any*** of 19 other amino acids. The scale of these genera is unfathomable. A collection of one molecule of each polypeptide in the smallest genus exceeds the weight of the Earth, and practicing the full scope of the narrowest claimed genus would require many lifetimes of "making and testing" using the patent's methodology.

These immensely broad claims, measured against the common disclosure of the '035 Patent and its ultimate parent '731 Application,[1] utterly fail the written description and enablement requirements of § 112(a). That renders every claim of the '035 Patent unpatentable. It also precludes the claims from a valid § 120

[1] 13/694,731 ('731 Application) (EX1026).

benefit claim to the ’731 Application, the only non-provisional application filed before March 16, 2013, thus making the ’035 Patent PGR eligible.

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by the enzymatically active, multiply-modified PH20 polypeptides within each claimed genus. The disclosed examples also are not representative of those structurally diverse genera: each has only ***one*** amino acid substitution in ***one*** PH20 sequence (1-447), while the claims encompass PH20 proteins with myriad ***undescribed*** combinations of 5, 10, 15, or 20+ substitutions anywhere within PH20 sequences of varying length. The claims even capture mutated PH20 polypeptides the disclosure says to avoid (*e.g.*, $PH20_{1\text{-}447}$ mutants rendered inactive by a single substitution, inactive truncated forms). The disclosure is nothing more than a research plan, lacking any blaze marks, and does not describe the claimed genera.

Regarding enablement, the common disclosure has equally fatal problems: it identifies ***no*** enzymatically active modified PH20 with 2 or more substitutions, much less affirmatively guides the selection of ***which*** combinations of substitutions yield such enzymes. The only disclosed process for making such multiply-substituted PH20 mutants is a prophetic, one that requires iterative “trial-and-error discovery” experiments the Supreme Court found incapable of enabling a

much smaller genus of polypeptides.[2] And practicing the full scope of the claims requires scientists to repeat this "make-and-test" methodology innumerable times until they had made and tested between 10^{59} and 10^{112} unique proteins. That is far more than undue experimentation—it is impossible.

Finally, each of claims 1-2 and 5-34 are unpatentable each captures one or both of two obvious $PH20_{1-447}$ mutants that change a ***single*** amino acid—the serine at position 312— to either threonine ("S312T") or asparagine ("S312N"). But Patentee's '429 Patent (EX1005) directs artisans to make such single amino acid substitutions in non-essential regions of $PH20_{1-447}$ (and expressly claimed them). Skilled artisans implementing that guidance in 2011 would have found Chao (EX1006)—a 2007 paper ignored in the common disclosure and never cited to the Office. That artisan, from their knowledge and the collective teachings of Chao and the '429 Patent, would have (i) readily identified position 312 as being in a non-essential region of PH20, and (ii) found it obvious to change serine to threonine or asparagine at position 312. They also would have reasonably expected both mutants to retain enzymatic activity because that is what Patentee said in its '429 Patent ("Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not

[2] *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023).

substantially alter biological activity").[3] Because the claims capture these obvious species, they are unpatentable, along with the dependent claims.

The '035 Patent claims are unpatentable. The Board should institute trial.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the '035 Patent's issuance. Petitioner certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '035 Patent.

The '035 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

A patent is PGR eligible if it issued from an application filed after March 16, 2013 "if the patent contains … at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought." *See Inguran, LLC v. Premium Genetics (UK) Ltd.*, Case PGR2015-00017, Paper 8 at 16-17 (P.T.A.B. Dec. 22, 2015); *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17

[3] EX1005, 16:17-22.

at 8 (P.T.A.B. Jan. 29, 2016); *Collegium Pharm., Inc. v. Purdue Pharma L.P.*, 2021 WL 6340198, at *14-18 (P.T.A.B. Nov. 19, 2021) (same) *aff'd Purdue Pharma L.P. v. Collegium Pharm., Inc.*, 86 F.4th 1338, 1346 (Fed. Cir. 2023); *Intex Recreation Corp. v. Team Worldwide Corp.*, 2020 WL 2071543, at *26 (P.T.A.B. Apr. 29, 2020) (same).

Only one of the applications to which the '035 Patent claims benefit under 35 U.S.C. § 120 and/or § 121—U.S. Application No. 13/694,731 (the '731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011) and WO 01/3087 ("WO087"). The '731 Application, however, alters several passages of the provisional disclosures, adds new examples and tested mutants and makes other changes.[4]

The '731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '035 Patent (§§ V.A, V.B). The same is true for the '035 Patent, whose

[4] EX1026, 153:15-163:26, 324-34, 19:25-26, 28; EX1051; EX1052.

disclosure relative to the claims is generally identical to the '731 Application.[5] The '035 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the '731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

Merck Sharp & Dohme LLC is the real party-in-interest for this Petition.

2. Related Proceedings

PGR2025-00003, PGR2025-00004, and PGR2025-00006 are related proceedings.

3. Counsel and Service Information

Lead Counsel	Backup Counsel	Backup Counsel
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[5] The "common disclosure" refers to the shared disclosure of the '035 Patent and the '731 Application (EX1026). Citations are to the '035 Patent; EX1015 correlates citations to the '731 Application. The '035 Patent alters the classification of one mutant ("I083K" $PH20_{1-447}$) relative to the '731 Application. EX1045, 215; EX1068, ¶ 6.

Petitioner consents to service via e-mail at the email addresses listed above.

III. Grounds

The grounds advanced in this Petition are:

(a) Claims 1-34 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.

(b) Claims 1-34 are unpatentable under 35 U.S.C. § 112 as not being enabled.

(c) Claims 1-2 and 5-34 are unpatentable as obvious under 35 U.S.C. § 103 based on the '429 Patent (EX1005), Chao (EX1006) and knowledge held by a person of ordinary skill in the art.

Petitioner's grounds are supported by the evidence submitted with this Petition, including testimony from Dr. Michael Hecht (EX1003) and Dr. Sheldon Park (EX1004).

In this Petition, "PH20" refers to the human PH20 hyaluronidase protein. The full-length PH20 protein (SEQ ID NO: 6) includes a 35 amino acid signal sequence, which is absent in mature forms of PH20, yielding positional numbers that differ from SEQ ID NO: 6 by 35 residues.[6] The annotation "$PH20_{1\text{-}n}$" refers to

[6] EX1003, ¶ 15.

a sequence of 1-n residues in PH20 (*e.g.*, $PH20_{1-447}$ is SEQ ID NO: 3), and "AxxxB" is used to identify the position of a substitution (*e.g.*, "S312T").

IV. Background on the '035 Patent

A. Field of the Patent

The '035 Patent concerns the human PH20 hyaluronidase enzyme, and structurally altered forms of that protein that retain enzymatic activity.[7]

1. Protein Structures

Proteins are comprised of sequences of amino acids. A protein's activity, however, derives from its unique, three-dimensional shape—its structure.[8] That is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary structures and structural motifs, which are packed into compact domains that define the protein's overall structure (tertiary structure).[9]

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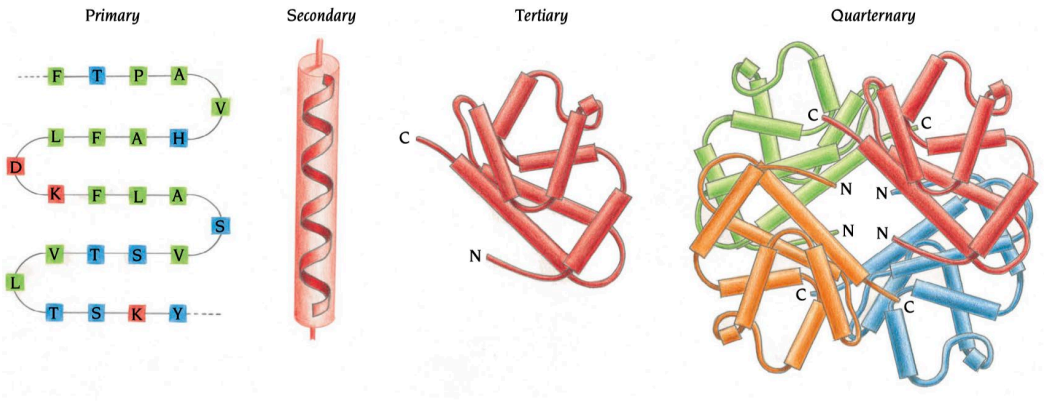
[7] EX1001, 4:16-20.

[8] EX1003, ¶ 36.

[9] EX1014, 3-4, 24-32, Figure 1.1; EX1039, 136-37 (Figure 3-11); EX1003, ¶¶ 36-40.



Secondary structures, such as α-helices or β-strands, are formed and stabilized by different but characteristic patterns of amino acids (below).[10]

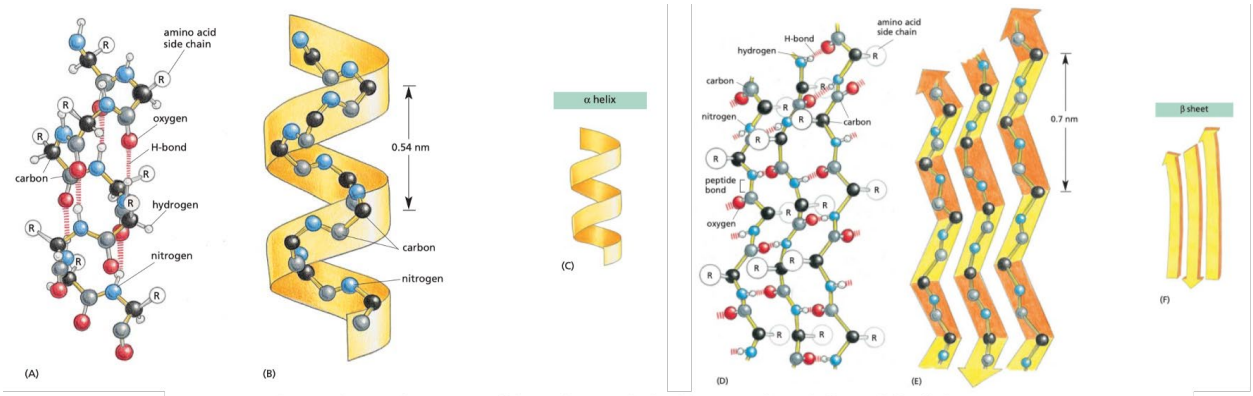


Figure 3–7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N–H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N–H groups point up in this diagram and that all of the C=O groups point down (toward the C-terminus); this gives a polarity to the helix, with the C-terminus having a partial negative and the N-terminus a partial positive charge. (D, E, and F) The β sheet. In this example, adjacent peptide chains run in opposite (antiparallel) directions. Hydrogen-bonding between peptide bonds in different strands holds the individual polypeptide chains (strands) together in a β sheet, and the amino acid side chains in each strand alternately project above and below the plane of the sheet. (A) and (D) show all the atoms in the polypeptide backbone, but the amino acid side chains are truncated and denoted by R. In contrast, (B) and (E) show the backbone atoms only, while (C) and (F) display the shorthand symbols that are used to represent the α helix and the β sheet in ribbon drawings of proteins (see Panel 3–2B).

[10] EX1039, 134; EX1014, 14-22, Figures 2.2, 2.5, Table 2.1; EX1047, 2031-32; EX1003, ¶¶ 40-43.

Intervening sequences between those characteristic sequences are important too; they direct and facilitate positioning and arrangement of the various secondary structures into structural motifs and the protein's tertiary structure.[11]

Changes to a protein's amino acid sequence can affect the folding, formation and stability of these various structures that define the protein's overall shape. For example, changing even a single residue known to be critical to the protein's structure or activity can render a protein inactive.[12]

Making many concurrent changes to a protein's sequence can cause myriad effects on the protein's structure, especially when they are in or affect the same region(s) of the protein.[13] For example, it can disrupt the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of secondary structures, and disrupt folding and positioning of the secondary structures and structural motifs into the protein's tertiary structure.[14] Multiple changes in different regions of the amino acid sequence also cause unfavorable

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11 EX1003, ¶¶ 44-46; EX1014, 21-22.

12 EX1003, ¶¶ 54, 150; EX1004, ¶¶ 20, 25.

13 EX1003, ¶ 158.

14 EX1003, ¶¶ 55-56, 142; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

spatial interactions that destabilize or impair folding.[15] Consequently, in 2011, predicting the effects of the myriad interactions that may be disrupted by multiple concurrent substitutions was beyond the capacity of skilled artisans and available computational tools.[16]

2. Hyaluronidase Enzymes

PH20 is one of five structurally similar hyaluronidases in humans and is homologous—evolutionarily related to—hyaluronidases in many species.[17] It breaks down hyaluronan ("HA") by selectively hydrolyzing glycosidic linkages.[18] PH20 exists naturally as a GPI anchored protein; deletion of its GPI-anchoring sequence yields a soluble, neutral active enzyme.[19]

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15 EX1003, ¶¶ 57-59.

16 EX1003, ¶¶ 50, 158, 190, 228; EX1004, ¶¶ 142-144.

17 EX1007, 10:18-30; EX1006, 6911, 6916 (Figure 3); EX1003, ¶¶ 33, 77.

18 EX1003, ¶ 77; EX1008, 819.

19 EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 89, 196; EX1029, 546, Figure 1.

Before 2011, many essential residues in PH20 were known. Several are in the shared catalytic site of the protein;[20] mutating certain residues in or near that site can abolish enzymatic activity.[21] Conserved cysteine residues that stabilize the protein structure are another example,[22] as are certain conserved asparagine residues involved in glycosylation.[23]

In 2007, Chao reported an experimentally determined structure of the human HYAL1 hyaluronidase, and used an alignment of the five human hyaluronidases to illustrate shared secondary structures and conserved residues in these proteins.[24] Among its findings was that human hyaluronidases contain a unique structure—the Hyal-EGF domain.[25] Using its sequence analysis, an earlier structure of bee

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20 EX1006, 6914-16, Figure 3; EX1007, 35:28-36:10; EX1011, 810-14; EX1008, 824-25; EX1009, 6912-17.

21 EX1011, 812-14; EX1010, 9435-39, Table 1.

22 EX1006, 6914-16, Figure 3; EX1011, 810-11; EX1005, 88:21-22.

23 EX1005, 7:9-27; EX1007, 36:12-20; EX1010, 9433, 9435-40.

24 EX1006, 6914-18.

25 EX1006, 6916-18; EX1010, 9439-40; EX1003, ¶¶ 84-86; EX1004, ¶¶ 97-99.

venom hyaluronidase and a computer model of the protein structures, Chao identified residues in the catalytic site that interact with HA.[26]

3. Protein Engineering

In 2011, skilled artisans used two general approaches to engineer changes into proteins.[27] In "rational design," skilled artisans employed computational tools—sequence alignments and protein structure models—to study the protein and then select where and what changes to introduce.[28] For example, a "multiple-sequence alignment" ("MSA")[29] produced by aligning known sequences of homologous, naturally occurring proteins identifies positions with no or little amino acid variation ("conserved" / "essential" residues) and positions where different amino acids occur ("non-conserved" / "non-essential" residues).[30] A

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[26] EX1006, 6912-13, 6916-18, Figures 2C, 4A; EX1033, 1028-29, 1035; EX1010, 9434, 9436, Figure 1.

[27] EX1003, ¶ 47.

[28] EX1016, 181-82; EX1017, 223, 236; EX1003, ¶¶ 48-50.

[29] EX1017, 224-27; EX1016, 181-86 (Figure 1); EX1003, ¶¶ 48-50; EX1004, ¶¶ 22-23, 29.

[30] EX1003, ¶¶ 213-14; EX1004, ¶¶ 21-22, 25, 30-31; EX1016, 181-84; EX1017, 224-25; EX1014, 351.

structural model using the protein's sequence but based on a known structure of a homologous protein enabled assessment of interactions between amino acids at a particular positions.[31] In 2011, using rational design techniques, a skilled artisan could assess, with varying effort, effects of changing one or a few amino acids, but could not use those techniques to predict the effects of many concurrent changes, given the escalating complexity of numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.[32]

"Directed evolution" techniques arose due to the limits of rational design.[33] They use "trial-and-error" experiments to find mutants with randomly distributed changes that exhibit desired properties, but require creation and screening of large libraries of mutants, each with one amino acid randomly changed at one position in its sequence.[34] Importantly, until a desired mutant is made, found and tested,

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31 EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶ 37, *also id.* 33-36; EX1003, ¶¶ 223, 225.

32 EX1003, ¶¶ 50, 158; EX1004, ¶¶ 142-144.

33 EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

34 EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

whether it exists and its sequence are unknown.[35] Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale of experimentation this approach requires.[36] The '035 Patent embodies this approach.[37]

B. Person of Ordinary Skill in the Art

While the '035 Patent claims priority to provisional applications dating to December 30, 2011 and benefit to the '731 Application (filed December 28, 2012), they are not supported as § 112(a) requires by those earlier-filed applications. *See* §§ II.A, V.A, V.B. Regardless, the prior art of the grounds was published before December 2011, and the obviousness grounds use that date to assess the knowledge and perspectives of the skilled artisan.

In 2011, a person of ordinary skill in the art would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production

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35 EX1003, ¶ 184.

36 EX1003, ¶¶ 52-53.

37 EX1003, ¶¶ 138, 173, 183, 186.

of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).[38]

C. Prosecution History

One Office action issued during examination of the '035 Patent. In it, the Examiner rejected certain dependent claims directed to post-translational modifications and conjugation for indefiniteness.[39] Patentee overcame each rejection by amending the claims as the Examiner suggested.[40]

D. The Challenged Claims

The terms used in the claims are either expressly defined in the common disclosure or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition. A clear understanding of the ***breadth*** of the claims, however, is important to assessing the grounds. Specifically, each claim captures a massive genus of structurally distinct

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[38] EX1003, ¶ 13.

[39] EX1002, 465-67.

[40] EX1002, 538-41.

mutant PH20 polypeptides that is neither adequately described in nor enabled by the common disclosure of the ’731 Application and the ’035 Patent.

1. The Claims Encompass a Staggering Number of Modified PH20 Polypeptides

The claims capture an incredibly broad and diverse genus of “modified PH20 polypeptides,” which the common disclosure defines as “a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement … in its sequence of amino acids compared to a reference unmodified PH20 polypeptide.”[41]

Claim 1 defines the genus as containing modified PH20 polypeptides that:

- ***must*** contain ***one*** amino acid replacement at position 312 (*i.e.*, from S to any of G, K, L, N, and T); and
- ***may*** contain ***additional*** modifications, provided each polypeptide retains ***at least 91% sequence identity*** to one of the 37 unmodified sequences (SEQ ID NOs: 3, 7 or 32-66), ranging in length from 430 (SEQ ID NO: 32) to 474 residues (SEQ ID NO: 7).

Certain dependent claims restrict these parameters: (i) claims 2 and 24-25 limit (*inter alia*) sequence identity to 95%, (ii) claims 8-14 narrow the comparator

[41] EX1001, 48:38-43. Dependent claims 23-34 reference genera of PH20 polypeptides defined by claims 1 or 6.

unmodified sequences (*e.g.*, removing SEQ ID NO: 7 or requiring only SEQ ID NOs: 35 or 32), (iii) claims 6 and 7 require the position 312 substitutions to be T or N, respectively (S312T or S312N), and (iv) claims 3-5 and 15 add functional requirements (*e.g.*, increased "stability" or activity, solubility).

Claims 16-23 and 26-34 depend from claim 1 but do not alter the parameters governing the number of PH20 polypeptides in each genus. Claims 16-22 specify additional features of the PH20 polypeptides (e.g., glycosylation) while claims 23 and 26-34 define pharmaceutical compositions and methods of use.

The specification explains that "sequence identity can be determined by standard alignment algorithm programs …"[42] and provides an example, explaining a polypeptide that is "'at least 90% identical to' refers to percent identities from 90 to 100% relative to the reference polypeptide" where "no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides."[43]

It further explains that "differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence" and that

[42] EX1001, 60:14-16.

[43] EX1001, 60:49-58.

"[d]ifferences are defined as [] amino acid substitutions, insertions or deletions."[44] Also, "amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids" (*e.g.*, 10-18 of the 19 alternative amino acids).[45] Likewise, except for position 312, no language in the claims restricts ***where*** substitutions can occur within the modified PH20 sequence, or ***which*** of 19 other amino acids can be substituted at those positions.

The claim parameters cause them to encompass an immense number of distinct polypeptides, each with a unique amino acid sequence.[46] In particular, the sequence identity limitations capture modified PH20 polypeptides with up to 21-42 total changes but require only one: a substitution at position 312, with either 5 alternatives (claims 1-5, 8, 10-11, 15-23, 26-34) or one ("T" (claims 6, 9, 12-14, 24-25), or "N" (claim 7)). Dr. Park's calculations show each claim's parameters capture an immense number of distinct polypeptides:[47]

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44 EX1001, 60:59-67; *see also id.* at 5:1-2; 47:43-47, 56-58.

45 EX1001, 127:29-36; *see also id.* at 132:49-51.

46 EX1003, ¶¶ 120, 122.

47 EX1004, ¶¶ 150-154, Appendix F.

Claims	*Max Length*	*Max Changes*	*Pos. 312 Choices*	*# of Distinct Polypeptides*
1, 3-5, 15-23, 26-34	474	42	5	3.16×10^{112}
2	474	23	5	2.59×10^{66}
6-7	474	42	1	6.32×10^{111}
8, 21	465	41	5	7.06×10^{109}
9, 14	465	41	1	1.41×10^{109}
10	433	38	5	5.01×10^{101}
11	430	38	5	3.83×10^{101}
12	433	38	1	1.00×10^{101}
13	430	38	1	7.66×10^{100}
24	430	21	1	4.40×10^{59}
25	433	21	1	5.08×10^{59}

2. The Claims Encompass Two Particular $PH20_{1-447}$ Mutants: S312T and S312N $PH20_{1-447}$

The claims' parameters also cause them to capture one or both of two modified $PH20_{1-447}$ polypeptides that change the serine at position 312 to either threonine (T) ("S312T") or asparagine (N)("S312N"). These single-replacement $PH20_{1-447}$ mutants are: (i) 99.7% identical to SEQ ID NO: 3 (1 change / 447 residues), (ii) 96.5% identical to SEQ ID NO: 35 (15 changes / 433 residues), and

(iii) 95.9% identical to SEQ ID NO: 32 (18 changes / 430 residues).[48] Both satisfy claims 1-5, 8-13, and 15-34, the S312T mutant satisfies claims 6 and 14, and the S312N mutant satisfies claim 7.

3. The Claims Are Restricted to One of Two Alternative Embodiments in the Patents: "Active Mutants"

When a specification discloses alternative embodiments, the claim language may limit the claims to only one.[49] That is the case here: the specification describes two mutually exclusive categories of "modified PH20 polypeptides" (*i.e.*, "active mutants" vs. "inactive mutants") but the claims are limited to one (*i.e.*, "active mutants").

According to the specification:

- "***Active mutants***" are modified PH20 polypeptides that "exhibit at least 40% of the hyaluronidase activity of the corresponding PH20

[48] EX1003, ¶ 136.

[49] *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008).

polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[50]

- "***Inactive mutants***" are modified PH20 polypeptides that "generally exhibit less than 20% … of the hyaluronidase activity of a wildtype or reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7."[51]

It then classifies mutants into tables of "active" and "inactive" mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).[52]

The common disclosure reports no examples of an "active mutant" modified PH20 with two or more replacements.[53] Notably, it reports no examples of an

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50 EX1001, 75:47-52; *see also id.* at 79:29-33 ("active mutants" "can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide …"); *id.* at 79:26-29.

51 EX1001, 115:58-67. *See also id*. at 259:11-15 (mutants with <20% activity "were rescreened to confirm that the dead mutants are inactive" in Table 10).

52 EX1001, 80:60-82:10, 224:15-17, 116:58-118:7, 260:17-20 ("reconfirmed inactive mutants are set forth in Table 10."); EX1003 ¶¶ 98, 104-105, 107, 126-28.

53 *E.g.*, EX1003, ¶¶ 141, 172.

enzymatically active $PH20_{1-447}$ that incorporates: (i) a mutation that preserved activity in Tables 3 and 9 ("active mutants") plus (ii) a second mutation that eliminated activity in Tables 5 and 10 ("inactive mutants").

The specification also portrays "active" and "inactive" mutants as having distinct utilities requiring mutually exclusive properties.

- "Active mutants" are portrayed as being therapeutically useful ***because they possess hyaluronidase activity***. For example, the specification explains that ***due to*** having hyaluronidase activity, "the modified PH20 polypeptides can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents."[54]
- "Inactive mutants" are portrayed as being therapeutically useful ***because they lack hyaluronidase activity***. Their only identified utility

[54] EX1001, 171:27-33; *see also id*. at 4:33-36, 73:33-47, 171:27-184:54; EX1003, ¶ 108.

is "as antigens in contraception vaccines," which is implausible (*see* § V.C) but ostensibly requires them to lack activity.[55]

The specification does not portray "active mutants" as having contraceptive utility even though they may differ by only one amino acid from an inactive mutant; it proposes using them instead ***in combination*** with contraceptive agents.[56]

The claim language reinforces that they are limited to the "active mutant" embodiment.

First, every claim requires modified PH20 polypeptides with one of five replacements at position 312 that yielded an "active mutant" as a single-replacement $PH20_{1-447}$ polypeptide (*i.e.*, S312G, S312K, S312L, S312N, or S312T). All 5 mutants are identified as "Active Mutants" in Table 3, and have at least ~40% activity per Table 9.[57]

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55 EX1001, 72:60-62; *see also id.* at 184:55-56, 75:56-58, 184:54-185:6 (for "contraception" "the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.").

56 EX1001, 147:50-63; EX1003, ¶ 113; EX1060, 1711.

57 EX1001, 85 (Table 3), 248 (Table 9), 97:49-61; EX1003, ¶¶ 127-128.

Second, claim 4 restricts the genus of active mutants in claim 1 (*i.e.*, those with hyaluronidase activity) to modified PH20 polypeptides that have at least 100% of the activity of unmodified PH20.[58]

Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one amino acid modification," but can also "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity.***"[59] This aligns with the specification's prophetic methodology for discovering PH20 polypeptides with multiple changes, which selects "active mutants" with one substitution, randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity.[60] This also tracks the claims, which require one substitution and permit others.

Patentee may contend the claims should be read as encompassing both alternative embodiments (*i.e.*, "active" and "inactive" mutants). Reading the

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[58] Claim 3 requires mutants with increased resistance to or stability in denaturing conditions. The specification portrays increased stability as an additional attribute of an "active mutant." EX1001, 52:41-47, 124:28-47, 170:15-18, 310:36-311:59.

[59] EX1001, 48:38-53; *see also id*. at 47:61-65, 76:5-8, 76:67-77:7, 81:1-82:10.

[60] EX1001, 132:14-26; *see also id*. at 42:48-55.

claims in that manner is incorrect. It also exacerbates the § 112 problems, as every claim still necessarily includes (and thus must describe and enable) the full sub-genus of "active mutants" in claim 1 defined by claim 4.[61]

V. All Challenged Claims Are Unpatentable Under § 112 and None Are Entitled to Benefit to Any Pre-March 13, 2013 Application

Claims 1-34 are unpatentable because each lacks written description in and was not enabled by the common disclosure of the '035 Patent and the '731 Application in 2011.

As explained in § IV.D.1, the claim language defines enormous genera: between 10^{59} and 10^{112} distinct polypeptides. To illustrate the real-world absurdity of those claims, consider what practicing the claims' full scope requires. Excluding single-replacement $PH20_{1-447}$ mutants, and only considering multiply-substituted mutants of $PH20_{1-447}$, a skilled artisan would need to make-and-test at least ~10^{59} mutants. Producing only one molecule of each mutant—each must be made and tested to see if it is active or inactive (and also exhibits increased stability per claim 3)—would require consuming an aggregate mass (~3.93 x 10^{37}

[61] EX1003, ¶ 135.

kg) that exceeds the mass of the Earth (~6 x 10^{24} kg).[62] Testing every polypeptide within the claims' scope in search of "active mutants" is impossible—literally.

In support of that broad scope, the '035 Patent and the '731 Application provide only a meager disclosure: ***singly***-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones. It nowhere demonstrates possession of the vast remainder of multiply-modified polypeptides in the claims' scope, nor does it enable a skilled artisan to practice that full-range of mutant polypeptides without undue experimentation.

A. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.[63] "To fulfill the written description requirement, a patent owner 'must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by

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62 EX1003, ¶¶ 123, 189; *see also, e.g.*, EX1039, 136-37 (cell theoretically can make 10^{390} forms of a polypeptide with 300 amino acids).

63 *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

disclosure in the specification of the patent."[64] If the claims define a genus, the written description must "show that one has truly invented a genus …," "[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus."[65]

"[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus."[66] "One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent … [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus."[67]

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64 *Idenix Pharm., LLC v. Gilead Scis., Inc.,* 941 F.3d 1149, 1163 (Fed. Cir. 2019).

65 *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1300 (Fed. Cir. 2014).

66 *Idenix*, 941 F.3d at 1164.

67 *AbbVie*, 759 F.3d at 1299-1300.

A disclosure that fails to "provide sufficient blaze marks to direct a POSA to the specific subset" of a genus with the claimed function or characteristic does not satisfy § 112(a).[68] And "merely drawing a fence around the outer limits of a purported genus" is insufficient.[69] Instead, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."[70]

Three cases are especially probative. First, in *AbbVie*, the Federal Circuit found a disclosure of 300 examples of IL-12 antibodies to not be representative of a functionally defined antibody genus:

> Although the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.[71]

It also criticized patentee's attempt to use a prophetic description for the remaining claim scope, portraying it as "only a research plan, leaving it to others to explore

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68 *Idenix*, 941 F.3d at 1164.

69 *Ariad*, 598 F.3d at 1350-54.

70 *Ariad*, 598 F.3d at 1349.

71 *AbbVie*, 59 F.3d at 1300-1301.

the unknown contours of the claimed genus" and a "trial and error approach."[72] Both criticisms apply to the present disclosure, which exemplifies only singly-substituted PH20 mutants and provides only a prophetic research plan, yet claims all multiply-modified PH20 mutants with many additional substitutions.

Second, *Idenix* addressed claims to methods of treatment with a broad genera of compounds defined by formulas analogous to the challenged claims here: "eighteen position-by-position formulas describing 'principal embodiments' of compounds that may treat HCV," each with "more than a dozen options" at each position (totaling "more than 7,000 unique configurations").[73] The court criticized the specification's failure to indicate which of the thousands of compounds would be effective, and found that "providing lists or examples of supposedly effective nucleosides," without "explain[ing] what makes them effective, or why" deprives a skilled artisan "of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result" because they "fail to provide sufficient blaze marks to direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV." That logic resonates strongly with the deficiencies of the common disclosure here.

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72 *Id.*

73 *Idenix*, 941 F.3d at 1158-64.

Finally, the Board in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found*., PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) considered claims that used "90% sequence homology" language to capture "a broad genus of amino acid sequence homologues" but (like here) imposed no restrictions on where particular amino acids replacements could be made, thus causing the claim "to cover, at minimum, thousands of amino acid sequences."[74] The Board found the specification's failure to "explain what, if any, structural features exist (*e.g.*, remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification" was fatal, and the homology limitation "serves to merely draw a fence around the outer limits of a purported genus [which] is not an adequate substitute for describing a variety of materials constituting the genus" for purposes of section 112(a).[75]

The deficiencies of the claims here dwarf those in these three cases. They define much larger, much less predictable and much more diverse genera of modified PH20 polypeptides, and the common disclosure is far more limited. Because the common disclosure neither discloses a representative number of

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[74] *Boehringer*, at 16. The claims were directed to compositions and methods of using proteins. *Id.* at 6.

[75] *Id.* at 35-36.

species within each immense claimed genus, nor identifies sufficient structural features common to the members of each claimed genus, it fails to demonstrate possession of the genera defined by the claims of the '035 Patent.

1. Claims 1-2, 6-15, and 24-25 Lack Written Description

a) The Claims Capture Massive and Diverse Genera of Enzymatically Active PH20 Polypeptides

The sequence identity language in claims 1-2, 6-14, and 24-25 define genera of modified PH20 polypeptides of varying size that are not only immense, but are structurally and functionally diverse. These genera capture PH20 mutants with 2 substitutions, 3 substitutions and so on up to a number set by the sequence identity boundary (*i.e.*, 21 for the narrowest claims (*e.g.* claims 24 and 25) to 42 for the broadest (claim 1)). The optional substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, and arranged in any manner.[76] They thus capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with up to 42 substitutions that mix polar, charged, aliphatic, and aromatic amino acids together in any manner.[77]

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[76] EX1003, ¶ 119; EX1001, 60:59-66, 47:43-47, 47:56-58, 42:3-9.

[77] EX1003, ¶¶ 119-20.

Each claim also encompasses substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 37 alternative sequences that terminate at positions 430 to 474. The claims' sequence identity language, however, also causes them to capture PH20 polypeptides that terminate at positions well before 430. For example, claims referencing SEQ ID NO:32 require one substitution at position 312 but permit between 20 and 41 additional changes, which can be any mixture of deletions and other substitutions (*e.g.*, the 312 substitution, 5 more substitutions, and 14 deletions, yielding a PH20 terminating at position 416). But removing many residues from the C-terminus of wild-type PH20 can render it inactive, and nothing in the common disclosure shows (much less suggests) that adding the S312T mutant restores activity to such mutants. Patentee nonetheless claims all these polypeptides.[78]

b) The Claims Capture Modified PH20 Polypeptides the Common Disclosure Says to Avoid or Not Make

The claims' unconstrained sequence identity language capture three categories of PH20 mutants a skilled artisan would understand the disclosure to be saying to avoid. Each raises unique questions relative to the remainder of the genus and are thus "sub-genera" of PH20 mutants that are not representative of other "sub-genera" within the claimed genera. But instead of providing guidance

[78] EX1003, ¶¶ 164-67.

that navigates this confusing landscape, the patent simply instructs the skilled artisan "to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein."[79] In other words, it directs the skilled artisan to blindly make-and-test all such candidate mutants using trial-and-error experimentation.[80]

(i) Multiply-Modified PH20 Mutants to Not Make

The common disclosure affirmatively addresses only six, specific modified PH20 polypeptides with more than one identified (*i.e.*, position and amino acid) substitution, but its guidance is to ***not make those polypeptides***:

> [W]here the modified PH20 polypeptide contains only two amino acid replacements, the amino acid replacements are ***not*** P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A or N333A/N358A. In a further example, where the modified PH20 polypeptide contains only three amino acid replacements, the amino acid replacements are ***not*** N47A/N131A/N219A.[81]

No explanation is provided why these particular combinations of replacements should be avoided, and nor any data testing their activity or other

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79 EX1001, 78:34-38.

80 EX1003, ¶ 193.

81 EX1001, 77:45-57 (emphases added).

characteristics.[82] The substitutions are not included in Tables 5 and 10 (i.e., "inactive mutants") and N219A $PH20_{1-447}$ showed increased activity (129%).[83] Nothing in the claim language excludes these combinations.

(ii) Substitutions to Avoid in Active Mutants

The common disclosure indicates that active mutant modified PH20 polypeptides should not incorporate amino acid substitutions that rendered $PH20_{1-447}$ inactive, stating:

> ***To retain hyaluronidase activity***, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.[84]

It identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10 that are made at other positions.[85] It does not limit this observation to single-replacement $PH20_{1-447}$ mutants, or suggest including any of the substitutions that rendered $PH20_{1-447}$ inactive into enzymatically active, multiply-modified PH20

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82 EX1003, ¶¶ 146-47; EX1001, 49:30-35.

83 EX1001, 242 (Table 9).

84 EX1001, 80:13-15 (emphases added).

85 EX1001, 80:15-55 ("For example, generally modifications are not made at a position corresponding to position …").

polypeptides (much less identify specific combinations including them).[86] Instead, by stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that the ***claimed*** enzymatically active multiply-modified PH20 polypeptides do not and should not contain them.[87]

(iii) PH20 with Significant C-terminal Truncations Can Lose Activity

The common disclosure describes no multiply-modified "active mutant" PH20 polypeptides having fewer than 447 residues (or even unmodified PH20s with such lengths) and provides no guidance about making such multiply-modified, truncated and enzymatically active PH20 mutants.[88]

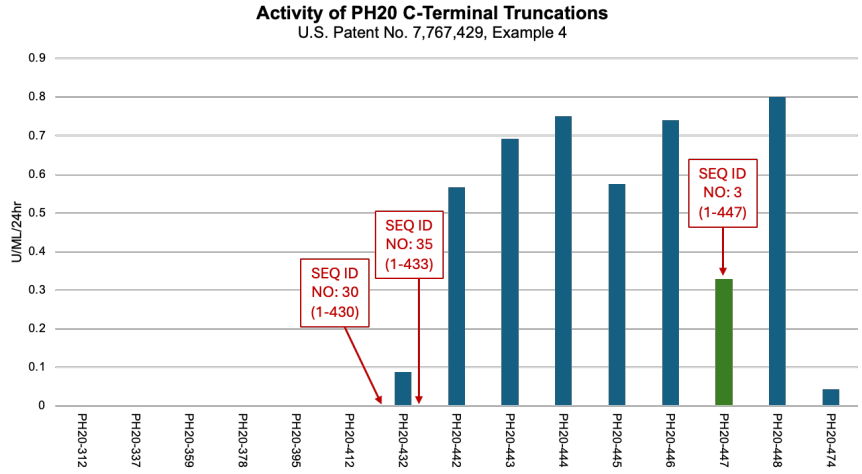
These omissions create significant uncertainty because both the common disclosure and the prior art report that truncations that yield PH20 polypeptides that terminate at or below position 442 have ***significantly reduced or no*** hyaluronidase activity. For example, Patentee's '429 Patent reported that PH20 mutants terminating below position 432 residues lacked hyaluronidase activity,

86 EX1003, ¶¶ 151, 161-62, 169.

87 EX1003, ¶¶ 148-51, 162; EX1001, 80:13-55, 70:46-56.

88 EX1003, ¶¶ 94, 97, 167-69; EX1001, 74:9-15.

while those terminating between positions 432 and 448 had widely varying activities (below):[89]



Position (w/leader)	Mutant	U/ML/24hr	Normalized to PH20(1-447)
347	PH20-312	0	0.00
372	PH20-337	0	0.00
394	PH20-359	0	0.00
413	PH20-378	0	0.00
430	PH20-395	0	0.00
447	PH20-412	0	0.00
467	**PH20-432**	**0.089**	**27.05**
477	PH20-442	0.567	172.34
478	PH20-443	0.692	210.33
479	PH20-444	0.75	227.96
480	PH20-445	0.575	174.77
481	PH20-446	0.74	224.92
482	**PH20-447**	**0.329**	**100.00**
483	PH20-448	0.8	243.16
509	PH20-474	0.044	13.37

The '429 Patent also reported that "a very narrow range spanning … [437-447] … defined the minimally active domain" of human PH20, and elsewhere observed this "minimally active" human PH20 domain contains at least residues 1-429.[90] The common disclosure agrees, stating that PH20 polypeptides must extend to at least position 429 to exhibit hyaluronidase activity:

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89 EX1005, 87:52-88:24 ($PH20_{1-442}$ activity "decreased to approximately 10%"); EX1013, Figure 2, 430-32 ("[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA").

90 EX1005, 6:65-7:7 ("… sHASEGP from amino acids 36 to Cys 464 [429] … comprise the minimally active human sHASEGP hyaluronidase domain").

> A mature PH20 polypeptide … containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue ***464*** of SEQ ID NO: 6 [position ***429*** without signal] … ***is the minimal sequence required for hyaluronidase activity***.[91]

In 2007, Chao reported that the C-terminal region of PH20 contained a unique domain ("Hyal-EGF") linked to a characteristic pattern of sequences.[92] In PH20, the Hyal-EGF domain runs from positions 337-409, and in 2009 it was shown to be necessary for hyaluronidase activity.[93]

The C-terminus of PH20 is illustrated below, showing (i) the positions where SEQ ID NOS: **3** (447), **32** (430) and **35** (433) terminate, (ii) the "minimally active domain" at 437-447, and (iii) residues below position 429.[94] Positions resulting from deletion of 21 or 16 residues from SEQ ID NOS: 32 and 35 end before position 429.

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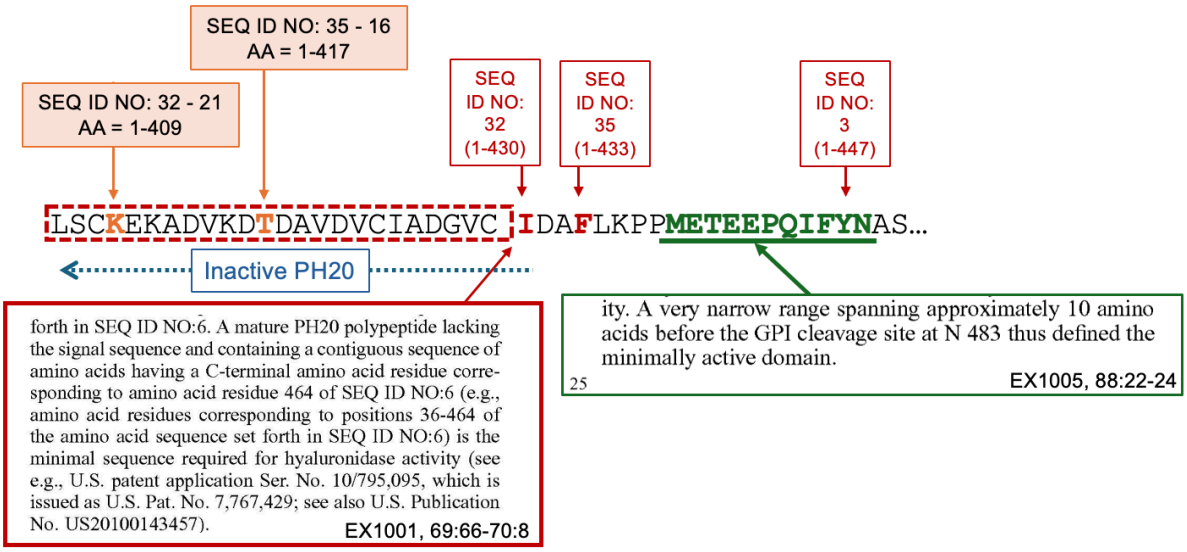
91 EX1001, 69:66-70:8 (emphases added).

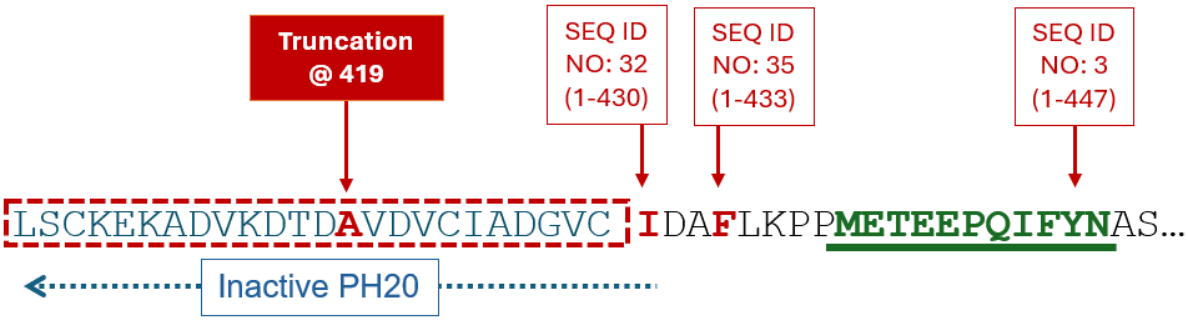
92 EX1006, 6912; EX1003, ¶¶ 84-96, 153.

93 EX1004, ¶¶ 97-99; EX1010, 9438; EX1003, ¶¶ 95-97.

94 EX1003, ¶ 153.



Thus, a skilled artisan in 2011 would have believed that C-terminal deletions yielding PH20 polypeptides terminating before position 430 would be inactive (below).[95]



The common disclosure provides no examples of (or guidance concerning) PH20 mutants truncated below position 447 with one or more substitutions and that are enzymatically active. It thus ignores the uncertainty existing in 2011 about

95 EX1003, ¶¶ 92-93, 97, 165-167.

PH20 truncation mutants that terminate between positions 419 to 433.[96] The claims nonetheless expressly encompass modified PH20 polypeptides with truncations down to and beyond position 419.[97]

c) Empirical Test Results of Single-Replacement Modified PH20 Polypeptides Do Not Identify Multiply-Modified Enzymatically Active PH20 Polypeptides

The empirical results in the common disclosure provide no predictive guidance to a skilled artisan about the structural features of multiply-modified PH20 polypeptides within the claimed genera that are enzymatically active.

(i) The Data Concerning Single-Replacements Is Not Probative of Multiple-Replacement Mutants

The common disclosure reports results from testing a portion of a randomly generated library of ~6,743 single-replacement $PH20_{1-447}$ polypeptides.[98] These mutants were generated via a mutagenesis process which substituted one of ~15 amino acids into random positions in $PH20_{1-447}$ "such that each member contained a single amino change."[99] Approximately 5,917 were tested, while ~846 were

96 EX1003, ¶¶ 143, 159, 167-69.

97 EX1003, ¶¶ 160-65.

98 EX1001, 124:48-59, 192:14-16, 191:10-16.

99 EX1001, 191:10-192:3.

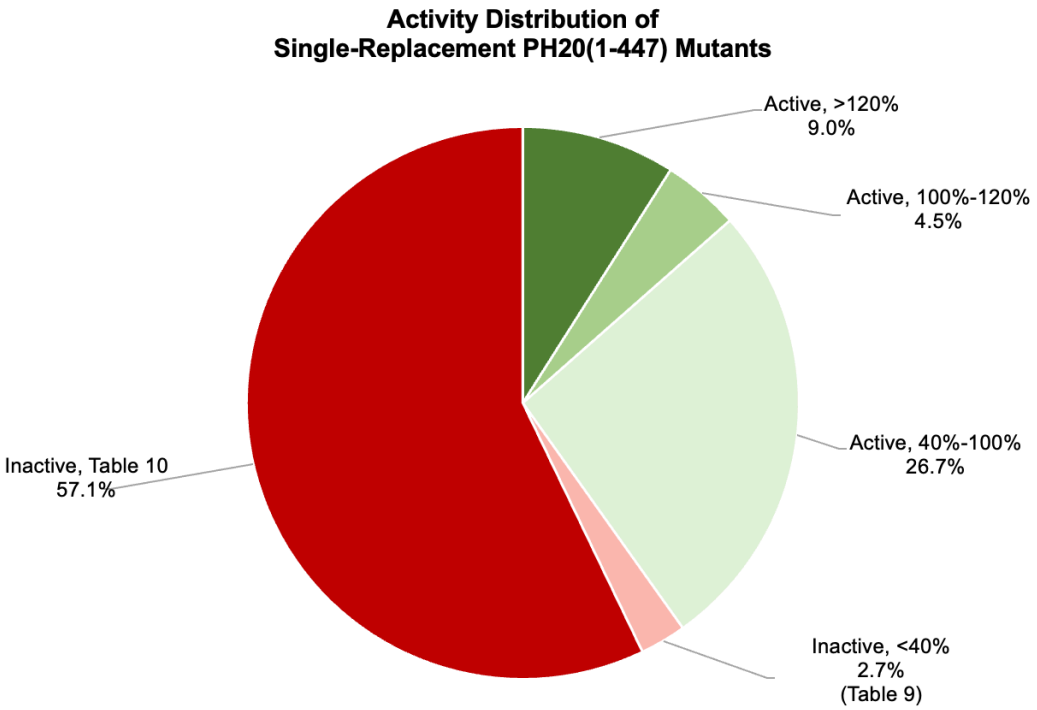
uncharacterized.[100] More than half (~57%) of these mutants were classified as "inactive mutants," while ~30% (1335) were reported to have less activity than unmodified $PH20_{1-447}$ (20%-100%).[101] In other words, ~87% of the single-replacement $PH20_{1-447}$ polypeptides had ***less*** activity than unmodified $PH20_{1-447}$.[102]

Activity vs. Unmodified PH20	**Number**	**% of Tested (5916)**
Active Mutants (Table 9)		
>120%	532	9.0%
100%-120%	267	4.5%
40%-100%	1577	26.7%
Inactive Mutants (Table 9)		
<40%	160	2.7%
Inactive Mutants (Table 10)		
Table 10 'inactive mutants"	3,380	57.1%

[100] EX1003, ¶¶ 103-104. Inconsistent numbers of tested mutants and classifications of mutants are reported but not explained: (i) Table 3 lists 2,516 single-replacement $PH20_{1-447}$ mutants as "active mutants," but Table 9 identifies only 2,376 mutants that exhibit >40% hyaluronidase activity; (ii) Tables 5 and 10 list 3,368 and 3,380 $PH20_{1-447}$ "inactive mutants," respectively.

[101] EX1003, ¶ 105.

[102] *Id.*



The measured activity of single-replacement $PH20_{1-447}$ mutants shows no trends or correlations even for single-replacement $PH20_{1-447}$ polypeptides.[103] Instead, numerous examples show that even introducing different amino acids at the same position in $PH20_{1-447}$ resulted in (i) increased activity, (ii) decreased activity, or (iii) inactive mutants (below).[104]

[103] EX1003, ¶¶ 106, 142-43.

[104] Data from Tables 3, 5, 9, 10.

Position	Inactive	Decreased Activity	Increased Activity
008	P	L, M	I
067	R	L, Y	V
092	H	M, T	C, L, V
165	C	A, R, Y	D, F, N, S, V, W
426	K, S	E, G, N, Q, Y	P

The data on activities of tested single-replacement $PH20_{1-447}$ mutants is not analyzed or explained in the common disclosure—it is simply presented. There is no attempt to extrapolate its results to any combinations of substitutions in PH20 polypeptides, or to assess the impact of a single substitution on the protein's structure.[105] The quality of the data is also questionable: no control values or statistical assessments are provided.[106] All the data shows is that most of the tested single-substitution mutants impaired PH20's activity.[107]

The results from single substitutions provide no insights into PH20 polypeptides with multiple concurrent mutations, which together can cause complex and unpredictable effects on a protein's structure and resulting

[105] EX1003, ¶ 139.

[106] EX1003, ¶ 106.

[107] EX1003, ¶ 138.

function.[108] The patent's empirical test results thus provide no guidance to a skilled artisan about which of the many possible PH20 mutants with different sets of 2-42 substitutions will be enzymatically active.[109]

(ii) Purported Stability Data Is Not Reliable or Probative

The common disclosure reports results in Tables 11 and 12 from two runs of "stability" testing of ~409 single-replacement $PH20_{1-447}$ polypeptides.[110] Table 11 reports the hyaluronidase activity of single-replacement $PH20_{1-447}$ mutants tested at 4° C and 37° C, and in the presence of a "phenolic preservative" (m-cresol),[111] while Table 12 compares relative activities under pairs of these conditions.[112]

The data in Tables 11 and 12 provides no meaningful insights.[113] For example, unsurprisingly, single-replacement $PH20_{1-447}$ polypeptides showed higher activity at 37° C than at 4° C, given that PH20 exists at the former temperature in

[108] EX1003, ¶¶ 139, 142.

[109] EX1003, ¶¶ 140, 143.

[110] EX1001, 269:60-272:47.

[111] EX1001, 272:50-283:25 (Table 11).

[112] EX1001, 283:26-295:50 (Table 12).

[113] EX1003, ¶ 76.

humans.[114] And all that testing with m-cresol showed was that only a few mutants were able to resist its effects, with no explanation why.[115]

With one exception, there is no evidence the measured activity data was attributable to improved stability of PH20.[116] More directly, the common disclosure does not identify which ***combinations*** of substitutions improve stability.[117] It thus provides no probative insight regarding multiply-modified PH20 polypeptides with increased stability.[118]

The data is also largely meaningless, as many of their values fall within the range of activity observed for the positive control.[119] The charts and table below show that the positive control had activity that varied by 97% and 87% in two rounds of testing.[120]

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114 EX1003, ¶ 73; EX1001, 168:4-13.

115 EX1003, ¶ 69.

116 EX1003, ¶ 69.

117 EX1003, ¶¶ 75-76.

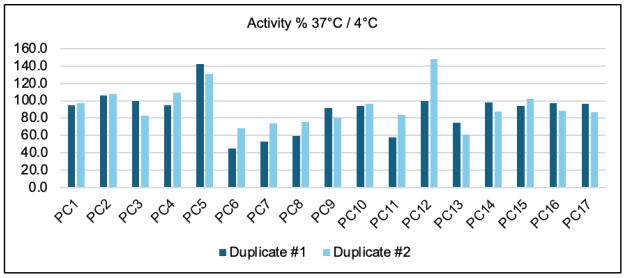
118 *Id*.

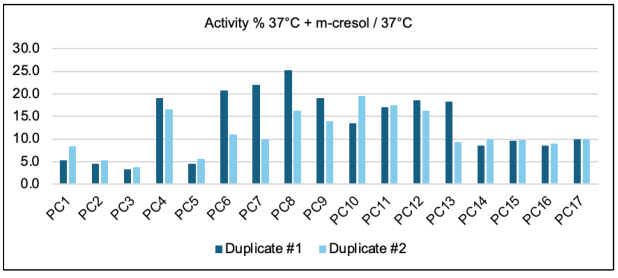
119 EX1003, ¶ 71; EX1001, 295 (Table 12).

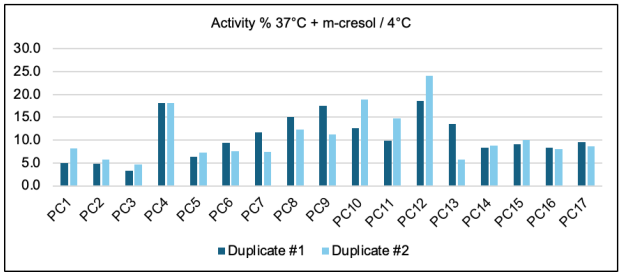
120 EX1003, ¶ 71, Appendix A-7, A-8.

Positive Control ("PC") (OHO)	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C+mcr/4°C
PC1	94.998	5.230	4.970	96.871	8.456	8.190
PC2	105.798	4.480	4.740	108.066	5.246	5.670
PC3	100.000	3.330	3.330	82.778	3.759	4.590
PC4	94.762	19.070	18.070	109.539	16.529	18.110
PC5	142.024	4.480	6.360	130.947	5.595	7.330
PC6	45.115	20.770	9.370	68.017	11.035	7.510
PC7	53.324	21.950	11.710	74.253	9.960	7.400
PC8	59.581	25.240	15.040	75.872	16.231	12.310
PC9	91.844	19.050	17.500	80.371	13.977	11.230
PC10	93.828	13.470	12.630	96.630	19.454	18.800
PC11	57.773	17.040	9.850	83.536	17.573	14.680
PC12	100.000	18.560	18.560	148.226	16.239	24.070
PC13	74.325	18.290	13.600	61.119	9.286	5.680
PC14	98.132	8.480	8.320	87.677	10.006	8.770
PC15	93.817	9.620	9.020	102.223	9.745	9.960
PC16	96.922	8.560	8.300	87.993	9.064	7.980
PC17	96.648	9.910	9.580	86.891	9.938	8.630

KEY
Coloration of Percent (%) Activity Values
n/a
>120
between 100 and 120
between 80 and 100
between 40 and 80
between 20 and 40
between 10 and 20
between 0 and < 10







	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C + m-cresol	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol	% Activity at 37°C+mcr/ 4°C
High	142.02	25.24	18.56	148.23	19.45	24.07
Low	45.12	3.33	3.33	61.12	3.76	4.59
Range	96.91	21.91	15.23	87.11	15.70	19.48
Average	88.17	13.38	10.64	93.00	11.30	10.64
Mean	94.76	13.47	9.58	87.68	9.96	8.63

As Dr. Hecht observes, this "significant variation raises serious doubts about how probative or instructive the values of individual tested mutants that fall within the range of variability observed for the control can possibly be."[121] The data not only fails to identify specific combinations of substitutions that yield PH20 mutants with increased resistance to or stability in denaturing conditions, it is unreliable.

d) The Common Disclosure's Research Plan Does Not Identify Multiply-Mutated Enzymatically Active PH20 Polypeptides

Instead of describing any multiply-modified PH20 polypeptides that are "active mutants," the common disclosure provides only a prophetic research plan based on iterative rounds of "make-and-test" experiments that were never

[121] EX1003, ¶¶ 70-72; *see also* EX1001, 295:57-67 (positive control also varied).

performed. This prophetic method provides absolutely no insights into which multiply-modified PH20 polypeptides are active mutants.[122]

The common disclosure merely outlines ***the idea*** of multiply-modified PH20 polypeptides. It declares that "[a] modified PH20 polypeptide can have up to 150 amino acid replacements," "[t]ypically" contains between 1 and 50 amino acid replacements and "can include any one or more other modifications**,** in addition to at least one amino acid replacement as described herein."[123] In addition to PH20 polypeptides with single amino acid replacements, it contends that a modified PH20 polypeptide "having a sequence of amino acids that exhibits" between 68% and 99% sequence identity with any of unmodified Sequence ID Nos. 74-855 "***can*** exhibit altered, such as improved or increased, properties or activities compared to the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[124]

None of these statements identify ***any*** actual multiply-modified PH20 polypeptides (*i.e.*, particular sets of specific amino acid substitutions), much less

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[122] EX1003, ¶¶ 173, 184-85, 190; EX1001, 44:1-3; *see generally id.*, 124:48-125:26, 125:35-127:10, 127:38-132:12.

[123] EX1001, 48:43-53.

[124] EX1001, 97:1-15 (emphasis added).

provide results from testing any. They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides.

The common disclosure instead outlines a prophetic, "iterative" make-and-test research plan for discovering modified PH20 polypeptides with multiple substitutions that might exhibit hyaluronidase activity, stating:

> The method provided herein [] is ***iterative***. In one example, after the method is performed, any modified hyaluronan-degrading enzymes identified as exhibiting stability … ***can be modified or further modified*** to increase or optimize the stability. A secondary library ***can be*** created by introducing additional modifications in a first identified modified hyaluronan-degrading enzyme. … The secondary library ***can be*** tested using the assays and methods described herein.[125]

The guidance in this research plan is effectively meaningless. It says to make mutants, test them to find activity and/or stability, and keep repeating the process until you find something via screening. It does not indicate that any useful multiply-modified PH20 polypeptides will be found, much less what their specific characteristics or activities are.[126]

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[125] EX1001, 132:13-26 (emphases added); *see also id.* at 42:48-55, 125:27-32; EX1003, ¶¶ 173-177.

[126] EX1003, ¶¶ 187-90.

The specification also incorrectly portrays the experimental readout—hyaluronidase activity—as a measure of "stability."[127] As Dr. Hecht explains, to assess a protein's stability directly one performs experiments that measure the energy associated with the protein's transition between its folded and unfolded states.[128] Activity may or may not be influenced by stability but is not itself a measure of stability.[129]

An alternative focus is then proposed: mutations can be "targeted near" "critical residues" which supposedly "can be identified because, when mutated, a normal activity of the protein is ablated or reduced."[130] But Tables 5 and 10 show that at least one substitution at each of 405 positions between positions 1 and 444 of $PH20_{1-447}$ resulted in an inactive mutant.[131] In other words, the common disclosure's guidance is to target locations "near" ~90% of the amino acids in

127 EX1003, ¶¶ 67, 69, 179.

128 EX1003, ¶¶ 63-66.

129 EX1003, ¶ 67.

130 EX1001, 132:27-53; EX1003, ¶¶ 178-79.

131 EX1003, ¶ 180, Appendix A-3.

$PH20_{1-447}$, which is no different than targeting every residue in the protein.[132] It is, like the first proposed "iterative" process, meaningless.

These prophetic research plans, based entirely on unfocused, iterative "make-and-test" experiments, provide no direction to the skilled artisan about which of the trillions and trillions of possible multiply-modified PH20 polypeptides are "active mutant" PH20 polypeptides. Instead, they require the skilled artisan to repeat the cycle of mutagenesis iteratively, screening and selecting until 10^{59} to 10^{112} modified PH20 polypeptides are produced and screened for activity.[133] That in no way demonstrates possession of the claimed genus.

e) The Common Disclosure Does Not Identify a Structure-Function Relationship for Multiply-Modified, Enzymatically Active PH20 Polypeptides

The common disclosure does not identify the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20

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132 EX1003, ¶ 180.

133 EX1003, ¶¶ 175-77, 181, 187-88; EX1001, 127:19-24, 127:11-36, 130:31-35, 130:46-51; 131:1-15.

polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.[134] Instead, it simply lists single replacements to random amino acids at random positions that were classified as "active mutants" by a hyaluronidase assay, without further explanation; nothing is said about the effects (if any) of substitutions on the protein's structure.[135]

The common disclosure also does not identify any ***sets*** of specific amino acid replacements that correlate to structural domains or motifs that positively or negatively influence hyaluronidase activity, much less ***predictably*** increase activity to defined thresholds.[136] Again, it simply reported activity data from testing randomly generated ***single***-replacement $PH20_{1-447}$ mutants.

The common disclosure's empirically identified examples of "active mutant" single-replacement $PH20_{1-447}$ mutants also do not ***by themselves*** identify any "structure-function" relationship between "active mutants" and the set of single-replacement modified $PH20_{1-447}$ polypeptides.[137] They certainly do not do so

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134 EX1003, ¶¶ 139-40, 151.

135 EX1001, 224:15-43; EX1003, ¶¶ 139-40, 142.

136 EX1003, ¶¶ 55, 142-43.

137 EX1003, ¶¶ 61, 143, 157, 159.

for the much larger genus of modified PH20 polypeptides of varying lengths and between 2 and 42 substitutions.[138]

Critically, the common disclosure ***does not even contend*** that a particular amino acid replacement at a particular position (*e.g.*, 312) that makes a $PH20_{1-447}$ an "active mutant" will make any other modified PH20 polypeptide with that same amino acid replacement (plus between 1 and 41 additional replacements or truncations) an "active mutant."[139] Such an assertion would have no scientific credibility—the activity of a protein such as PH20 is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.[140] Thus, even the inventors did not view their compilation of test results as identifying a structure-function correlation for multiply-modified PH20 polypeptides.

The common disclosure, thus, does not identify to a skilled artisan ***any*** structural features shared by the many, diverse "active mutant" modified PH20 polypeptides within the scope of the claims,[141] and thus cannot satisfy the written

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138 EX1003, ¶ 157.

139 EX1003, ¶¶ 168, 192-93.

140 EX1003, ¶¶ 56-57.

141 EX1003, ¶ 157.

description requirement of § 112(a) as a disclosure that links a functional property to a particular structure ***shared*** by the members of the genus.

f) The Common Disclosure Does Not Describe a Representative Number of Multiply-Modified Enzymatically Active PH20 Polypeptides

The ~2,500 single-replacement $PH20_{1-447}$ polypeptides that are "active mutants" are not examples representative of the claimed genera of the claims, much less their various sub-genera captured in the dependent claims.[142]

First, the single-replacement $PH20_{1-447}$ examples are not representative of the trillions and trillions of $PH20_{1-447}$ polypeptides with between ***2 and 42 substitutions*** at any of hundreds of positions within the protein.[143] The latter group of proteins is structurally distinct from single replacement PH20 polypeptides, both as to their sequence and due to the various structures within the folded protein that, when incorporating different amino acid substitutions, may alter their structures and their interactions with neighboring residues.[144] The effects of those numerous substitutions on a protein's various secondary structures and structural motifs within the protein is not described in the common disclosure, and the magnitude of

142 EX1003, ¶¶ 61, 143, 155, 159.

143 *See* § IV.D.1; EX1003, ¶¶ 61, 143, 159.

144 EX1003, ¶¶ 54-56, 58, 120, 156, 159.

concurrent substitutions encompassed by the claims was unknowable in 2011.[145] The overall activity of a protein with multiple substitutions also will not be due to one amino acid, but to the unique structure of each protein that reflects ***the totality*** of effects of those many substitutions.[146]

More specifically, introducing a first amino acid substitution often affects the neighbors of that original/replaced amino acid by, for example, (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, and/or (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).[147] Introducing a second substitution in that region may reverse those interactions (or not) with each neighboring residue, and a third substitution may do the same, with up to 21 rounds permitted by even the narrowest claims, each potentially impacting each interaction.[148] The data associated with a single amino acid substitution thus cannot be representative of the properties of any of these downstream, multiply-substituted mutants, which will have an unknowable

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145 EX1003, ¶ 228.

146 EX1003, ¶¶ 36, 61, 140, 143, 151.

147 EX1003, ¶¶ 56-58.

148 EX1003, ¶¶ 58-60, 142.

combination of substitutions that each uniquely impact the properties of the mutated protein.[149]

Enzymatically active single-replacement $PH20_{1-447}$ polypeptides also are not representative of enzymatically active, multiply modified PH20 polypeptides that incorporate changes that alone render PH20 proteins inactive (*e.g.*, truncations terminating below position 429, or single substitutions that render $PH20_{1-447}$ inactive).[150] That is because an ***active*** single-replacement $PH20_{1-447}$ polypeptide does not also contain the distinct structural features that render the latter types of PH20 polypeptides enzymatically ***inactive***. For example, an enzymatically active $PH20_{1-447}$ protein with a single amino acid substitution (*e.g.*, S312T) would not be considered representative of a PH20 that combines that S312T substitution with truncations at the C terminus ending at positions between 409 to 433 because the common disclosure would have led a skilled artisan to expect that PH20 proteins terminating at those positions would be inactive.[151] A skilled artisan could not have predicted—based on the examples in the common specification, all of which are limited to single-replacement $PH20_{1-447}$ polypeptides—whether enzymatic activity

[149] EX1003, ¶¶ 61, 142-43, 159, 169.

[150] EX1003, ¶¶ 161-64.

[151] EX1003, ¶¶ 167-69.

could be restored to such severely truncated PH20 mutants, much less the precise additional changes that would do so.[152]

The common disclosure thus provides a very narrow set of working examples relative to the diversity of modified PH20 polypeptides being claimed.[153] The examples are restricted to ***one type of change*** (a single amino acid replacement) in ***one type of PH20 polypeptide*** (SEQ ID NO: 3).[154] By contrast, the claims encompass changes in 37 different unmodified PH20 sequences, and include, in addition to one identified replacement at position 312, anywhere from 1 to 41 (claim 1) to 20 (claims 24-25) additional changes.[155] A simple illustration demonstrates how ***non-representative*** the examples are: all of the examples of single-replacement $PH20_{1\text{-}447}$ mutants fit into one box of the array below (claim 2).

[152] EX1003, ¶ 168.

[153] EX1003, ¶ 155.

[154] EX1003, ¶¶ 97, 99, 103.

[155] EX1003, ¶¶ 115-20.

	Number of Changes																					
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3																							
7																							
32																							
33																							
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Unlike claim 2, which requires 95% sequence identity, claim 1 permits 91% sequence identity, thus capturing an even ***larger*** genus (up to 42 permitted changes) than depicted above.

Consequently, a skilled artisan would not have viewed the Patents' examples of individual single amino acid replacements in $PH20_{1-447}$ as being ***representative*** of the diversity of modified PH20 polypeptides encompassed by the claims.[156]

[156] EX1003, ¶ 143.

g) The Claims Capture Multiply-Modified PH20 Polypeptides the Disclosure Excludes from the Class of Enzymatically Active PH20 Proteins

Patentee's position on the breadth of the claims is unknown. However, by their literal language, they capture several sub-genera of "active mutant" modified PH20 polypeptides that the common disclosure says caused single-replacement $PH20_{1-447}$ mutants to be inactive (*i.e.*, those with replacements in Tables 5/10 or in PH20 sequences terminated before position 429). Likewise, the claim language captures modified PH20 polypeptides with the six combinations of replacements the common disclosure explicitly says to not make: P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, N333A/N358A and N47A/N131A/N219A.[157] The claims thus improperly capture subject matter the common disclosure affirmatively excluded from the genus of enzymatically active modified PH20 polypeptides having multiple substitutions and other changes.

The common disclosure provides no exemplification of multiply-modified species of PH20 polypeptides that disregard these restrictions in the common disclosure.[158] Specifically, there is no explanation of the types of substitutions that might be made to restore activity that, under the logic of the common disclosure,

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157 *See* § V.A.2.a; EX1001, 77:45-57.

158 EX1003, ¶ 161.

will result in enzymatically inactive PH20 polypeptides or which the specification teaches ***not*** to make.[159] Yet the claims encompass such proteins. The claims therefore independently violate the written description requirement for the reasons articulated by the Federal Circuit in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998)—if a disclosure "unambiguously limited" the invention, but the claims circumvent that limitation, those claims are "broader than the supporting disclosure" and are unpatentable.

2. Dependent Claims 3-5 and 15 Lack Written Description

a) Claims 3 and 4

Claims 3 and 4 specify additional functional properties of the modified PH20 polypeptides in the genus defined by claim 1: either (i)increased hyaluronidase activity (claim 4) or (ii) increased stability (claim 3) relative to unmodified $PH20_{1\text{-}447}$.

The reasons provided in § V.A.1 explaining why the claims generally lack written description apply with full force to claims 3 and 4. Stated simply, the common disclosure's recitation of a ***desired*** level of stability or hyaluronidase activity in claims 3 and 4 does not identify ***which*** of the many trillions of PH20 polypeptides having 91% or 95% sequence identity with SEQ ID NOS: 3, 7, or 32-

[159] EX1003, ¶ 168.

66 and one of five replacements at position 312 will exhibit either of those functional properties.[160]

First, the identification of one $PH20_{1-447}$ mutation at position 312 that exhibited increased activity (S312N) compared to unmodified $PH20_{1-447}$ is not representative of each claim's genus of PH20 polypeptides with 1 to 41 additional substitutions and/or truncations, and even other substitutions at position 312 that, when made as single-substitutions, did not result in increased activity.[161] Notably, no test results are provided showing that a PH20 protein with a substitution at position 312 exhibits increased stability.

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides and exhibiting increased activity or stability.[162] The mere presence of a position 312 replacement in a multiply-modified PH20 thus does not demonstrate possession of a modified PH20 polypeptide with increased activity or stability, and the common disclosure makes no claim that it does.[163]

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160 EX1003, ¶¶ 185, 191-92.

161 EX1001, 248 (Table 9); EX1003, ¶¶ 191-92.

162 EX1003, ¶¶ 68-69, 76, 157, 185, 190.

163 EX1003, ¶¶ 76, 143, 168, 185, 192-93.

The common disclosure also provides no description of multiply-modified PH20 polypeptides with the claimed substitutions at 312, much less one that identifies the 1 to 41 more substitutions that retain elevated enzymatic activity or exhibit increased stability.[164] Indeed, the common specification does not identify even one multiply-modified PH20 polypeptide with any level of hyaluronidase activity.[165] Similarly, even if the data reported in Tables 11 and 12 was not flawed and unreliable as a measure of "stability" (as discussed above, it is), it too is limited to single-substituted PH20 polypeptides, and, provides no "stability" data on multiply-modified PH20 polypeptides.[166]

Claims 3 and 4 lack written description in the common disclosure.

b) Claims 5 and 15

Claims 5 and 15 require an additional functional property: that the modified PH20 polypeptide be "soluble." Each lacks written description support (i) for the same reasons identified for claim 1, and (ii) because they encompass modified PH20 polypeptides that the common disclosure suggests would be insoluble.

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164 EX1003, ¶¶ 140, 190-93.

165 EX1003, ¶¶ 130, 172.

166 EX1001, Tables 11, 12.

The common disclosure explains that "a soluble PH20 lacks all or a portion of a glycophosphatidyl anchor (GPI) attachment sequence,"[167] which was known to be hydrophobic.[168] Citing prior art, it identifies the first residue of the GPI sequence in human PH20 as position 456 (position 491 in SEQ ID NO: 6).[169] It also states that a soluble PH20 "is a polypeptide that is truncated after amino acid 482 of … SEQ ID NO: 6" (*i.e.*, 447 in SEQ ID NO:3)."[170] It thus suggests that human PH20 sequences that terminate below position 448 are soluble and those that terminate above position 456 are insoluble.[171]

Claims 5 and 15 encompass PH20 polypeptides based on SEQ ID NOS:59-66, which terminate between positions at 457 to 464 respectively (*i.e.*, beyond position 456), and does not restrict where in the PH20 polypeptide changes are

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167 EX1001, 46:28-30, 72:8-9; 74:26-38.

168 EX1001, 72:32-44; EX1005, 86:18-22.

169 EX1001, 72:32-44; *also* EX1005, 2:56-61 ("Attempts to make human PH20 DNA constructs that would not introduce a lipid anchor into the polypeptide resulted in either a catalytically inactive enzyme, or an insoluble enzyme") (citing EX1011).

170 EX1001, 75:16-18; EX1005, 3:57-62.

171 EX1003, ¶¶ 89-90.

made, other than the replacement at position 312. Consequently, claims 5 and 15 capture modified PH20 polypeptides that are C-terminally truncated but, per the common disclosure, ***are not*** "soluble modified PH20 polypeptide[s]" because each contains "all or a portion of" the GPI attachment sequence.[172]

Patentee may contend that some unidentified number of modified PH20 polypeptides based on SEQ ID NOS: 59-66 ***may*** be soluble, citing the common disclosure as suggesting that between 1-10 residues within the GPI anchor "can be retained, provided the polypeptide is soluble."[173] But the common disclosure does not identify ***which*** modified PH20 polypeptides terminating above position 448 (and especially terminating between 457 and 464) ***are*** soluble, provides no examples of such soluble PH20 mutants, and provides no reason to expect that many modified PH20 polypeptides within the claim's scope are soluble.

Thus, claims 5 and 15 are unpatentable for lack of written description for this additional, independent reason.

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172 EX1001, 46:55-61.

173 EX1001, 74:19-25.

3. The Remaining Dependent Claims Lack Written Description

The remaining dependent claims (16-23 and 26-34) do not meaningfully alter the number of PH20 polypeptides in the genus of claim 1.[174] They instead specify additional features (claims 16-22, 33-34), or pharmaceutical compositions or methods of treatment that reference the genus of claim 1. They lack written description for the same reasons explained in § V.A.1.[175]

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

"If a patent claims an entire class of … compositions of matter, the patent's specification must enable a person skilled in the art to make and use the ***entire*** class," *i.e.*, "the ***full scope*** of the invention" and so the "more one claims, the more

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[174] Claim 21 omits reference SEQ ID NO:7.

[175] *Idenix*, 941 F.3d at 1155, 1165 (method of treatment claims involving immense genus of modified proteins invalid for lack of written description and non-enablement); *Boehringer*, PGR2020-00076, Paper 42, at 40-41 (methods of treatment claims found to lack written description because specification did not provide an adequate written description of compositions being administered).

one must enable."[176] "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."[177] "Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation."[178]

Although not required, enablement may be assessed using the *Wands* factors, which consider: "(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention."[179]

Where the scope of the claims is large, there are few working examples disclosed in the patent, and the only guidance to practice "the full scope of the

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176 *Amgen*, 598 U.S. at 610 (emphases added).

177 *Idenix*, 941 F.3d at 1159.

178 *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

179 *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims' functional limitations—the asserted claims are not enabled."[180]

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the 10^{59}+ PH20 polypeptides having multiple amino acid replacements and/or truncations within the scope of the claims are "active mutant" PH20 polypeptides.[181]

1. The Genera of PH20 Polypeptides of Claims 1-2, 6-14, 21, and 24-25 Are Not Enabled

The facts of this case are a textbook example of claims that are not enabled under the reasoning articulated by the Supreme Court in *Amgen*. An analysis of the common disclosure under the Federal Circuit's framework for assessing undue experimentation using the factors in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) compels the same conclusion.

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[180] *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, T., sitting by designation) *aff'd* 81 F.4th 1362 (Fed. Cir. 2023).

[181] EX1003, ¶¶ 170-71, 190.

a) Extreme Scope of the Claims

As explained in § IV.D.1, each of claims 1-2, 6-14, 21, and 24-25 define an immense and diverse genus of between 10^{59} and 10^{112} enzymatically active modified PH20 polypeptides. Practicing that full genus, however, raises substantial scientific questions left unanswered by the common disclosure:

(i) The claims encompass many modified PH20 polypeptides that terminate below position 429.[182] The common disclosure and the prior art, however, report that unmodified human PH20 must include residues through position 429 to have hyaluronidase activity.[183]

(ii) Several claims (1-2, 6-9, 14, 21) encompass modified PH20 polypeptides that, per the common disclosure's guidance, would be expected to be insoluble because they include all or some of the GPI anchor sequence.[184]

(iii) The mathematical "sequence identity" boundaries set by the claim language cause the claims to capture (without restriction) modified PH20 polypeptides with 2 to 42 amino acid replacements that the

[182] EX1003, ¶¶ 154, 164.

[183] EX1001, 69:66-70:8; EX1003, ¶¶ 93, 152-53.

[184] EX1001, 46:28-30, 72:8-9, 74:19-25, 75:16-18; EX1005, 2:56-61, 3:57-62.

common disclosure instructs "are less tolerant to change or required for hyaluronidase activity"[185] or which the common disclosure affirmatively says to not make.[186]

In other words, the claims capture massive genera of modified PH20 polypeptides, most of which would have unknowable properties absent individual production and testing.[187]

Claims that capture a massive and diverse genus of proteins have routinely been found non-enabled. For example, the claims in *Amgen* covered "millions" of different, untested antibodies,[188] while in *Idenix*, a skilled artisan would "understand that 'billions and billions' of compounds literally meet the structural limitations of the claim."[189] In both cases, the enormous claim scope was found non-enabled after being contrasted to the limited working examples in the patent, the existence of unpredictability, and the quantity of experimentation needed to practice the full scope of the claims (*Wands* Factors 1, 3, 4, and 7). And, as the

185 EX1001, 80:13-15.

186 EX1001, 77:45-57.

187 EX1003, ¶ 158.

188 598 U.S. at 603.

189 941 F.3d at 1157.

Idenix court observed, one cannot rely on the knowledge and efforts of a skilled artisan to try to "fill the gaps in the specification" regarding which of the "many, many thousands" of possible compounds should be selected for screening, and which in this case is impossible.[190]

b) Limited Working Examples and Only a Research Plan for Discovering Active Mutant PH20 Polypeptides

The common disclosure provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement $PH20_{1-447}$ polypeptides, of which ~2500 were "active mutants."[191] Those examples are a tiny fraction of the 10^{59} to 10^{112} modified PH20 polypeptides covered by the claims, and provide no guidance that would help a skilled artisan navigate the "trial-and-error" methodology the common disclosure describes using to make modified PH20 polypeptides; indeed, none incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.[192]

The common disclosure provides no credible guidance on the full scope of the genus comprising multiple combinations of changes to PH20 polypeptides.[193]

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190 *Id.* at 1159.

191 EX1003, ¶ 103.

192 EX1003, ¶¶ 155, 159, 167.

193 EX1003, ¶¶ 131, 139.

Instead, it describes an explicitly prophetic and "iterative" process for ***discovering*** active mutant PH20 polypeptides. *See* § V.A.1.d.

The purely prospective research plan in the common disclosure demands that a skilled artisan engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of ***randomized*** mutations (up to 41 rounds per starting molecule under the broadest claims) to ***discover*** which of the 10^{59}+ possible modified PH20 polypeptides having 2 to 41 replacements to any of 19 other amino acids in any of 35 starting PH20 sequences might possess hyaluronidase activity.[194]

Second, it provides no meaningful guidance in producing "active mutant" modified PH20 polypeptides:

[194] EX1003, ¶¶ 188-90; *see also* EX1018, 382 ("combinatorial randomization of only five residues generates a library of 205 possibilities (3.2 x 10^6 mutants), too large a number for manual screening"). Chica also credited a supposed "ground-breaking" advancement in predictive molecular modeling techniques. EX1018, 384, 382. That supposed advancement, however, was later shown to be false. EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

(i) it does not identify ***any*** specific combination of two or more replacements within any PH20 polypeptide that yield "active mutants";

(ii) it provides no data from testing ***any*** PH20 polypeptide with two or more substitutions; and

(iii) it does not identify any regions or residues that are "associated with the activity and/or stability of the molecule" or "'critical residues involved in structural folding or other activities' of the molecule" when two or more concurrent replacements have been made.[195]

From the common disclosure and their knowledge in 2011, a skilled artisan could not predict whether a particular multiply-modified PH20 polypeptide will be enzymatically active without making and testing each one.[196]

Regardless whether individual rounds of "iterative" production and testing might be considered "routine," the process described in the common disclosure is indistinguishable from the "***iterative, trial-and-error process[es]***" that have

[195] EX1003, ¶¶ 144, 158, 172, 184-85.

[196] EX1003, ¶ 190.

consistently been found to not enable broad genus claims to modified proteins.[197] Simply put, the common disclosure's prophetic, iterative and labor-intensive process requires making and screening an immense number of modified PH20 polypeptides, before which the skilled artisan will not know which multiply-modified PH20 polypeptides are within the claims' scope.[198]

c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable

Like any protein, the activity of PH20 can be unpredictably influenced by changes to its amino acid sequence.[199] Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary structures or structural motifs within the protein that are important to its biological activity (*e.g.*, catalysis, ligand binding, etc.) and/or stability.[200]

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197 *Idenix*, 941 F.3d at 1161-63 (emphasis added); *see also Amgen,* 598 U.S. at 612-15; *Wyeth*, 720 F.3d at 1384-86; *Baxalta*, 597 F. Supp. 3d at 616-19; *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 n.2 (Fed. Cir. 2020).

198 EX1003, ¶¶ 172, 183-85, 189.

199 EX1003, ¶ 61.

200 *Id.*

As explained in § VI, below, by 2011, skilled artisans could have assessed whether certain ***single*** amino acid substitutions at certain positions would be tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.[201] That person, using a rational design approach, would have performed such an assessment by, *inter alia*, analyzing evolutionarily non-conserved positions and evaluating specific changed residues using a PH20 protein structure model using experimental evidence available before 2011 that is not disclosed in or referenced by the common disclosure.[202]

By contrast, the skilled artisan could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011.[203] Introducing ***multiple*** concurrent changes into a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity and/or stability, and can even introduce new ones into the protein.[204] Replacing multiple amino

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201 EX1003, ¶ 194.

202 EX1003, ¶¶ 20-22, 49, 215-16, 220.

203 EX1003, ¶ 228.

204 EX1003, ¶¶ 59-60, 185.

acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.[205]

The cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure in 2011. For example, the further away the modeled amino acid sequence gets from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model became.[206] In addition, depending on the structural template used to produce the model, regions of the protein not supported by a corresponding structure cannot be reliably used to assess particular changes.[207] And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.[208]

Consequently, a skilled artisan could not have used conventional rational design techniques to identify, much less predict the outcome of attempts to make, the enormous number of PH20 polypeptide sequences that incorporate the myriad

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205 EX1003, ¶ 58.

206 EX1003, ¶¶ 158, 190, 228; EX1004, ¶¶ 143-144.

207 EX1003, ¶¶ 158, 228; EX1004, ¶¶ 133-135; EX1012, 4, 8.

208 EX1003, ¶ 51, 190; EX1059, 1225-26; EX1018, 378.

possible combinations of between 5 and up to 42 substitutions the claims encompass.[209] Stated another way, practicing the full scope of the claims would have been well beyond the ability of the skilled artisan's ability to reasonably predict which multiply-modified PH20 polypeptides would be enzymatically active, and, even if possible, doing so would have taken an extreme amount of time and effort even for a small handful of the vast universe of multiply-modified polypeptides within the claims.[210]

d) Other Wands Factors and Conclusion

The remaining *Wands* factors either support the conclusion that practicing the full scope of the claims would require undue experimentation or are neutral.

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed.[211] Likewise, while there was significant knowledge in the public art about hyaluronidases, there was no solved structure of the PH20 protein, experimental reports generally reported on ***loss of activity*** from mutations, and did not

[209] EX1003, ¶¶ 61, 158, 228.

[210] EX1003, ¶¶ 158, 190.

[211] EX1003, ¶¶ 158, 228.

predictably teach how to introduce changes that ***enhanced*** stability or activity. Indeed, the non-enabled patent disclosure at issue in *Amgen* dates to the same 2011 timeframe as the common disclosure.

Practicing the full scope of claims 1-2, 6-14, 21, and 24-25 thus would have required a skilled artisan to engage in undue experimentation, which renders those claims non-enabled.

2. Dependent Claims Additionally Are Not Enabled

a) Claims 3 and 4

Claims 3 and 4 require the modified PH20 polypeptides to have increased activity (*i.e.*, >100% of unmodified PH20) or increased resistance to or stability in denaturing conditions.

The reasons why claims 1-2, 6-14, 21, and 24-25 are not enabled (*see* § V.B.1) establish why claims 3 and 4 are also not enabled. Specifically, a skilled artisan could not have predicted which of the trillions of PH20 polypeptides having up to 41 changes beyond a required change at position 312 would exhibit increased activity or stability compared to an unmodified PH20.[212] Instead, a skilled artisan

[212] EX1003, ¶¶ 185, 190.

would need to make-and-test each molecule in order to practice the "full scope" of the claims.[213]

b) Claims 5 and 15

Because claims 5 and 15 encompass a substantial portion of the genus defined by claim 1, they are not enabled for the same reasons.

Additionally, as explained in § V.A.2.b, the common disclosure suggests that PH20 polypeptides (modified or unmodified) that extend past position 456 would be "insoluble." Based on it and published literature, a skilled artisan would have expected the presence of the hydrophobic GPI sequence in the PH20 protein could cause aggregation, loss of activity, and/or reduced expression.[214] The common disclosure reinforces that these problems can occur, but provides no guidance as to how solve them and no examples of modified PH20 polypeptides extending past position 456 that are soluble. Claims 5 and 15 are thus not enabled.

c) Claims 16-20, 22-23, 26-34

The remaining claims employ the genus definition used in claim 1 and recite either further modifications to the modified polypeptides, pharmaceutical compositions, or methods of treatment using the claimed genus. These claims do

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213 *Id.*

214 EX1003, ¶¶ 89-90, 196; EX1001, 51:2-4, 72:32-44; *also* EX1005, 2:56-61.

not add requirements that limit the numbers of polypeptides in the claim 1 genus.[215] They are therefore not enabled for the same reasons.[216]

C. Inactive PH20 Polypeptides Are Not Useful and Do Not Remedy the § 112(a) Deficiencies of the Claims

Patentee may contend the claims do not require the modified PH20 polypeptides to be "active mutants." Such a contention, even if accepted, does not solve the written description and enablement problems of the claims.

First, it ignores that at least ***a portion*** of the claimed genus ***does*** require the modified PH20 polypeptides to be an "active mutant." *See* § V.B.2.b. Because dependent claim 4 requires the modified PH20 polypeptides to exhibit increased hyaluronidase activity, parent claim 1 necessarily encompasses a sub-genus comprised of "active mutant" modified PH20 polypeptides. A failure to enable or describe a subgenus within the scope of the claims demonstrates that the claim ***as a whole*** is unpatentable for lack of written description and non-enablement.[217]

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[215] Claim 21 limits the genus by removing SEQ ID NO:7, but defines an immense genus otherwise identical to claim 1.

[216] *See, e.g.*, *Idenix*, 941 F.3d at 1155, 1165.

[217] *ABS Glob., Inc. v. Inguran*, 914 F.3d 1054, 1070, 1074 (7th Cir. 2019) ("If the specification failed to enable [a limitation] in the dependent claim, then [] the full scope of the invention is also not enabled in the independent claim, and

Second, the common disclosure fails to provide any correlation between changes to PH20 polypeptides and ***either*** active or inactive mutants.[218] Rather, it leaves to the skilled artisan the burdensome task of making and testing, through trial-and-error iteration, each of the 10^{59}+ candidate polypeptides within the claims' scope to determine which exhibit hyaluronidase activity and which are inactive mutants.[219]

Third, the only putative utility identified for "inactive" polypeptides is as "antigens in contraception vaccines."[220] This assertion is not scientifically credible, but regardless, the common disclosure provides no guidance about which epitopes on the PH20 protein must be preserved in an "inactive mutant" (if any) to induce contraceptive antibody production in a human subject.[221] Notably, while the specification cites two studies in guinea pigs,[222] it ignores numerous

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both claims are invalid for non-enablement") (citing *Alcon Research, Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1367-68 (Fed. Cir. 2012)).

218 EX1003, ¶ 143.

219 EX1003, ¶¶ 173-74, 182-84.

220 EX1001, 75:56-58, 184:54-185:6.

221 EX1003, ¶ 113.

222 EX1001, 184:54-185:6; EX1022, 1142-43; EX1023, 1133-34.

publications before 2011 that showed that immunizing mammals with PH20 did ***not*** cause contraception.[223] Moreover, Patentee's own clinical studies of the unmodified $PH20_{1-447}$ protein reported in 2018 that, despite producing anti-PH20 antibodies, those anti-PH20 antibodies ***did not affect fertility*** in humans:

> Although some antisperm antibodies are associated with decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex.[224]

Notably, Patentee reported this clinical result before filing the application that issued as the '035 Patent.

Even if one considers the unlikely possibility than some epitope on human PH20 might induce contraceptive effects in a human, a skilled artisan could not have reasonably predicted from the common disclosure whether any "inactive mutant" modified PH20 polypeptides would preserve that epitope or induce

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223 *See* EX1019, 325, 331-33 ("recombinant mPH20 is not a useful antigen for inclusion in immunocontraceptive vaccines that target mice"); EX1020, 179-81 ("immunization [of rabbits] with reproductive antigens … are unlikely to result in reduced fertility …"); EX1021, 30310, 30314 ("PH-20 is not essential for fertilization, at least in the mouse …").

224 EX1024, 87-88; *see also* EX1061, 1154; EX1003, ¶¶ 110-11.

antibody production that would confer (contrary to Patentee's clinical evidence) contraceptive effects in humans.[225] Indeed, a skilled artisan would have expected the vast majority of "inactive mutant" PH20 polypeptides would have no utility at all.[226] Consequently, a skilled artisan would not have accepted the common disclosure's assertion that "inactive mutants" are useful as contraceptive vaccines, particularly in humans.[227]

Finally, and most significantly, the common disclosure does not identify a single inactive PH20 mutant (with any number of substitutions) that was shown to have contraceptive effect.[228] Therefore, at most, the common disclosure presents

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225 EX1003, ¶¶ 112-13.

226 *Id.*; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App'x. 26, 30 (Fed. Cir. 2007).

227 EX1003, ¶¶ 112-13; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

228 EX1003, ¶ 113.

only a "research proposal" to discover such "inactive mutants."[229] It does not demonstrate possession of or enable the immense and diverse genus of PH20 polypeptides claimed, regardless of whether the claims are appropriately limited to "active mutants" or, instead, include "inactive mutants."

D. The Original Claims of the '731 Application Do Not Cure the Written Description and Enablement Deficiencies

The specifications of the pre-AIA '731 Application and AIA '035 Patent are substantially identical, and neither supports the challenged claims as § 112(a) requires by either. The claims are both PGR eligible and unpatentable under § 112(a).

The original claims of the '731 Application provide no additional guidance or insight demonstrating written description or enablement of the genera of multiply-modified PH20 polypeptides presently claimed. Those original claims claimed equivalently broad genera via sequence identity language (e.g., 85% to SEQ ID NOS: 3, 7 or 32-66)(claims 1-3) or having up to "75 or more amino acid replacements" (claim 4). Dependent claims listed single positions (claim 12) or replacements (claims 13-16) in those polypeptides. And, while certain claims

[229] *See Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("[t]he utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research").

contemplated 2-3 particular combinations of amino acid replacements (from dozens listed), others encompassed substitutions at unspecified locations.[230]

Those the original claims do not provide § 112 support for the challenged claims.[231]

VI. Challenged Claims 1-2 and 5-34 Are Unpatentable Under § 103

Claims 1-2, 6-14, 21, and 24-25 each define genera including one or both of two specific modified PH20 polypeptides: S312T $PH20_{1-447}$ and S312N $PH20_{1-447}$. *See* § IV.D.2. Because both mutants would have been obvious from the '429 Patent in view of Chao and the knowledge of a skilled artisan, claims 1-2, 6-14 and 24-25 are unpatentable. Claims 5, 15-23, and 26-34 are also obvious: as each recites attributes met by S312T or S312N $PH20_{1-447}$, or is suggested by the '429 Patent alone or with other prior art.

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230 EX1026, at 335.

231 *See, e.g.*, *Ariad Pharms.*, 598 F.3d at 1349 ("original claim language" does not "necessarily disclose[] the subject matter that it claims"); *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993) (original claim amounted to no more than a "wish" or "plan" for obtaining the claimed DNA and "attempt[ed] to preempt the future before it has arrived").

A. The Prior Art

The ’429 Patent (EX1005) is owned by Patentee, was originally filed in 2003, and issued on Aug. 3, 2010.

Chao (EX1006) was published in “Biochemistry” in 2007. Chao is not discussed in the common disclosure of the ’035 Patent and ’731 Application and was not cited during examination.

Knowledge of the skilled artisan relevant to obviousness is described in the testimony of Drs. Hecht (EX1003) and Park (EX1004), and is also documented in the prior art, including Patentee’s earlier-published application, WO297 (EX1007).

B. Because S312T and S312N $PH20_{1-447}$ Would Have Been Obvious, Claims 1-2, 6-14, and 24-25 Are Unpatentable

Patentee’s ’429 Patent would have motivated a skilled artisan to produce modified $PH20_{1-447}$ polypeptides having a single amino acid substitution in non-essential regions of the protein. Guided by her familiarity with rational protein design and the teachings of the ’429 Patent and Chao, the artisan would have readily identified single amino acid substitutions in non-essential regions of $PH20_{1-447}$ that would have been tolerated (*i.e.*, a $PH20_{1-447}$ with that single substitution would retain its enzymatic activity). S312T $PH20_{1-447}$ and S312N $PH20_{1-447}$ are two such examples. Because claims 1-2, 6-14 and 24-25 encompass at least one of these obvious variants of $PH20_{1-447}$, each is unpatentable.

1. Patentee's '429 Patent Motivates a Skilled Artisan to Make Single Amino Acid Substitutions in Non-Essential Regions of $PH20_{1-447}$

Patentee's '429 Patent, filed in 2003, describes its invention as soluble PH20 hyaluronidase glycoproteins ("sHASEGPs") that are enzymatically active at neutral pH.[232] It exemplifies and claims one such "sHASEGP" that terminates at position 447 (positions 36-482 of SEQ ID NO: 1).[233]

The '429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, in pharmaceutical compositions, and combined with other therapeutic agents (e.g., antibodies, chemotherapeutics), and illustrates administering such combinations subcutaneously to treat cancer and hyaluronidase disorders.[234] $PH20_{1-447}$ was approved by the FDA as Hylenex® in 2005.[235] The '429 Patent's teachings combined with the status of $PH20_{1-447}$ as an approved

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232 EX1005, 6:4-10, 10:30-59.

233 EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

234 EX1005, 8:25-9:4, 54:40-65, 56:34-57:36, 60:38-61:4, 63:41-61, 74:10-29, 76:19-77:36, 99:28-100:47.

235 EX1049, 1.

human therapeutic before 2011 would have induced a skilled artisan to focus on this particular PH20 polypeptide.[236]

Patentee's '429 Patent defines sHASEGPs as including wild-type $PH20_{1-447}$ and "equivalent" proteins "with amino acid substitutions that do not substantially alter activity" of the protein.[237] It explains:

> Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity …[238]

The '429 Patent also explains that single amino acid substitutions can include "conservative" substitutions in Table 1, but that "[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions."[239]

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236 EX1003, ¶ 195.

237 EX1005, 9:65-10:13; *see also id.* at 18:64-19:6 ("equivalent" proteins).

238 EX1005, 16:14-22.

239 EX1005, 16:24-36.

The ’429 Patent thus teaches making a ***particular*** type of modification (a single amino acid substitution) in ***particular*** locations (non-essential regions of PH20) in a ***particular*** PH20 sequence ($PH20_{1-447}$) to yield equivalents of $PH20_{1-447}$ (*i.e.*, those that do not substantially alter the activity or function of $PH20_{1-447}$).[240]

The ’429 Patent also motivates skilled artisans to undertake this effort to design and produce such single-amino acid substituted $PH20_{1-447}$ proteins because it assures them their efforts will be successful.[241] As it states, skilled artisans recognized that such “single amino acid substitutions in non-essential regions” of $PH20_{1-447}$ “do not substantially alter biological activity” of $PH20_{1-447}$. As such, a skilled artisan would have expected a $PH20_{1-447}$ mutant with a single amino acid substitution in a non-essential region to have the same utility, therapeutic applications, and other characteristics that the ’429 Patent identifies for wild-type $PH20_{1-447}$ and other sHASEGPs.[242]

2. Chao Provides Information Useful for Engineering the Changes to $PH20_{1-447}$ that the ’429 Patent Suggests

In 2011, a skilled artisan looking to implement the ’429 Patent’s suggestion to make a single-amino acid modification in a non-essential region of $PH20_{1-447}$

240 EX1003, ¶¶ 206-208; EX1004, ¶ 32.

241 EX1003, ¶¶ 207-208.

242 EX1003, ¶¶ 199-202, 207, 222.

would have recognized such changes could best be accomplished using rational design, which here involves determining (i) which regions are non-essential in PH20, and (ii) which single amino acids to substitute into positions in those non-essential regions.[243]

The '429 Patent was written eight years before 2011. Given that, a skilled artisan would have looked for additional published insights into the structure of human hyaluronidase enzymes like PH20.[244] That would have led the person directly to Chao (EX1006), which reported an experimentally determined structure for human HYAL1, and provided new insights into the shared characteristics of human hyaluronidase enzymes.[245]

First, by superimposing the HYAL1 and bee venom hyaluronidase structures, Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues in it that interact with HA.[246]

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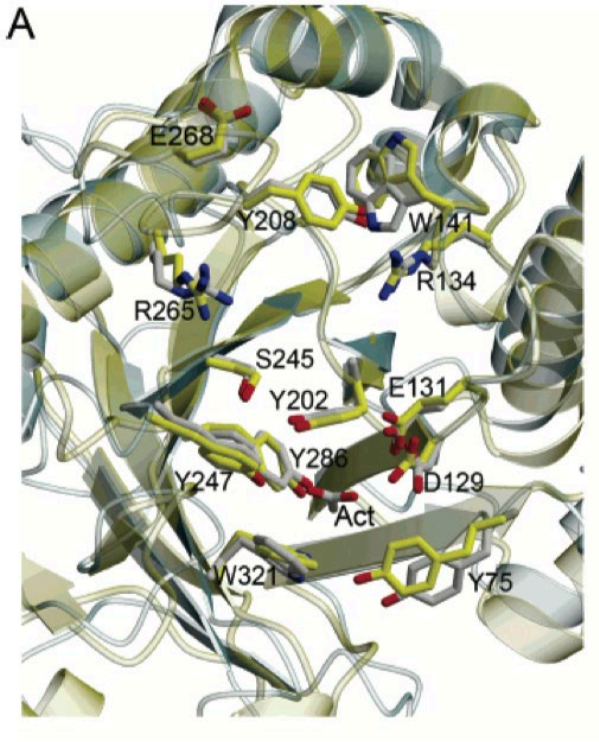
243 EX1003, ¶¶213-14.

244 EX1003, ¶¶ 86, 209; EX1004, ¶ 88.

245 EX1003, ¶¶ 86, 209-11; EX1004, ¶ 88; EX1006, 6912-17.

246 EX1006, 6917 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1004, ¶¶ 89-91; EX1003, ¶¶ 81-82.



The ’429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20,[247] and taught that hyaluronidase domains share similarity among and between species, including residues necessary for enzymatic activity.[248]

Second, using an alignment of five human hyaluronidases, Chao identified predicted secondary structures (*e.g.*, β-sheets, α-helices) (Figure 3, below), as well as invariant conserved positions (blue), residues involved in catalysis (red),

247 EX1005, 4:12-22, 86:49-53, 88:14-24.

248 EX1005, 2:6-67, 4:11-22.

conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).[249]

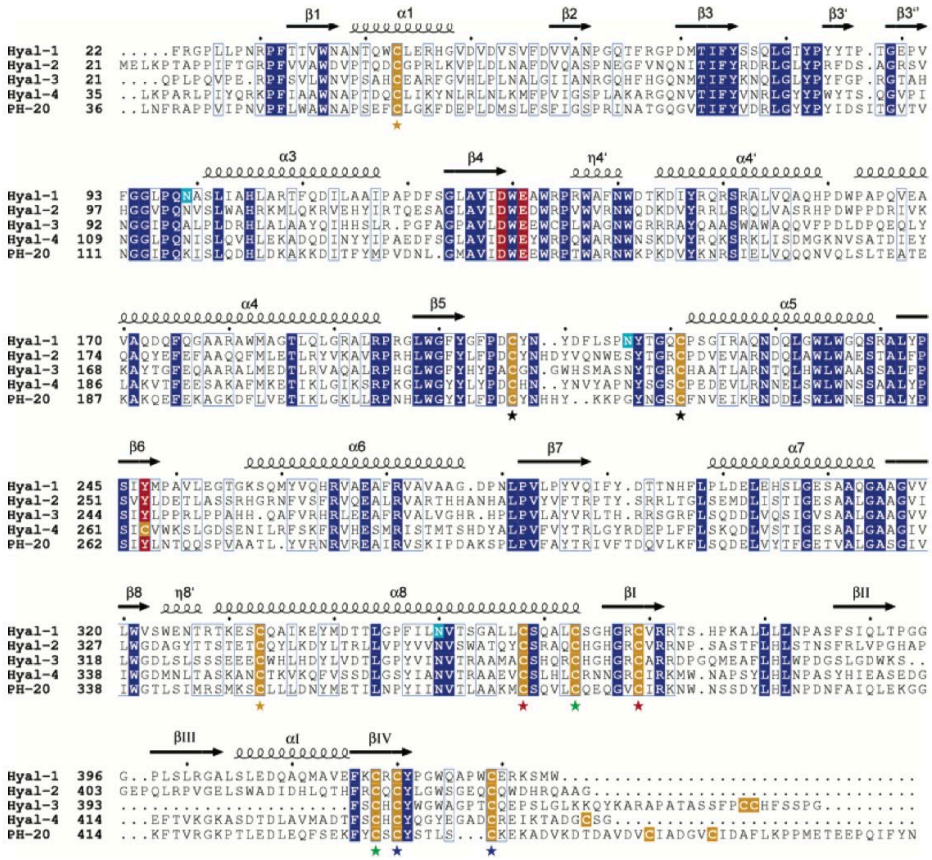


FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative replacements are blocked in blue. Pairs of cysteine residues that form disulfide bonds are indicated by stars with matching colors. Secondary structure units are labeled as in Figure 2B.

Third, Chao reported the presence of "a novel, EGF-like domain" in the C-terminal region of human hyaluronidases that was "closely associated" with the

[249] EX1006, 6916; EX1003, ¶ 83; EX1004, ¶ 92.

catalytic domain (discussed above, § V.A.1.b.iii), and identified a characteristic pattern for the Hyal-EGF domain in PH20 at positions 337-409.[250]

3. A Skilled Artisan Would Have Identified Position 312 as Being in a Non-Essential Region of $PH20_{1-447}$ in 2011

To implement the '429 Patent's suggestion to produce modified $PH20_{1-447}$ polypeptides with single amino acid substitutions in non-essential regions that retain hyaluronidase activity, the skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011.[251] The person would have done that using conventional sequence alignment tools in conjunction with the information in the '429 Patent and in Chao, as well as information publicly known in 2011.[252]

A multiple-sequence alignment identifies non-essential regions in PH20—they are the sequences between essential residues and are positions at which variations occur at a frequency above ~5% (illustrated using Chao below).[253]

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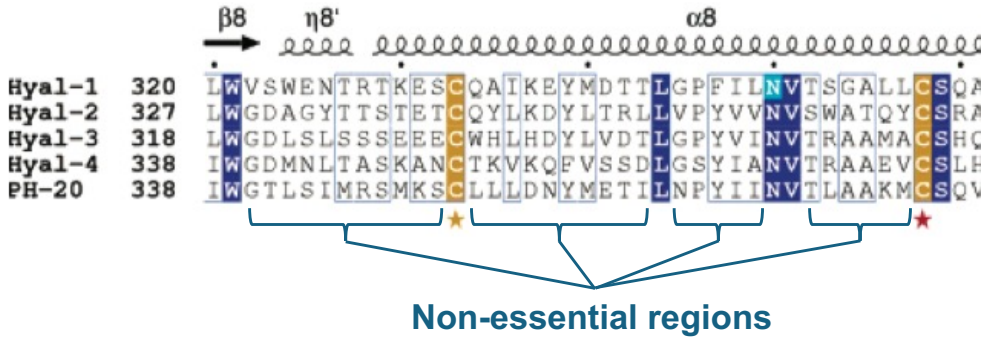
250 EX1006, 6911; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84-85.

251 EX1003, ¶¶ 212-214; EX1004, ¶¶ 22, 25-30, Appendix D-3.

252 EX1003, ¶¶ 20-21, 213-215; EX1004, ¶¶ 22-24; EX1017, 224-26.

253 EX1004, ¶¶ 31-32, Appendix D-2; EX1003, ¶ 215; EX1006, 6916.

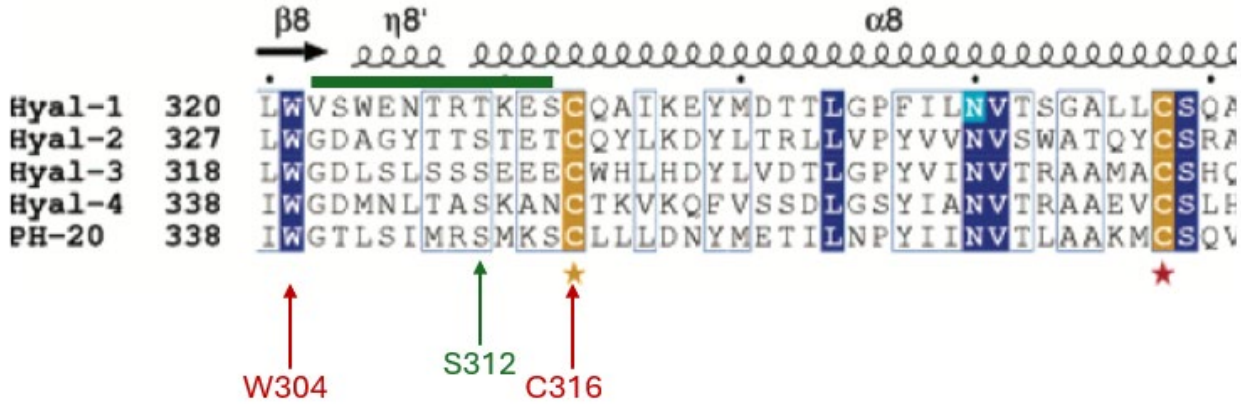


Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps. He first identified 88 homologous hyaluronidase protein sequences that had been published by December 29, 2011.[254] Dr. Park then prepared a multiple-sequence alignment of the 88 homologous proteins, similar to what Chao did with the five human hyaluronidases, and from that alignment identified essential (Appendix D-3) and non-essential (Appendix D-2) residues.[255]

[254] EX1004, ¶¶ 27, 125-128; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

[255] EX1004, ¶¶ 28-32, 129-130, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

Position 312 is within a non-essential region of $PH20_{1-447}$, which is shown by Dr. Park's analysis, and also by Chao's Figure 3; both report the same bounding essential residues (*i.e.*, W304 and C316) (below).[256]



Following the guidance and information in the '429 Patent and Chao, and assessing information publicly available in December 2011 using conventional sequence analysis tools, a skilled artisan would have readily identified position 312 as a position within a non-essential region $PH20_{1-447}$.[257]

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256 EX1003, ¶ 217; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.

257 EX1003, ¶ 220; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

4. A Skilled Artisan Would Have Found Threonine or Asparagine to Be Suggested as an Obvious Single Amino Acid Substitution for Serine at Position 312 of $PH20_{1-447}$

The multiple-sequence alignment reveals a second powerful insight: it identifies ***which*** amino acids have been tolerated at specific positions in the amino acid sequence of homologous, stable and active naturally occurring hyaluronidase enzymes.[258] This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms those variations in the sequences of a protein that do not yield stable and active forms of the protein.[259] A skilled artisan can readily compile a list of amino acids that have been tolerated at positions within non-essential regions of PH20 using a multiple-sequence alignment of homologous hyaluronidase enzymes.[260]

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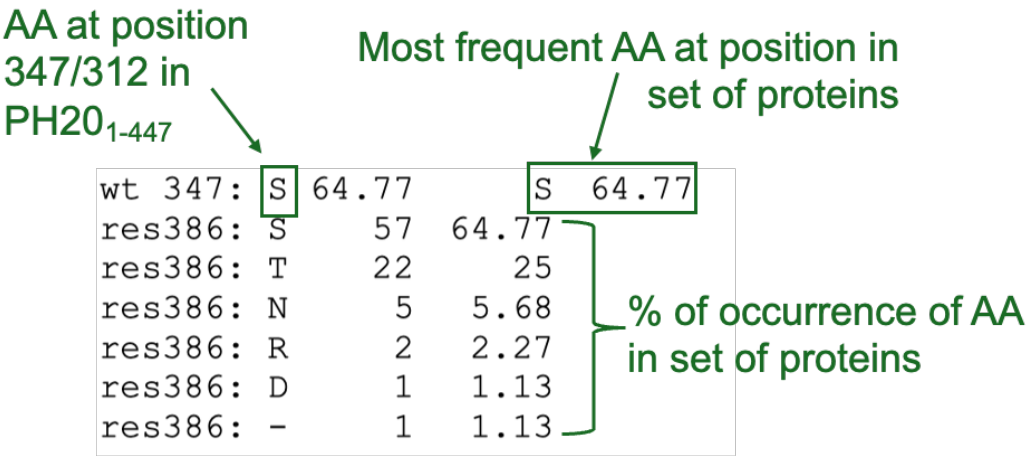
[258] EX1003, ¶¶ 20, 49, 214, 218, 220; EX1004, ¶¶ 21-22.

[259] EX1003, ¶¶ 20, 214; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 ("Evolution provides a tremendously useful model for protein design. … By considering the common features of the sequences of these proteins, it is possible to deduce the key elements that determine protein structure and function—even in absence of any explicit structural information."); EX1014, 351.

[260] EX1003, ¶¶ 218, 220; EX1004, ¶¶ 21-22.

Using his multiple-sequence alignment of the 88 hyaluronidase proteins known by December 2011, Dr. Park identified and calculated the frequency of each amino acid that occurs at positions corresponding to position 312 in PH20 (shown below).[261] The wild-type residue at position 312 in PH20 is serine (S), which occurs in ~65% of the proteins (including PH20). The second-most prevalent amino acid at position 312 is threonine (T) (~25%), which is present in 22 different hyaluronidase proteins. Asparagine (N) appears third-most frequently (~6%, 5 proteins).



A skilled artisan would have found it obvious to substitute threonine (T) or asparagine (N) for serine (S) at position 312 as a single amino acid substitution in a non-essential region of PH20$_{1-447}$. [262]

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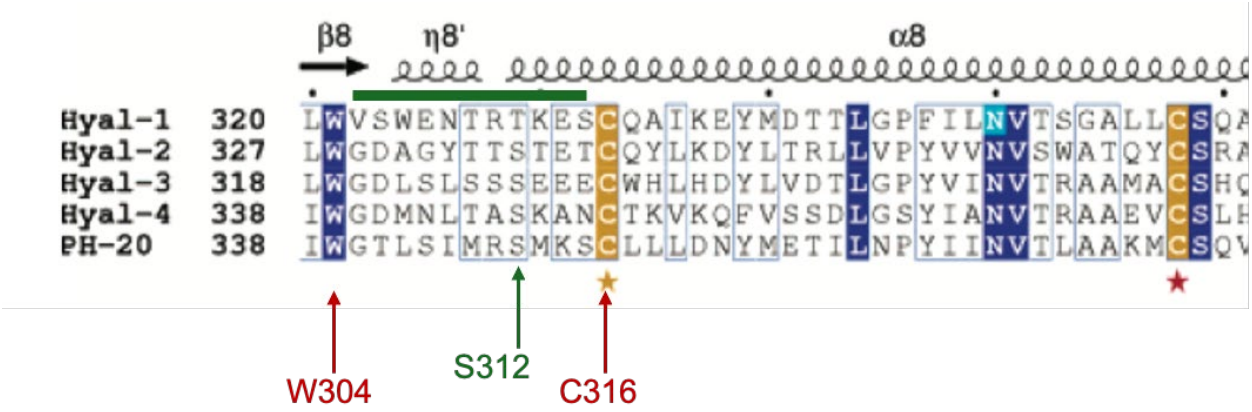
[261] EX1004, ¶¶ 30-32, 41-43, 106, 111, 121, Appendix D-1; EX1003, ¶ 218;

[262] EX1003, ¶¶ 214, 218-22; EX1004, ¶¶ 41-42, 106.

First, threonine and asparagine are the second and third-most prevalent amino acids found at positions corresponding to 312 in PH20, respectively.[263] These amino acids would have been the obvious candidates to substitute for serine at position 312 of PH20, as they are each tolerated at that position in many naturally occurring homologous hyaluronidase enzymes.[264] Threonine also occurs at the position corresponding to 312 in another human hyaluronidase, HYAL1.[265]



Second, Chao identifies residue S312 as being the first residue of the α8 α-helix in PH20, which is termed the "N-cap" residue (above).[266] Asparagine was known to be the most preferred residue for an N-cap residue at the start of an α-

263 EX1004, ¶¶ 43, 106, 111, 121; EX1003, ¶ 218.

264 EX1003, ¶¶ 218-21; EX1004, ¶¶ 106, 111, 121.

265 EX1006, 6916, Fig. 3.

266 EX1003, ¶ 219; EX1004, ¶¶ 108-109.

helix, in proteins, and threonine was known to be highly favored at that position.[267] A skilled artisan thus would have found both asparagine and threonine to be obvious substitutes for the serine in the N-cap residue at position 312 for the α8 helix in PH20.[268]

Third, the serine at position 312 is solvent-exposed.[269] A skilled artisan would recognize that other hydrophilic amino acids, such as asparagine and threonine, would be favored in this hydrophilic position, and would be obvious choices for this reason.[270]

Fourth, the '429 Patent identifies threonine as a conservative amino acid substitution for serine in its Table 1.[271] A skilled artisan would understand the '429 Patent to be suggesting replacing a serine residue in a non-essential position in PH20 (such as at position 312) with a threonine residue.[272]

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267 EX1003, ¶ 220; EX1004, ¶ 120; EX1077, 1325; EX1076, 1650-52; EX1078, 2-3.

268 EX1003, ¶ 220; EX1004, ¶¶ 120-121.

269 EX1003, ¶ 219; EX1004, ¶¶ 32, 108.

270 EX1003, ¶ 220; EX1004, ¶¶ 32, 108-10, 115, 119.

271 EX1005, 16:7-36.

272 EX1003, ¶¶ 208, 220.

For all these reasons, a skilled person would have found it obvious to change the serine (S) at position 312 to either threonine (T) or asparagine (N) in $PH20_{1-447}$.[273]

5. A Skilled Artisan Would Have Reasonably Expected the S312T and S312N Substitutions in $PH20_{1-447}$ to Yield Enzymatically Active PH20 Proteins

a) Patent Owner Cannot Contradict Its Past Representations to the PTO

Replacing the serine (S) at position 312 with threonine (T) or asparagine (N) yields a $PH20_{1-447}$ with a single amino acid substitution in a non-essential region of the polypeptide.[274] In its '429 Patent, Patentee stated:

> Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.[275]

Patentee also secured claims in the '429 patent to modified $PH20_{1-447}$ proteins with at least one substitution (*e.g.*, claim 1), despite not providing examples of PH20 proteins with any substitutions. Patentee, thus, made and relied on its statements that a skilled artisan would have expected ***any*** single amino acid

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[273] EX1003, ¶¶ 217-220.

[274] *See* § VI.B.3; EX1003, ¶¶ 217-218; EX1004, ¶ 32.

[275] EX1005, 16:17-20.

substitution in ***any*** non-essential position of $PH20_{1-447}$ to not substantially affect the activity of the enzyme, and particularly ones in Table 1. Patentee should not be permitted to now contend a skilled artisan would not have reasonably expected that the S312T or S312N substitutions in $PH20_{1-447}$ would yield an enzyme with substantially the same activity as unmodified $PH20_{1-447}$.

b) Skilled Artisans Would Reasonably Expect S312T and S312N to be Tolerated in $PH20_{1-447}$

Independently, a skilled artisan would have reasonably expected the S312T and S312N substitutions to not substantially alter the biological activity (hyaluronidase activity) of $PH20_{1-447}$. Both experts noted that many naturally occurring homologous hyaluronidase proteins contain either threonine or asparagine at the position corresponding to position 312 in PH20 (including for threonine in human HYAL1 (Chao)), which suggests both would be tolerated at position 312 in PH20.[276] Asparagine and threonine are both commonly n-cap positions of an α-helix, and both have hydrophilic characteristics compatible with the solvent-exposed environment of position 312.[277] A skilled artisan thus would

[276] EX1003, ¶ 214; EX1004, ¶¶ 111, 121.

[277] EX1003, ¶ 220; EX1004, ¶ 120; EX1077, 1325; EX1076, 1650-52; EX1078, 2-3.

have reasonably expected the S312T and S312N substitutions to be tolerated in $PH20_{1-447}$.[278]

c) A PH20 Structural Model Confirms that $PH20_{1-447}$ Would Tolerate Threonine and Asparagine at 312

Dr. Park further assessed whether single amino acid substitutions in $PH20_{1-447}$ would be tolerated, including S312T and S312N, using a PH20 protein structural model generated by SWISS-MODEL using Chao's HYAL1 structure as the template, as would have been done in 2011 by a skilled artisan.[279]

Dr. Park explains that his PH20 model was reliable in the region of position 312 of PH20 based on QMEAN values,[280] and would be very similar to a PH20 model generated by SWISS-MODEL in 2011 (*e.g.*, it used 165 conserved positions in the backbone of the two proteins).[281]

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278 EX1003, ¶¶ 221-222.

279 EX1004, ¶¶ 39-40, 131-32; EX1003, ¶¶ 225, 227; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

280 EX1004, ¶¶ 133-35 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

281 EX1004, ¶¶ 136-37, 141; EX1038, 3382-4; EX1017, 229-230; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

Dr. Park also devised a consistent, objective methodology for assessing substitutions using the $PH20_{1-447}$ model.[282] Factors he considered included, *inter alia*, the number of neighboring residues at position 312 (*i.e.*, those within 5 Å), the various possible interactions between neighbors (*e.g.*, hydrophobic, charged, van der Walls, steric, etc.), and solvent accessibility.[283] Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*, hydrophobic-hydrophilic, effects on secondary structures, size related issues such as steric clashes or creation/filling of "holes" in the structure).[284]

Dr. Park assessed the environment of position 312 visually by comparing the wild-type with the version incorporating substituted amino acids at position 312 using functionality within the viewer (PyMol) and as a modeled sequence generated from the $PH20_{1-447}$ sequence incorporating the single substitution in

[282] EX1004, ¶¶ 102-103; *see generally id.* at § IV.C (description of Dr. Park's methodology).

[283] EX1004, ¶¶ 44-47, 53-60, 65-85, Appendix D-5; EX1035, 1408, Table 2; EX1043, 2, Table 1.

[284] EX1004, ¶¶ 62-63, 85.

SWISS-MODEL.[285] These technologies were available in 2011.[286] He used his methodology to assess substitutions representing diverse interactions, and confirmed it provided a consistent, objective and unbiased evaluation of substitutions.[287]

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed (below).[288]

Score	***Expected Impact***	***Expected Toleration***
1	Significantly Destabilized	Likely Not Tolerated
2	Neutral or Minor Impacts	Tolerated
3	Improved Stability	Tolerated

Dr. Park assigned a score of 2 for the S312T and S312N substitutions in $PH20_{1\text{-}447}$, indicating that each would not be expected to significantly impact stability.[289] He observed that in the wild-type environment, position 312 is a

[285] EX1004, ¶¶ 61, 107, 110, 116, 122, 146-48; EX1003, ¶¶ 22, 49, 225, 227.

[286] EX1004, ¶¶ 131, 136-37, 145, 147-49; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4.

[287] EX1004, ¶¶ 102-103.

[288] EX1004, ¶¶ 85-87.

[289] EX1004, ¶¶ 117, 123, Appendix C.

solvent exposed position, and that several amino acids (including T and N) occur at this position in homologous proteins.[290]

Dr. Park identified several reasons why threonine would be tolerated at position 312 of PH20. One is that threonine is a hydrophilic residue, making it compatible with the solvent-exposed environment at position 312.[291] Also, like the S312 in PH20, the oxygen of threonine's hydroxyl group plays a stabilizing role by acting as a hydrogen bond acceptor for the hydrogen on the amide bond between positions 314 and 315 (image below, 3.1 line).[292] This interaction occurs in the HYAL1 and bee venom structures, which both have threonine at the position corresponding to 312.[293] Threonine in position 312 also will have van der Waals interactions with another nearby residue (M313) (4.0 line below), further enhancing stability around this position.[294] Overall, Dr. Park found that the S312T substitution would have a neutral effect on the protein's stability.[295]

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290 EX1004, ¶¶ 108, 106.

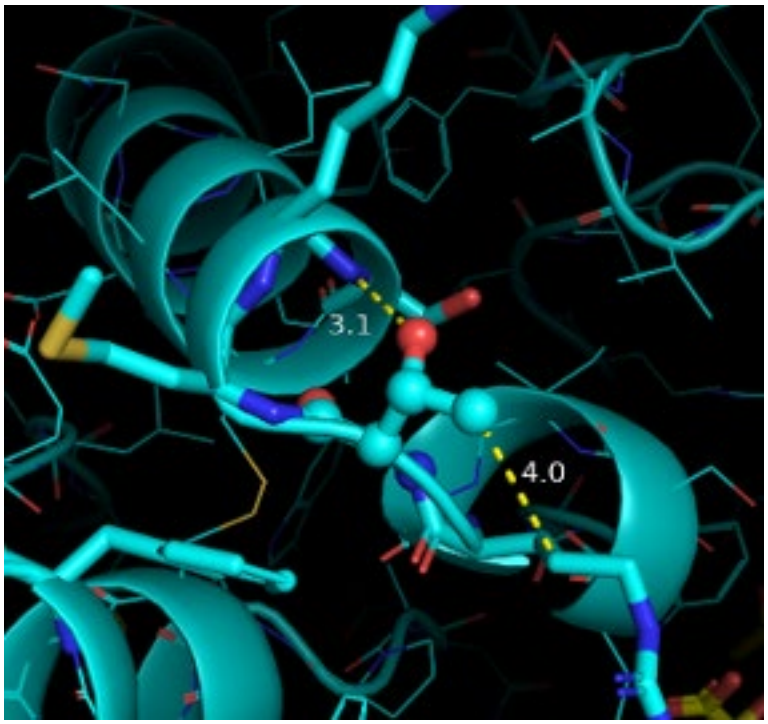
291 EX1004, ¶ 112.

292 EX1004, ¶ 114.

293 EX1004, ¶ 115.

294 EX1004, ¶ 114.

295 EX1004, ¶ 117.



Dr. Park also identified several reasons why asparagine would be tolerated at position 312 of PH20. Like threonine and serine, it is a hydrophilic residue and compatible with the solvent-exposed environment at position 312.[296] He also observed that the carbonyl oxygen in asparagine can dynamically form hydrogen bonds with the hydrogen on the amide bond between positions 314 and 315.[297] Further, Dr. Park identified asparagine as the most common n-cap residue for α-

[296] EX1004, ¶ 120.

[297] *Id.*

helices.[298] Overall, Dr. Park found that the S312N substitution would have a neutral effect on the stability of the protein.[299]

Dr. Park's visualization-based assessment is a technique that was prevalent in 2011.[300] Similarly, his technique of assessing interactions between neighbors and assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications.[301]

Dr. Hecht reviewed Dr. Park's analysis and conclusions and agreed with both.[302] Through his own assessment, he observed that threonine and asparagine would be likely tolerated at position 312. For example, he explained that each

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298 EX1004, ¶ 120.

299 EX1004, ¶ 123.

300 EX1017, 228 ("… a structural biologist's intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this."); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 22, 49, 225, 227.

301 EX1004, ¶¶ 48-52; EX1031, 459, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 227.

302 EX1003, ¶ 229.

amino acid's hydrophilic character would be compatible with the high solvent accessibility of position 312.[303] He also pointed out that asparagine was known to be the most common N-cap residue in α-helix structures in proteins, while threonine was known to have a high prevalence at N-cap positions; both points suggest they will be tolerated at position 312.[304]

The common disclosure defines an "active mutant" as a modified PH20 polypeptide with at least ~40% of the activity of unmodified $PH20_{1-447}$.[305] Drs. Hecht and Park each independently concluded that the S312T and S312N substitutions would have been tolerated by $PH20_{1-447}$, meaning it would exhibit comparable hyaluronidase activity to unmodified $PH20_{1-447}$ (*i.e.*, activity well above 40%).[306] A skilled artisan considering the S312T and S312N substitutions in $PH20_{1-447}$ would have reasonably expected that both would exhibit at least 40% of the activity of unmodified $PH20_{1-447}$.[307]

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303 EX1003, ¶ 230.

304 EX1003, ¶¶ 220, 231-32; EX1076, 1648, 1650-52; EX1077, 1325, 1331, 1334; EX1078, 2-3.

305 EX1001, 75:47-52; *also id.* at 79:29-33.

306 EX1003, ¶¶ 229-232, 234; EX1004, ¶¶ 117, 123.

307 EX1003, ¶ 234.

Based on the '429 Patent, Chao, and information available in 2011, the S312T and S312N $PH20_{1-447}$ mutant polypeptides would have been obvious to a skilled artisan in 2011. And because claims 1-2, 6-14, and 24-25 each encompass one or both of the single-replacement modified S312T and S312N $PH20_{1-447}$ polypeptides, each claim is unpatentable.

C. Dependent Claims 5, 15-23, and 26-34 Are Obvious

None of the dependent claims define subject matter that is independently patentable from claims 1-2, 6-14, and 24-25. For the reasons below, each would have been obvious to a skilled artisan.

1. Claims 5 and 15

Claims 5 and 15 require the modified PH20 polypeptide to be "a soluble PH20 polypeptide" and, in the case of claim 15, "C-terminally truncated."

The '429 Patent indicates that $PH20_{1-447}$ exists as a soluble form of the PH20 protein because it omits the C-terminal residues above position 448 (483) containing the GPI anchor sequence.[308] A skilled artisan would have expected that changing serine to threonine or asparagine at position 312 would not change the

[308] EX1005, 3:57-62; 87:52-88:24.

solubility of the $PH20_{1-447}$ as it would not meaningfully alter the structure of the protein.[309]

2. Claims 16-18

Claims 16-18 require the modified PH20 polypeptide to "comprise[] one or more post-translational modifications" including glycosylation (claims 16-17) and be a "glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues" (18).

The '429 Patent teaches (i) that human PH20 must be glycosylated to exhibit activity, and (ii) expression of $PH20_{1-447}$ in mammalian (CHO) host cells that yield active forms of $PH20_{1-447}$.[310] It further teaches that "N- and O-linked glycans are attached to polypeptides through asparagine-N-acetyl-D-glucosamine … linkages," and claims PH20 polypeptides (including $PH20_{1-447}$) having asparagine-linked sugar moieties.[311] Frost reports that the recombinant production of $PH20_{1-447}$ in CHO cells "resulted in a 447 amino acid 61 kDA glycoprotein with a properly processed amino terminus and 6 N-linked glycosylation sites."[312]

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309 EX1003, ¶¶ 196, 203, 222.

310 EX1005, 95:13-30; 40:41-51, 89:53-91:67; 88:5-9.

311 EX1005, 3:27-35, claims 1, 6.

312 EX1013, 432.

Based on the ’429 Patent and knowledge in the art, a skilled artisan would have found it obvious to produce S312T $PH20_{1-447}$ in a CHO cell, and that doing so causes six N-linked glycosylation sites to be glycosylated.[313]

3. Claims 23, 26-32

Claim 23 specifies a pharmaceutical composition comprising any modified PH20 polypeptide in the genus of claim 1. Claims 26-29 add a “therapeutically active agent formulated in the same composition or in a separate composition” (26), and that the active agent may be a “drug” (27) or “chemotherapeutic agent” (28) or “antibody” (29).

Claims 30-32 concern methods of treating “hyaluronan-associated disease” (29) such as cancer (30) or a “solid tumor” by administering any of the modified PH20 polypeptides captured by claim 1.

The ’429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*, $PH20_{1-447}$), alone or in combination with other therapeutic agents including antibodies, small molecule drugs, chemotherapeutics, and agents used in treating

[313] EX1003, ¶¶ 197-98, 203-04.

cancer and hyaluronan-associated disease.[314] It similarly describes and claims methods of administering them subcutaneously via formulations that combine an enzymatically active hyaluronidase protein with another therapeutic agent, which together enable "spreading" of the therapeutic agent after injection.[315]

A skilled artisan would have appreciated that a single-replacement $PH20_{1-447}$ polypeptide with comparable hyaluronidase activity to $PH20_{1-447}$ (such as the S312T mutant) would be equivalently useful in the therapeutic compositions, methods of administration, and methods of treatment described in the '429 Patent for $PH20_{1-447}$.[316] Indeed, in the '429 Patent, Patentee secured claims encompassing pharmaceutical compositions containing certain modified PH20 polypeptides and chemotherapeutic agents despite the absence of any exemplification.[317] Claims 23 and 26-32 also impose no restrictions on the makeup of the pharmaceutical

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[314] EX1005, 8:60-9:4, 54:40-55:35, 56:28-57:21, 55:61-56:9, 56:66-57:21, 63:41-44, 73:4-74:29, claims 14, 29, 33.

[315] EX1005, 8:25-38, 56:28-56, 57:22-36, 58:59-59:12, 63:40-64:4, 76:18-77:37, claim 27.

[316] EX1003, ¶¶ 199-202, 207, 221-22, 234.

[317] EX1005, claims 29, 30, 50.

composition. A skilled artisan would have found such compositions and methods of administration/treatment to have been obvious from the '429 Patent.[318]

4. Claims 19-22, 33-34

Claims 19-20 and 33-34 concern conjugation of a modified PH20 polypeptide to (i) a polymer (claim 19) that may be polyethylene glycol (claim 20), (ii) a moiety such as a toxin, drug, label or multimerization domain (claim 33) or (iii) to an Fc domain (claim 34). Claim 21 specifies that the modified PH20 polypeptide further comprises a heterologous signal sequence, while Claim 22 specifies a chimeric peptide comprising the modified PH20 polypeptides of claim 1.

A skilled artisan would have found these further modifications to the S312T or S312N $PH20_{1-447}$ mutants obvious from the '429 Patent.[319] The '429 Patent teaches $PH20_{1-447}$ proteins with mutations ("sHASEPGs") can be (i) "modif[ied]" "with polymers such as polyethylene glycol";[320] (ii) conjugated to "one or more targeting agents" (*e.g.*, any moiety that specifically binds to a receptor);[321] (iii)

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318 EX1003, ¶¶ 199-202, 207.

319 EX1003, ¶¶ 203, 205.

320 EX1005, 3:64-4:1, 4:45-53, 26:20-28:4.

321 EX1005, 18:33-52.

attached to a label;[322] and (iv) incorporated into fusion (*i.e.*, "chimeric") proteins.[323] It also teaches expression of modified PH20 polypeptides that incorporate a heterologous signal sequence.[324]

D. There Is No Nexus Between the Claims and Any Evidence of Putative Secondary Indicia

Well-established law holds that evidence of secondary indicia cannot support non-obviousness if it does not have nexus to the claims. A key question in a nexus analysis is whether such evidence is commensurate with the scope of the claims. The answer here is a definitive no.

Patentee is likely to dispute that the S312T and S312N $PH20_{1-447}$ are obvious, for example, because the S312N variant is reported to have unexpectedly high hyaluronidase activity as a single substitution mutant. Demonstrating that result for one mutant out of the ~10^{59} and 10^{112} modified PH20 polypeptides encompassed by the claims, however, utterly fails to establish a nexus between that evidence and the claims. The argument is inapplicable to the S312T mutant, which

322 EX1005, 38:40-49, 40:15-21.

323 EX1005, 18:33-52, 47:10-22, 51:25-30.

324 EX1005, 34:33-37; 88:28-90:15 ("Kappa leader sequence" used in expression of PH20 polypeptides).

exhibits reduced activity.[325] As explained in § V.A.1, the single-substitution S312T and S312N $PH20_{1-447}$ mutants are not representative of the numerous, structurally different proteins encompassed by the claims, particularly those expected to be inactive. No evidence or explanation is provided in the common disclosure that resolves this confusion.

If Patentee advances evidence or arguments concerning nexus, consideration of that issue should be deferred until after institution, and Petitioner reserves its right to contest such evidence.

VII. The Board Should Not Exercise Its Discretion Under § 324(a) or § 325(d)

No litigation involving the ’035 Patent is pending, making discretionary denial unwarranted under the factors in *Apple Inc. v. Fintiv, Inc.,* IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020).

The examination record also does not warrant the Board exercising its discretion to not institute. As explained in § IV.C, no obviousness rejections were raised during prosecution.[326] The present obviousness grounds also are based in part on Chao (EX1006), which was not cited or considered during examination,

[325] EX1001, Table 9, column 248.

[326] EX1002, 465-67.

and are supported by evidence not available to the Examiner (*e.g.*, expert testimony of Drs. Hecht and Park).

Also, while certain indefiniteness rejections were imposed and overcome by claim amendments,[327] the Examiner erred by not rejecting the claims for lack of written description and non-enablement. *See* §§ V.A and V.B.

There is no proper basis for the Board to exercise its discretion to not institute trial.

VIII. CONCLUSION

For the foregoing reasons, the challenged claims are unpatentable.

Dated: December 27, 2024

Respectfully Submitted,

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[327] EX1002, 465-67, 538-41.

EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,123,035
1002	File History of U.S. Patent No. 12,123,035
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Brandon & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '035 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," Methods in Enzymology, 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," Protein Eng'g & Design, Ch. 10, 223-237 (2010)
1018	Chica et al., "Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design," Curr. Opin. Biotechnol., (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," Reprod., 127:325-334 (2004)
1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," Am. J. Reprod. Immunol., (3):174-82 (2002)
1021	Baba et al., "Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg," J. Biol. Chem., 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," Biol Reprod., 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 56(5):1133-41 (1997)
1024	Rosengren et al., "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects," BioDrugs, 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	[Reserved]
1028	[Reserved]
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," FEBS Letters, 3:545-548 (1993)

No.	Exhibit Description
1030	Sills, "Retraction," Science, 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," J. Mol. Biol., 353:459-473 (2005)
1032	Wang & Moult, "SNPs, Protein Structure, and Disease," Hum. Mutation, 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," Structure, 8:1025-1035 (2000)
1034	"Negative Results," Nature: Editorials, 453:258 (2008)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," Protein Sci., 12:1406-1417 (2003)
1036	Hayden, "Chemistry: Designer Debacle," Nature, 453:275-278 (2008)
1037	Benkert et al., "Toward the Estimation of the Absolute Quality of Individual Protein Structure Models," Bioinformatics, 27:343-350 (2010)
1038	Schwede et al., "SWISS-MODEL: An Automated Protein Homology-Modeling Server," Nucleic Acids Rsch., 31:3381-3385 (2003)
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007).
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," PNAS, 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," PNAS, 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," Nature Comm., 14 (2023)
1043	Sievers et al., "Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega," Molecular Sys. Biology, 7.1 (2011)
1044	Mihel, "PSAIA – Protein Structure and Interaction Analyzer," BMC Structural Biology, 8:21 (2008)

No.	Exhibit Description
1045	Redline Comparison of the ’731 and ’035 Specifications
1046	Beasley & Hecht, “Protein Design: The Choice of *de Novo* Sequences,” J. Biological Chemistry, 272:2031-2034 (1997)
1047	Xiong et al., “Periodicity of Polar and Nonpolar Amino Acids is the Major Determinant of Secondary Structure in Self-Assembling Oligomeric Peptides,” PNAS, 92: 6349-6353 (1995)
1048	Hayden, “Key Protein-Design Papers Challenged,” Nature, 461:859 (2009)
1049	KEGG, *DRUG: Hyaluronidase (human recombinant)*, available at: https://www.genome.jp/entry/D06604
1050	Pace & Scholtz, “A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins,” Biophysical J. 75:422-427 (1998)
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
1057	Ph20_pre2011.aln-clustal_num
1058	Ph20_pre2011 Alignment html
1059	Leisola & Turunen, “Protein Engineering: Opportunities and Challenges,” Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	Hecht et al., “De Novo Proteins from Designed Combinatorial Libraries,” Protein Sci., 13:1711-1723 (2004)
1061	Rosengren et al., “Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration,” AAPS J., 17:1144-1156 (2015)
1062	[Reserved]
1063	[Reserved]

No.	Exhibit Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with S312T Mutation
1071	Swiss Model Printout of PH20 Model with S312N Mutation
1072	[Reserved]
1073	[Reserved]
1074	[Reserved]
1075	[Reserved]
1076	Richardson & Richardson, "Amino Acid Preferences for Specific Locations at the Ends of α Helices," Science, 240, 1648-1652 (1988)
1077	Doig & Baldwin, "N- and C-capping Preferences for All 20 Amino Acids in α-helical Peptides," Protein Science, 4:1325-1336 (1995)
1078	Keedy et al., "The Role of Local Backrub Motions in Evolved and Designed Mutations," PLoS Computational Biology, 8(8):1-10 (August 2012)

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,644 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

Dated: December 27, 2024

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 27th day of December, 2024, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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Paper No. 1
Filed: December 10, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00006
U.S. Patent No. 12,152,262

PETITION FOR POST GRANT REVIEW

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I. Introduction

Petitioner Merck Sharp & Dohme LLC ("Merck") requests post grant review of claims 1-12 of U.S. Patent No. 12,152,262 ("'262 Patent").

The '262 Patent claims are unpatentable for three independent reasons.

The first two are linked to the extreme breadth of the claims, which encompass between 10^{49} and 10^{66} different enzymatically active human hyaluronidase ("PH20") polypeptides. That breadth results from the unconstrained language in claims 1 to 4, which each define a genus of PH20 polypeptides that ***requires one*** amino acid substitution at position 317, but then ***permits*** (via sequence identity language) up to 16, 20, 21, or 22 additional substitutions at ***any*** of between 430 and 465 positions of PH20, and to ***any*** of 19 other amino acids. The scale of this genus is unfathomable. The weight of a set of one molecule of each polypeptide in one genus exceeds that of the Earth, and a skilled artisan would require many lifetimes of "making and testing" using the patent's iterative methodology to practice the claims' full scope .

These immensely broad claims, measured against the common disclosure of the '262 Patent and its ultimate parent '731 Application,[1] utterly fail to satisfy the written description and enablement requirements of § 112(a). That renders every

[1] 13/694,731 ('731 Application) (EX1026).

claim of the ’262 Patent unpatentable. It also precludes those claims from a valid § 120 benefit claim to the ’731 Application, the only non-provisional application filed before March 16, 2013, thus making the ’262 Patent PGR eligible.

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by enzymatically active, multiply-modified PH20 polypeptides within each claimed genus. The disclosed examples also are not representative of that structurally diverse genus: every disclosed mutant has only ***one*** amino acid substitution in ***one*** PH20 sequence (1-447), while the claims encompass myriad structural variants of PH20, resulting from incorporation of innumerable, ***undescribed*** combinations of 5, 10, 15, or 20+ substitutions anywhere in the PH20 sequence. The claims even capture mutated PH20 polypeptides the disclosure says to exclude, such as those which rendered $PH20_{1\text{-}447}$ inactive by a single mutation, or truncated forms the disclosure and prior art describe as inactive. The disclosure is nothing more than a research plan, lacking any blaze marks, while the claims improperly capture any enzymatically active, multiply-mutated PH20 polypeptides that might be discovered.

Regarding enablement, the common disclosure has equally fatal problems: it neither describes nor characterizes ***any*** modified PH20 with 2 or more substitutions that is enzymatically active, much less affirmatively guides the selection of ***which*** combinations of substitutions yield such proteins. And the only disclosed process

for making PH20 mutants with multiple substitutions is a prophetic, "iterative" research plan that explicitly requires the same type of 2011-era "trial-and-error" experiments the Supreme Court recently found incapable of enabling a large genus of diverse polypeptides.[2] Indeed, to practice the full scope of the claims would require scientists to repeat this "make-and-test" methodology innumerable times until they had made and tested between 10^{49} and 10^{66} unique proteins. That is far more than undue experimentation—it is impossible.

Finally, claims 1-4 and 7-12 are independently unpatentable because each captures a ***single*** PH20 mutant with a ***single*** amino acid substitution at position 317 (from leucine (L) to glutamine (Q)) ("L317Q $PH20_{1-447}$"). But Patentee's earlier '429 Patent (EX1005)[3] makes that mutant obvious, along with methods of making and using it—it directs artisans to make single amino acid substitutions in non-essential regions of the $PH20_{1-447}$ sequence and explicitly claimed them. Implementing that guidance in 2011 would have led the skilled artisan to an intervening publication—Chao (EX1006)— ignored in Patentee's 2011-era disclosure and never cited to the Office during examination. The collective guidance of the '429 Patent and Chao (i) readily identifies position 317 as being in

[2] *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023).

[3] U.S. Patent No. 7,767,429.

a non-essential region of PH20, and (ii) motivates the skilled artisan to substitute glutamine at that position—the most commonly occurring amino acid in that position in known, homologous hyaluronidases. And the skilled artisan would have reasonably expected L317Q $PH20_{1-447}$ to retain the enzymatic activity of its parent because that is precisely what Patentee's '429 Patent says ("Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity").[4] A skilled artisan, in 2011, would have considered L317Q $PH20_{1-447}$ to be ***one*** obvious PH20 mutant in the claimed genus.

The evidence demonstrates the '262 Patent claims are unpatentable. The Board should institute post grant review.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the '262 Patent's issuance. Petitioner certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '262 Patent.

[4] EX1005, 16:17-22.

The ’262 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

A patent is PGR eligible if it issued from an application filed after March 16, 2013 “if the patent contains … at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought.” *See Inguran, LLC v. Premium Genetics (UK) Ltd.*, Case PGR2015-00017, Paper 8 at 16-17 (P.T.A.B. Dec. 22, 2015); *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17 at 8 (P.T.A.B. Jan. 29, 2016); *Collegium Pharm., Inc. v. Purdue Pharma L.P.*, 2021 WL 6340198, at *14-18 (P.T.A.B. Nov. 19, 2021) (same) *aff’d Purdue Pharma L.P. v. Collegium Pharm., Inc.*, 86 F.4th 1338, 1346 (Fed. Cir. 2023); *Intex Recreation Corp. v. Team Worldwide Corp.*, 2020 WL 2071543, at *26 (P.T.A.B. Apr. 29, 2020) (same).

The ’262 Patent claims benefit under 35 U.S.C. § 120 and/or § 121 to numerous earlier-filed non-provisional applications. Only one—U.S. Application No. 13/694,731 (the ’731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to and incorporates by reference the disclosures of two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011),

as well as WO 01/3087 ("WO087"). The '731 Application alters several passages of the provisional disclosures, adds new examples and tested mutants and makes other changes.[5]

The disclosure of the '731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '262 Patent (§§ V.A, V.B). The same is true for the '262 Patent, whose disclosure is substantively identical to the '731 Application.[6] The '262 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the '731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

Merck Sharp & Dohme LLC is the real party-in-interest for this Petition.

2. Related Proceedings

PGR2025-00003 and PGR2025-00004 are related proceedings.

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[5] EX1026, 153:15-163:26, 324-34, 19:25-26, 28; EX1051; EX1052.

[6] The "common disclosure" refers to the shared disclosure of the '262 Patent and the '731 Application (EX1026). Citations are to the '262 Patent; EX1015 correlates citations to the '731 Application.

3. Counsel and Service Information

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III. Grounds

The grounds advanced in this Petition are:

(a) Claims 1-13 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.

(b) Claims 1-13 are unpatentable under 35 U.S.C. § 112 as not being enabled.

(c) Claims 1-4 and 7-13 are unpatentable as obvious under 35 U.S.C. § 103 based on the ’429 Patent (EX1005), Chao (EX1006) and knowledge held by a person of ordinary skill in the art.

Petitioner’s grounds are supported by the evidence submitted with this Petition, including testimony from Dr. Michael Hecht (EX1003) and Dr. Sheldon Park (EX1004).

In this Petition, “PH20” refers to the human PH20 hyaluronidase protein. The full-length PH20 protein (SEQ ID NO: 6) includes a 35 amino acid signal

sequence, which is absent in mature forms of PH20, yielding positional numbers that differ from SEQ ID NO: 6 by 35 residues.[7] The annotation "$PH20_{1-n}$" refers to a sequence of 1-n residues in PH20 (*e.g.*, $PH20_{1-447}$ is SEQ ID NO: 3), and "AxxxB" is used to identify the position of a substitution ("L317Q").

IV. Background on the '262 Patent

A. Field of the Patent

The '262 Patent concerns the human PH20 hyaluronidase enzyme, and structurally altered forms of that protein that retain enzymatic activity.[8]

1. Protein Structures

Proteins are comprised of sequences of amino acids. The activity of a protein, however, derives from its unique, three-dimensional shape—its structure.[9] That, in turn, is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary structures and structural motifs, which are packed into compact domains that define the protein's overall structure (tertiary structure).[10]

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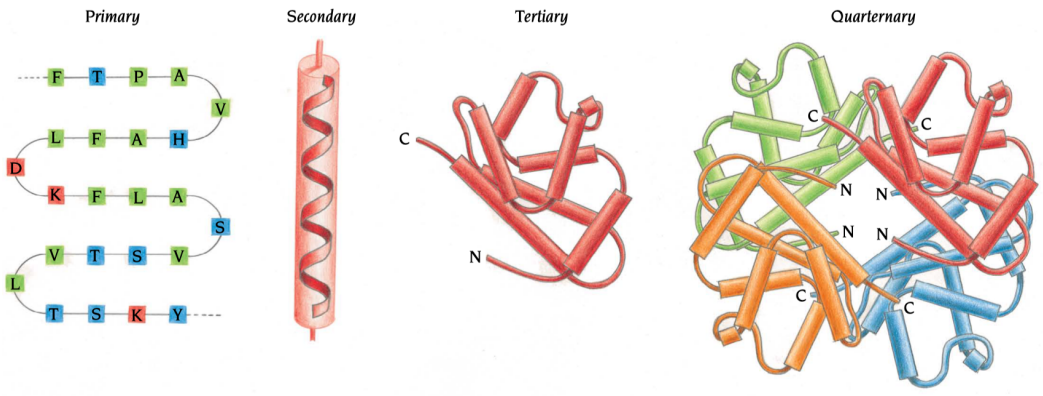
[7] EX1003, ¶ 15.

[8] EX1001, 4:13-16.

[9] EX1003, ¶ 36.

[10] EX1014, 3-4, 24-32, Figure 1.1; EX1039, 136-37 (Figure 3-11); EX1003, ¶¶ 36-40.



Secondary structures, such as α-helices or β-strands, are formed and stabilized by different but characteristic patterns of amino acids (below).[11]

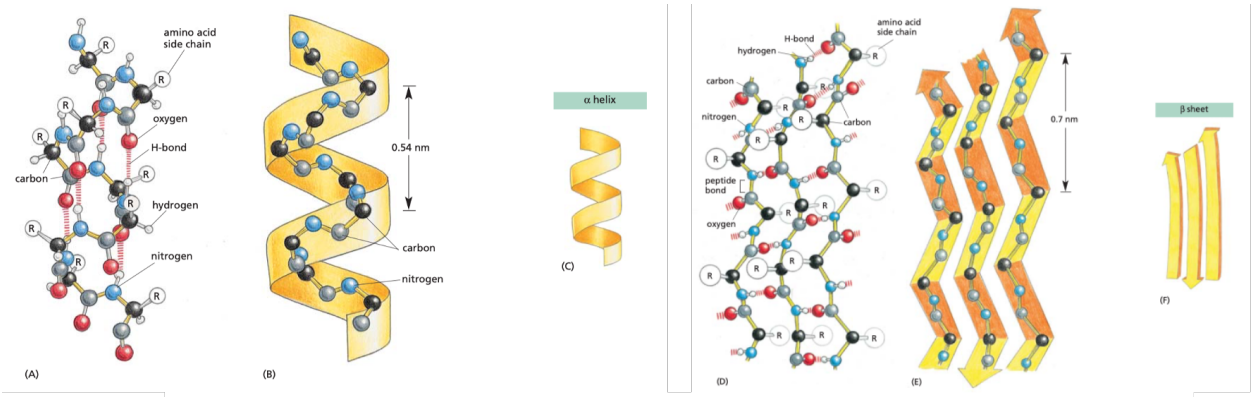


Figure 3–7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N–H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N–H groups point up in this diagram and that all of the C=O groups point down (toward the C-terminus); this gives a polarity to the helix, with the C-terminus having a partial negative and the N-terminus a partial positive charge. (D, E, and F) The β sheet. In this example, adjacent peptide chains run in opposite (antiparallel) directions. Hydrogen-bonding between peptide bonds in different strands holds the individual polypeptide chains (strands) together in a β sheet, and the amino acid side chains in each strand alternately project above and below the plane of the sheet. (A) and (D) show all the atoms in the polypeptide backbone, but the amino acid side chains are truncated and denoted by R. In contrast, (B) and (E) show the backbone atoms only, while (C) and (F) display the shorthand symbols that are used to represent the α helix and the β sheet in ribbon drawings of proteins (see Panel 3–2B).

[11] EX1039, 134; EX1014, 14-22, Figures 2.2, 2.5, Table 2.1; EX1047, 2031-32; EX1003, ¶¶ 40-43.

Intervening sequences between those characteristic sequences are important too; they direct and facilitate positioning and arrangement of the various secondary structures into structural motifs and the protein's tertiary structure.[12]

Changes to a protein's amino acid sequence can affect the folding, formation and stability of these various structures that define the protein's overall shape. For example, changing even a single residue known to be critical to the protein's structure or activity can render a protein inactive.[13]

In 2011, making many concurrent changes to a protein's sequence was highly unpredictable, which can cause myriad effects on the protein's structure, especially when they are in or affect the same region(s) of the protein.[14] For example, introducing numerous changes in a protein's sequence can disrupt the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of secondary structures, while changes to intervening sequences can disrupt folding and positioning of the secondary structures and

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12 EX1003, ¶¶ 44-46; EX1014, 21-22.

13 EX1003, ¶¶ 54, 150; EX1004, ¶¶ 20, 25.

14 EX1003, ¶ 158.

structural motifs into the protein's tertiary structure.[15] Multiple changes introduced at different regions of the amino acid sequence also can cause unfavorable spatial interactions that destabilize or impair folding.[16] In 2011, predicting the possible effects of the myriad interactions that may be disrupted by multiple concurrent substitutions was beyond the capacity of skilled artisans and available computational tools.[17]

2. Hyaluronidase Enzymes

PH20 is one of five structurally similar hyaluronidase proteins in humans and is homologous—evolutionarily related to—hyaluronidases in many species.[18] It breaks down hyaluronan ("HA") by selectively hydrolyzing glycosidic linkages

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15 EX1003, ¶¶ 55-56, 142; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

16 EX1003, ¶¶ 57-59.

17 EX1003, ¶¶ 50, 158, 190, 224; EX1004, ¶¶ 162-64.

18 EX1007, 10:18-30; EX1006, 6911, 6916 (Figure 3); EX1003, ¶¶ 33, 77.

in it.[19] Human PH20 protein exists naturally as a GPI anchored protein, but deletion of its GPI-anchoring sequence yields a soluble, neutral active enzyme.[20]

Various groups before 2011 had identified essential residues in PH20. Several are in the catalytic site of the protein, a conserved structure shared by many species;[21] mutating certain residues in or near that site can abolish the enzymatic activity of hyaluronidases.[22] Conserved cysteine residues that stabilize the protein structure are another example,[23] as are conserved asparagine residues involved in glycosylation and known to be important for PH20 activity.[24]

In 2007, Chao reported an experimentally determined structure of the human HYAL1 hyaluronidase, and used an alignment of the five human hyaluronidases to

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19 EX1003, ¶ 77; EX1008, 819.

20 EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 89, 196; EX1029, 546, Figure 1.

21 EX1006, 6914-16, Figure 3; EX1007, 35:28-36:10; EX1011, 810-14; EX1008, 824-25; EX1009, 6912-17.

22 EX1011, 812-14; EX1010, 9435-39, Table 1.

23 EX1006, 6914-16, Figure 3; EX1011, 810-11; EX1005, 88:21-22.

24 EX1005, 7:9-27; EX1007, 36:12-20; EX1010, 9433, 9435-40.

illustrate shared secondary structures and conserved residues in these proteins.[25] Among its findings was that human hyaluronidases contain a unique structure—the Hyal-EGF domain.[26] Using its sequence analysis, an earlier structure of bee venom hyaluronidase and a computer model of the protein structures, Chao identified residues in the catalytic site that interact with HA.[27]

3. Protein Engineering

In 2011, skilled artisans used two general approaches to engineer changes into proteins.[28] In "rational design," skilled artisans employed computational tools–sequence alignments and protein structure models–to study the protein sequence and structure and then select where and what changes to introduce into the sequence.[29] For example, a "multiple-sequence alignment" ("MSA")[30]

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[25] EX1006, 6914-18.

[26] EX1006, 6916-18; EX1010, 9439-40; EX1003, ¶¶ 84-86; EX1004, ¶¶ 97-99.

[27] EX1006, 6912-13, 6916-18, Figures 2C, 4A; EX1033, 1028-29, 1035; EX1010, 9434, 9436, Figure 1.

[28] EX1003, ¶ 47.

[29] EX1016, 181-82; EX1017, 223, 236; EX1003, ¶¶ 48-50.

[30] EX1017, 224-27; EX1016, 181-86 (Figure 1); EX1003, ¶¶ 48-50; EX1004, ¶¶ 22-23, 29.

produced by aligning known sequences of naturally occurring proteins homologous to the one being studied identifies conserved ("essential") positions with no or little amino acid variation and non-conserved positions where different amino acids occur ("non-essential" residues).[31] A structural model using the sequence of the protein but based on a suitable known structure of a homologous protein would be used to identify and assess interactions between amino acids at that position.[32] In 2011, skilled artisans could use rational design techniques to assess, with varying amounts of effort, the effects of changing one or a few amino acids, but predicting the effects of many concurrent changes was not possible, given the escalating complexity of numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.[33]

"Directed evolution" techniques arose due to the limits of rational design.[34] They use "trial-and-error" experiments to find mutants with randomly distributed

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31 EX1003, ¶¶ 209-210; EX1004, ¶¶ 21-22, 25, 30-31; EX1016, 181-84; EX1017, 224-25; EX1014, 351.

32 EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶ 37, *also id.* 33-36; EX1003, ¶¶ 219, 221.

33 EX1003, ¶¶ 50, 158; EX1004, ¶¶ 162-164.

34 EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

changes that exhibit desired properties, but require creation and screening of large libraries of mutants, each with one amino acid randomly changed at one position in its sequence.[35] Importantly, until a desired mutant is made, found and tested, whether it exists and its sequence are unknown.[36] Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale of experimentation this approach requires.[37] The '262 Patent embodies this approach.[38]

B. Person of Ordinary Skill in the Art

The '262 Patent claims priority to provisional applications dating back to December 30, 2011. § II.A. Its claims, however, are not entitled to those dates or the filing date of the '731 Application (December 28, 2012), as they are not supported as § 112(a) requires by those earlier-filed applications. *See* §§ V.A, V.B. The prior art of the grounds was published before December 2011, and the obviousness grounds use that date to assess the knowledge and perspectives of the skilled artisan.

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35 EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

36 EX1003, ¶ 184.

37 EX1003, ¶¶ 52-53.

38 EX1003, ¶¶ 138, 173, 183, 186.

In 2011, a person of ordinary skill in the art would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).[39]

C. Prosecution History

Three rejections were imposed during examination of the ’262 Patent. First, non-statutory double patenting rejections were imposed,[40] which Patentee overcame with terminal disclaimers.[41] Second, certain dependent claims were rejected as indefinite due to a typographical error,[42] which Patentee overcame by

[39] EX1003, ¶ 13.

[40] EX1002, 485-88.

[41] EX1002, 511, 530.

[42] EX1002, 488-89.

amendments "to clarify that the modifications are 'post-translational' modifications."[43]

Third, claim 1, which encompassed substituting leucine at position 317 with alanine, was rejected as obvious over Lin et al. in view of Morrison.[44] The Examiner cited Lin as disclosing the amino acid sequence of human and monkey PH20 and Morrison as teaching replacement of individual wild-type amino acids with alanine throughout the protein to assess the role of the substituted residue.[45] The Examiner reasoned it would have been obvious"to modify the PH20 polypeptide with an alanine anywhere along the protein sequence," and that "[i]t is not inventive to modify a protein with alanine in a polypeptide polymer."[46] Patentee ultimately overcame this rejection via an amendment to claim 1 that eliminated alanine ("A") as an option for the replacement at position 317.[47]

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43 EX1002, 509, 530.

44 EX1002, 489-91.

45 EX1002, 490-91.

46 EX1002, 491.

47 EX1002, 530-33.

D. The Challenged Claims

The terms used in the claims are either expressly defined in the common disclosure or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition. A clear understanding of the ***breadth*** of the claims, however, is important to assessing the grounds. Specifically, each claim captures a massive genus of structurally distinct mutant PH20 polypeptides that is neither adequately described in nor enabled by the common disclosure of the '731 Application and the '262 Patent.

1. The Claims Encompass a Staggering Number of Modified PH20 Polypeptides

Claim 1 defines an incredibly broad and diverse genus of "modified PH20 polypeptides," which are defined as "a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement … in its sequence of amino acids compared to a reference unmodified PH20 polypeptide."[48]

Claim 1 specifies the modified PH20 polypeptides in its genus:

- ***must*** contain ***one*** amino acid replacement at position 317 (*i.e.*, from L to any of H, I, K, M, Q, R, and S); and
- ***may*** contain ***additional*** modifications, provided each polypeptide retains ***at least 95% sequence identity*** to one of the 35 unmodified

[48] EX1001, 48:27-32.

sequences (SEQ ID NOs: 3 or 32-66), ranging in length from 430 (SEQ ID NO: 32) to 465 residues (SEQ ID NO: 35).

Claim 2 requires position 317 to be to glutamine (Q). Claims 3 and 4 restrict claim 1's genus by specifying each polypeptide has: (i) 96% sequence identity to SEQ ID NO: 35 ($PH20_{1-433}$), or (ii) 95% sequence identity to SEQ ID NO: 32 ($PH20_{1-430}$).

The specification explains that "sequence identity can be determined by standard alignment programs …"[49] and provides an example, explaining a polypeptide that is "'at least 90% identical' refers to percent identities from 90 to 100% relative to the reference polypeptide" where "no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides."[50] Per claim 1, "terminal gaps" are "treated as non-identical" residues.

It further explains that "differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence" and that "[d]ifferences are defined as [] amino acid substitutions, insertions or deletions."[51]

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49 EX1001, 60:4-6.

50 EX1001, 60:39-48.

51 EX1001, 60:49-57; *see also id.* at 4:65-66; 47:32-36, 45-47.

Also, "amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids" (*e.g.*, 10-18 of the 19 alternative amino acids).[52] Likewise, no language in the claims restricts ***where*** substitutions can occur within the modified PH20 sequence, or ***which*** of 19 other amino acids can be substituted at those positions.

The parameters in claims 1-4 cause them to encompass an immense number of distinct polypeptides, each with a unique amino acid sequence.[53] In particular, it permits the modified PH20 polypeptides to contain between 17 and 23 total changes but requires only one change: a substitution at position 317, with either 7 alternatives (claim 1) or one alternative ("Q") (claims 2, 3, 4). Based on Dr. Park's calculations, each claim's parameters capture an immense number of distinct polypeptides (below).[54]

Claim	**SEQ ID** / % Identity	PH20 length	# Changes	Pos. 317 Choices	Add'l Changes	# Distinct Polypeptides
1	**3** / 95%	447	22	7	21	2.35×10^{63}
	66 / 95%	465	23	7	22	2.63×10^{66}
2	**3** / 95%	447	22	1	21	3.76×10^{62}

[52] EX1001, 137:12-19; *see also id.* at 142:29-31.

[53] EX1003, ¶¶ 120, 122.

[54] EX1004, ¶¶ 170-173, Appendix F.

3	**35** / 96%	433	17	1	16	1.53 x 10^{49}
4	**32** / 95%	430	21	1	20	4.40 x 10^{59}

2. The Claims Encompass One Particular PH20 Mutant: L317Q PH20$_{1-447}$

The structural parameters of claims 1-4 also cause them to capture a ***single*** modified PH20 polypeptide with ***one*** replacement. That is the PH20$_{1-447}$ protein (SEQ ID NO: 3), in which the leucine (L) at position 317 is changed to glutamine (Q) ("L317Q PH20$_{1-447}$"). This single-replacement L317Q PH20$_{1-447}$ mutant is: (i) 99.7% identical to SEQ ID NO: 3 (1 change / 447 residues), (ii) 96.5% identical to SEQ ID NO: 35 (15 changes / 433 residues), and (iii) 95.9% identical to SEQ ID NO: 32 (18 changes / 430 residues).[55]

3. The Claims Are Restricted to One of Two Alternative Embodiments in the Patents: "Active Mutants"

When a specification discloses alternative embodiments, the language used in the claims may cause them to be limited to only one.[56] That is the case here: the specification describes two mutually exclusive categories of "modified PH20

[55] EX1003, ¶ 136.

[56] *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008).

polypeptides" (*i.e.*, "active mutants" vs. "inactive mutants") but the claims are limited to one (*i.e.*, "active mutants").

According to the specification:

- "***Active mutants***" are modified PH20 polypeptides that "exhibit at least 40% of the hyaluronidase activity of the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[57]
- "***Inactive mutants***" are modified PH20 polypeptides that "generally exhibit less than 20% … of the hyaluronidase activity of a wildtype or reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7."[58]

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[57] EX1001, 75:33-38; *see also id.* at 79:15-19 ("active mutants" "can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide …"); *id.* at 79:12-15.

[58] EX1001, 118:63-119:5. *See also id*. at 255:58-62 (mutants exhibiting <20% hyaluronidase activity "were rescreened to confirm that the dead mutants are inactive" in Table 10).

It then classifies mutants into tables of "active" and "inactive" mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).[59]

The common disclosure reports no examples of an "active mutant" modified PH20 with two replacements.[60] More directly, it reports no examples of an enzymatically active $PH20_{1-447}$ that incorporates: (i) a mutation listed in Tables 3 and 9 ("active mutants"), plus (ii) a second mutation listed in Tables 5 and 10 ("inactive mutant").

The specification also portrays "active" and "inactive" mutants as having distinct utilities requiring mutually exclusive properties.

- "Active mutants" are portrayed as being therapeutically useful ***because they possess hyaluronidase activity***. For example, the specification explains that ***due to*** having hyaluronidase activity, "the modified PH20 polypeptides can be used as a spreading factor to

[59] EX1001, 80:46-82:3 (Table 3 "Active Mutants"), 234:2-4 (Table 9 "Active Mutants"), 120:20-43 (Table 5 "Inactive Mutants"), 257:7-11 ("reconfirmed inactive mutants are set forth in Table 10."); EX1003 ¶¶ 98, 104-105, 107, 126-28.

[60] *E.g.*, EX1003, ¶¶ 141, 172.

increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents."[61]

- "Inactive mutants" are portrayed as being therapeutically useful ***because they lack hyaluronidase activity***. Their only identified utility is "as antigens in contraception vaccines," which is implausible (*see* § V.C) but ostensibly requires them to lack activity.[62]

The specification does not portray "active mutants" as having contraceptive utility even though they may differ by only one amino acid from an inactive mutant, but proposes using them ***in combination*** with contraceptive agents.[63]

The claim language reinforces that they are limited to the "active mutant" embodiment.

First, every claim requires each modified PH20 polypeptide in its scope to have one of seven replacements at position 317 that yielded an "active mutant" as a

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61 EX1001, 181:2-8; *see also id*. at 4:30-33, 73:21-35, 181:2-194:28; EX1003, ¶ 108.

62 EX1001, 72:48-50; *see also id.* at 194:29-30, 75:42-44, 194:28-47 (for "contraception" "the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.").

63 EX1001, 157:32-45; EX1003, ¶ 113; EX1060, 1711.

single-replacement $PH20_{1-447}$ polypeptide (*i.e.*, L317Q, L317H, L317I, L317K, L317M, L317R, or L317S). These mutants are listed in Table 3 and reported as having >40% activity in Table 9.[64]

Second, claims 5 and 6 restrict the genus of active mutants in claim 1 (*i.e.*, those with at least 40% activity) to active mutant modified PH20 polypeptides that have at least 100% or 120% of the activity of unmodified PH20, respectively.

Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one modification," but can also "have up to 150 changes, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity.***"[65] This aligns with the specification's prophetic methodology for discovering PH20 polypeptides with multiple changes, which starts with one substitution that yields an "active mutant," randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity.[66] This tracks the claims, which require one substitution and permit others.

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64 EX1001, 87 (Table 3), 237 (Table 9); EX1003, ¶¶ 127-128; EX1001, 100:54-66.

65 EX1001, 48:27-42; *see also id*. at 47:50-54, 75:58-61, 76:53-60, 80:54-82:3.

66 EX1001, 141:63-142:7; *see also id*. at 42:40-47.

Patentee may contend the claims should be read as encompassing both alternative embodiments (*i.e.*, "active" and "inactive" mutants). Reading the claims in that manner is incorrect. It also exacerbates the § 112 problems, as every claim still necessarily includes (and thus must describe and enable) the full sub-genus of "active mutants" in claim 1 defined by claims 5 and 6.[67]

V. All Challenged Claims Are Unpatentable Under § 112 and None Are Entitled to Benefit to Any Pre-March 13, 2013 Application

Claims 1-12 are unpatentable because each lacks written description in and was not enabled by the common disclosure of the '262 Patent and the '731 Application in 2011.

As explained in § IV.D.1, the claim language defines enormous genera: between 10^{49} and 10^{66} distinct polypeptides. To illustrate the real-world absurdity of those claims, consider what practicing the claims' full scope requires. Excluding single-replacement $PH20_{1-447}$ mutants, and only considering multiply-substituted mutants of $PH20_{1-447}$, a skilled artisan would need to make-and-test at least ~10^{49} mutants. Producing only one molecule of each mutant—each must be made and tested to see if it is active or inactive—would require consuming an aggregate mass (~1.37 x 10^{27} kg) that exceeds the mass of the Earth (~6 x 10^{24}

[67] EX1003, ¶ 135.

kg).[68] Testing every polypeptide within the claims' scope in search of "active mutants" is impossible—literally.

In support of that broad scope, the '262 Patent and the '731 Application provide only a meager disclosure: ***singly***-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones. The patent provides ***nothing*** that demonstrates possession of the vast remainder of multiply-modified polypeptides in the claims' scope or which enables a skilled artisan to practice that full-range of structurally diverse mutant polypeptides without undue experimentation.

A. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.[69] "To fulfill the written description requirement, a patent owner 'must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by

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[68] EX1003, ¶¶ 123, 189; *see also, e.g.*, EX1039, 136-37 (cell theoretically can make 10^{390} forms of a polypeptide with 300 amino acids).

[69] *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

disclosure in the specification of the patent."[70] If the claims define a genus, the written description must "show that one has truly invented a genus …," "[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus."[71]

"[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus."[72] "One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent … [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus."[73]

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70 *Idenix Pharm., LLC v. Gilead Scis., Inc.,* 941 F.3d 1149, 1163 (Fed. Cir. 2019).

71 *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1300 (Fed. Cir. 2014).

72 *Idenix*, 941 F.3d at 1164.

73 *AbbVie*, 759 F.3d at 1299-1300.

A disclosure that fails to "provide sufficient blaze marks to direct a POSA to the specific subset" of a genus with the claimed function or characteristic does not satisfy § 112(a).[74] And "merely drawing a fence around the outer limits of a purported genus" is insufficient.[75] Instead, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."[76]

Three cases applying these principles are particularly relevant here. First, in *AbbVie*, the Federal Circuit affirmed a finding that the disclosure of 300 examples of IL-12 antibodies was not representative of the functionally defined genus of antibodies, explaining:

> Although the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.[77]

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74 *Idenix*, 941 F.3d at 1164.

75 *Ariad*, 598 F.3d at 1350-54.

76 *Ariad*, 598 F.3d at 1349.

77 *AbbVie*, 59 F.3d at 1300-1301.

The court also criticized what that patentee cited to support the non-exemplified portion of the claim scope, portraying it as "only a research plan, leaving it to others to explore the unknown contours of the claimed genus" and being a "trial and error approach."[78] Both criticisms apply to the present disclosure, which exemplifies only single-substitution PH20 mutants and otherwise provides only a research plan, yet claims all multiply-modified PH20 mutants with 2 to 22 additional substitutions.

Second, in *Idenix,* the court considered claims to methods of treatment using a broad genera of compounds defined by formulas analogous to the challenged claims here: "eighteen position-by-position formulas describing 'principal embodiments' of compounds that may treat HCV," each with "more than a dozen options" at each position (totaling "more than 7,000 unique configurations").[79] The court criticized the specification's failure to indicate which of the thousands of compounds would be effective, and found that "providing lists or examples of supposedly effective nucleosides," without "explain[ing] what makes them effective, or why" deprives a skilled artisan "of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same

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78 *Id.*

79 *Idenix*, 941 F.3d at 1158-64.

result" because they "fail to provide sufficient blaze marks to direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV." Again, that logic resonates strongly with the deficiencies of the common disclosure here.

Finally, the Board in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found*., PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) considered sequence homology claims. Specifically, the claims used "90% sequence homology" language to capture "a broad genus of amino acid sequence homologues" but (like here) imposed no restrictions on where particular amino acids replacements could be made, thus causing the claim "to cover, at minimum, thousands of amino acid sequences."[80] The Board found the specification's failure to "explain what, if any, structural features exist (*e.g.*, remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification" fatal, and that the homology limitation "serves to merely draw a fence around the outer limits of a purported genus [which] is not an

[80] *Boehringer*, at 16. The claims were directed to compositions and methods of using proteins. *Id.* at 6.

adequate substitute for describing a variety of materials constituting the genus" for purposes of section 112(a).[81]

The deficiencies of claims 1 to 4 dwarf those identified in these three cases. The present claims define much larger, much less predictable and much more diverse genera of modified PH20 polypeptides, and the common disclosure is far more limited. As explained below, the common disclosure neither discloses a representative number of species within each immense claimed genus, nor identifies sufficient structural features common to the members of each claimed genus. It thus falls woefully short of demonstrating possession of the genera of modified PH20 polypeptides defined by claims 1 to 4 of the '262 Patent.

1. Claims 1-4 Define a Massive and Diverse Genus of Enzymatically Active PH20 Polypeptides

The incredible breadth of the genera defined by claims 1 to 4 has been described above. *See* § IV.D.1. Each claimed genus is also structurally and functionally diverse. The claims' use of a ***maximum*** sequence identity boundary with no restrictions other than a single identified substitution means the claims capture PH20 mutants with 2 substitutions, 3 substitutions and so on up to a number set by the boundary (*i.e.*, 17 for claim 3, 21 for claim 4, and 23 for claims 1-2). The substitutions also can be anywhere in the sequence (*i.e.*, clustered in a

[81] *Id.* at 35-36.

narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, and arranged in any manner.[82] They capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with 22 substitutions mixing polar, charged, aliphatic, and aromatic residues together in any manner.[83]

Each claim also encompasses substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 35 alternative sequences ranging from 430 to 465 residues. It also encompasses sequences of varying lengths due to the sequence identity language, which encompasses both "additions" and "deletions." To illustrate, if one makes the L317Q substitution and makes 5 more substitutions to SEQ ID NO: 32, claim 4's parameters would capture that mutant as well as one that also deletes 14 more residues from the C terminus. But, as explained in § V.A.2.c, removing that many residues from the C-terminus of the wild-type PH20 makes it inactive, and nothing in the common disclosure shows (much less suggests) that adding the L317Q

82 EX1003, ¶ 119; EX1001, 60:49-56, 47:32-36, 47:45-47, 41:62-42:1.

83 EX1003, ¶¶ 119-20.

mutant (plus up to 5 other substitutions) will restore activity to that C-terminally truncated mutant. Patentee nonetheless claims all these polypeptides.[84]

2. The Claims Capture Modified PH20 Polypeptides the Common Disclosure Says to Avoid or Not Make

The claims' unconstrained sequence identity language capture three categories of PH20 mutants a skilled artisan would understand the disclosure to be saying to avoid or not make. Each raises unique questions relative to the remainder of the genus, and are thus "sub-genera" of PH20 mutants that are not representative of other "sub-genera" within the claimed genera. But instead of providing guidance that navigates this confusing landscape, the patent simply instructs the skilled artisan "to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein."[85] In other words, it directs the skilled artisan to blindly make-and-test all such candidate mutants using trial-and-error experimentation.[86]

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84 EX1003, ¶¶ 164-67.

85 EX1001, 78:19-24.

86 EX1003, ¶ 193.

a) Multiply-Modified PH20 Mutants to Not Make

The common disclosure affirmatively addresses only six, specific modified PH20 polypeptides with more than one identified (*i.e.*, position and amino acid) substitution, but its guidance is to ***not make those polypeptides***:

> [W]here the modified PH20 polypeptide contains only two amino acid replacements, the amino acid replacements are ***not*** P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A or N333A/N358A. In a further example, where the modified PH20 polypeptide contains only three amino acid replacements, the amino acid replacements are ***not*** N47A/N131A/N219A.[87]

Notably, the common disclosure provides ***no explanation*** why these particular combinations of replacements should be avoided, and provides no data testing their activity or other characteristics.[88] Further, none (P13A, N47A, N131A, N219A, N333A, N358A, L464W) are included in Tables 5 and 10, which are single-replacements that rendered $PH20_{1-447}$ an "inactive mutant," and N219A $PH20_{1-447}$ showed increased activity (129%).[89] And nothing in the claim language excludes these combinations.

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87 EX1001, 77:31-43 (emphases added).

88 EX1003, ¶¶ 146-47; EX1001, 49:19-24.

89 EX1001, 247 (Table 9).

b) Substitutions to Avoid in Active Mutants

The common disclosure indicates that active mutant modified PH20 polypeptides should not incorporate specific amino acid substitutions that rendered $PH20_{1-447}$ inactive, stating:

> ***To retain hyaluronidase activity***, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.[90]

It identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10 that are made at other positions.[91]

Notably, the common disclosure does not condition this observation on single-replacement $PH20_{1-447}$ mutants, and as such, it clearly conveys to a skilled artisan that modified PH20 polypeptides with "hyaluronidase activity" do not include, and should not be modified to contain, the amino acid replacements listed in Tables 5 and 10, and that is true regardless of the length or the number of additional amino acid substitutions in the PH20 polypeptide.[92]

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90 EX1001, 79:66-80:1 (emphases added).

91 EX1001, 80:1-41 ("For example, generally modifications are not made at a position corresponding to position …").

92 EX1003, ¶¶ 148-51, 162; EX1001, 79:66-80:41, 70:34-44.

The skilled artisan also would find no description of, much less guidance concerning, ***which*** of these identified substitutions that did render $PH20_{1-447}$ inactive should be incorporated into enzymatically active multiply-modified PH20 polypeptides (and what other substitutions should be combined with them).[93] Instead, by stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that the ***claimed*** enzymatically active multiply-modified PH20 polypeptides do not contain them.[94] And again, nothing in the claim language excludes such combinations.

c) PH20 with Significant C-terminal Truncations Can Lose Activity

The common disclosure describes no multiply-modified "active mutant" PH20 polypeptides having fewer than 447 residues (or even unmodified PH20s with such lengths) and provides no guidance about making enzymatically active mutants based on PH20 sequences ending before position 447 and containing 2 or more substitutions.[95]

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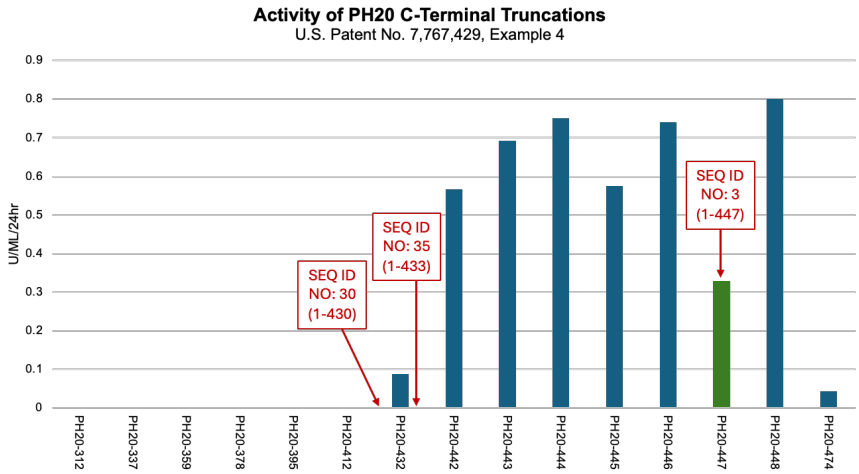
93 EX1003, ¶¶ 151, 161-62, 169.

94 EX1003, ¶¶ 148, 151.

95 EX1003, ¶¶ 94, 97, 167-69; EX1001, 73:64-74:3.

This omission creates significant uncertainty, because both the common disclosure and the prior art report that truncations that yield PH20 polypeptides that terminate at or below position 442 have significantly ***reduced or no*** hyaluronidase activity. For example, Patentee's prior art '429 Patent reported that PH20 with fewer than 432 residues lacked hyaluronidase activity, while those with between 432 and 448 residues had widely varying activities (below):[96]



Position (w/leader)	Mutant	U/ML/24hr	Normalized to PH20(1-447)
347	PH20-312	0	0.00
372	PH20-337	0	0.00
394	PH20-359	0	0.00
413	PH20-378	0	0.00
430	PH20-395	0	0.00
447	PH20-412	0	0.00
467	**PH20-432**	**0.089**	**27.05**
477	PH20-442	0.567	172.34
478	PH20-443	0.692	210.33
479	PH20-444	0.75	227.96
480	PH20-445	0.575	174.77
481	PH20-446	0.74	224.92
482	**PH20-447**	**0.329**	**100.00**
483	PH20-448	0.8	243.16
509	PH20-474	0.044	13.37

The '429 Patent also reported that "a very narrow range spanning … [437-447] … defined the minimally active domain" of human PH20, and elsewhere observed this "minimally active" human PH20 domain contains at least residues 1-

[96] EX1005, 87:52-88:24 ($PH20_{1-442}$ activity "decreased to approximately 10%"); EX1013, Figure 2, 430-32 ("[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA").

429.[97] The common disclosure concurs, stating that PH20 polypeptides must extend to at least position 429 to exhibit hyaluronidase activity:

> A mature PH20 polypeptide … containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue ***464*** of SEQ ID NO: 6 [position ***429*** without signal] … ***is the minimal sequence required for hyaluronidase activity***.[98]

Before 2011, the C-terminal region of PH20 was known to contain a unique domain linked to a characteristic pattern of sequences first reported in 2007 by Chao ("Hyal-EGF").[99] In PH20, the Hyal-EGF domain is found at positions 337-409, and it was shown in 2009 to be essential to hyaluronidase activity.[100]

The C-terminus of PH20 is illustrated below, showing (i) the location where SEQ ID NOS: **3** (447), **32** (430) and **35** (433) terminate (arrows), (ii) the "minimally active domain" at 437-447 in green, and (iii) residues below position

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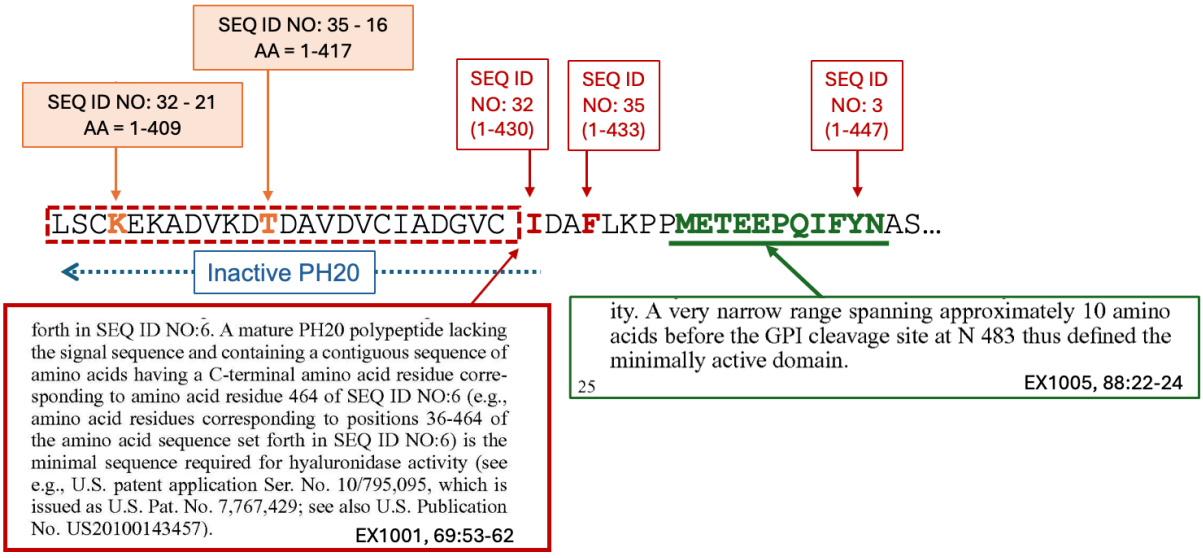
97 EX1005, 6:65-7:7 ("… sHASEGP from amino acids 36 to Cys 464 [429] … comprise the minimally active human sHASEGP hyaluronidase domain").

98 EX1001, 69:53-62 (emphases added).

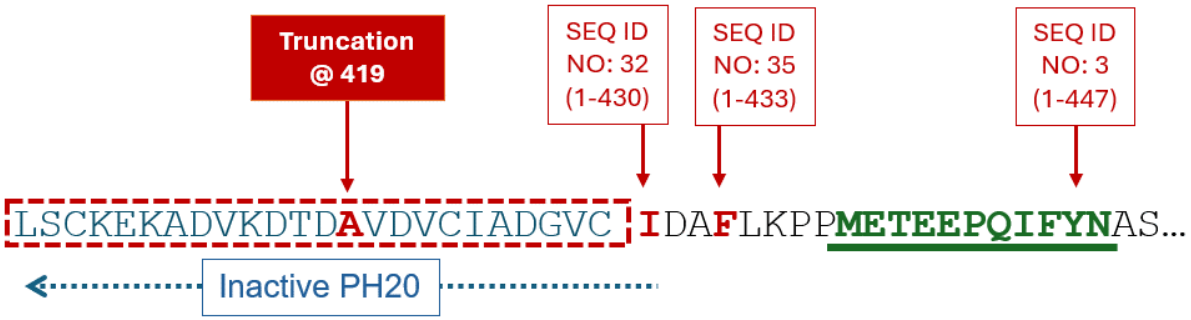
99 EX1006, 6912; EX1003, ¶¶ 84-96, 153.

100 EX1004, ¶¶ 97-99; EX1010, 9438; EX1003, ¶¶ 95-97.

429 in a red dashed box.[101] Positions that truncate 21 and 16 residues from SEQ ID NOS: 32 and 35 are also shown ending before position 429.



From the prior art and the common disclosure, a skilled artisan in 2011 would believe that C-terminal deletions yielding PH20 polypeptides that terminate before position 430 would be inactive(below).[102]



101 EX1003, ¶ 153.

102 EX1003, ¶¶ 92-93, 97, 166-167.

The common disclosure, however, provides no examples of (or guidance concerning) PH20 mutants truncated below position 447 with one or more substitutions and are is enzymatically active. It thus ignores the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433.[103] The claims nonetheless expressly encompass modified PH20 polypeptides with truncations down to and beyond position 419.[104]

3. Empirical Results from Testing Single-Replacement Modified PH20 Does Not Identify Multiply-Modified Enzymatically Active PH20 Polypeptides

The empirical results reported in the common disclosure provide no predictive guidance to a skilled artisan about the structural features of the vast genus of amino acid changes that can be combined to form multiply-modified PH20 polypeptides.

a) Data Showing Most Single-Replacements Were Inactive or Less Active Is Not Probative of Multiple-Replacement Mutants

The common disclosure reports results from testing a portion of a randomly generated library of ~6,743 single-replacement $PH20_{1\text{-}447}$ polypeptides.[105] It

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[103] EX1003, ¶¶ 143, 159, 167-69.

[104] EX1003, ¶¶ 160-65.

[105] EX1001, 134:32-43, 200:65-67, 200:46-52.

explains the mutants were generated with a mutagenesis process which substituted one of ~15 amino acids into random positions in $PH20_{1-447}$ "such that each member contained a single amino acid change."[106] Approximately 5,917 were tested, while ~846 were uncharacterized.[107] More than half (~57%) of these mutants were classified as "inactive mutants," while ~30% (1335) were reported to have less activity than unmodified $PH20_{1-447}$ (20%-100%).[108] In other words, ~87% of the single-replacement $PH20_{1-447}$ polypeptides had ***less*** activity than unmodified $PH20_{1-447}$.[109]

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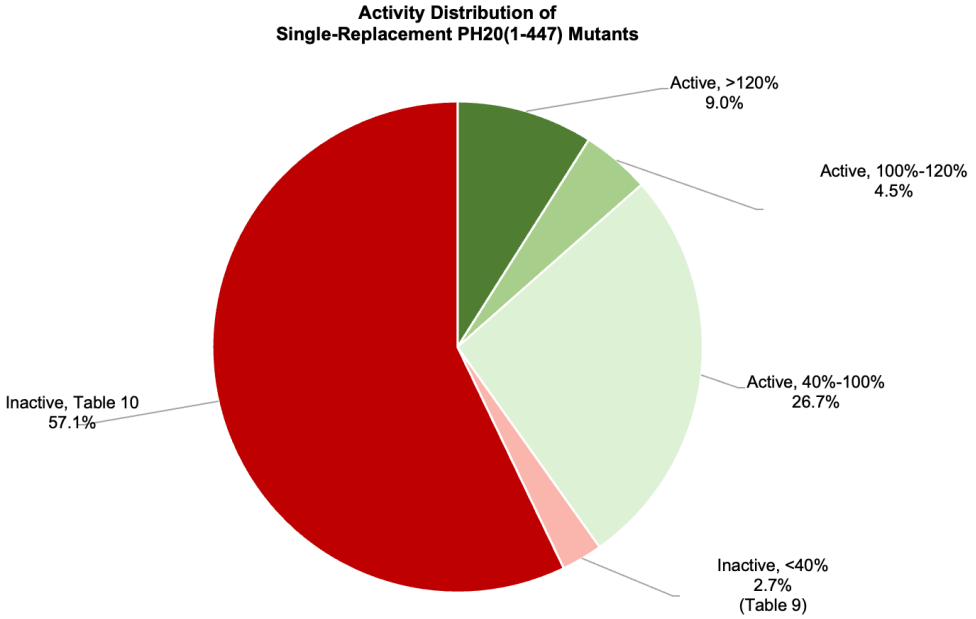
106 EX1001, 200:46-55.

107 EX1003, ¶¶ 103-104. Inconsistent numbers of tested mutants and classifications of mutants are reported but not explained: (i) Table 3 lists 2,516 single-replacement $PH20_{1-447}$ mutants as "active mutants," but Table 9 identifies only 2,376 mutants that exhibit >40% hyaluronidase activity; (ii) Tables 5 and 10 list 3,368 and 3,380 $PH20_{1-447}$ "inactive mutants," respectively.

108 EX1003, ¶ 105.

109 *Id.*

Activity vs. Unmodified PH20	Number	% of Tested (5916)
Active Mutants (Table 9)		
>120%	532	9.0%
100%-120%	267	4.5%
40%-100%	1577	26.7%
Inactive Mutants (Table 9)		
<40%	160	2.7%
Inactive Mutants (Table 10)		
Table 10 'inactive mutants"	3,380	57.1%



The measured activity of single-replacement $PH20_{1-447}$ mutants shows no trends or correlations even for single-replacement $PH20_{1-447}$ polypeptides.[110]

[110] EX1003, ¶¶ 106, 142-43.

Moreover, there are numerous examples in the dataset where the effects of introducing different amino acids into a single position in $PH20_{1-447}$ resulted in (i) increased activity, (ii) decreased activity, or (iii) inactive mutants (below).[111]

Position	Inactive	Decreased Activity	Increased Activity
008	P	L, M	I
067	R	L, Y	V
092	H	M, T	C, L, V
165	C	A, R, Y	D, F, N, S, V, W
426	K, S	E, G, N, Q, Y	P

The data on activities of tested single-replacement $PH20_{1-447}$ mutants is not analyzed or explained in the common disclosure—it is simply presented. There is no attempt to extrapolate its results to particular combinations of substitutions in PH20 polypeptides, or to even assess the impact the single substitution had on the protein's structure.[112] The quality of the data is also questionable: no control values are reported or statistical assessments.[113] The only realistic takeaway from the data is that most of the tested, random single-substitution mutants impaired

[111] Data from Tables 3, 5, 9, 10.

[112] EX1003, ¶ 139.

[113] EX1003, ¶ 106.

PH20's activity.[114] Unlike single substitutions, multiple concurrent mutations can cause complex and unpredictable effects on a protein's structure and resulting function.[115] The patent's empirical set of test results provides no insights of value to a skilled artisan attempting to identify which of the many possible mutants with different sets of 2-22 substitutions will be enzymatically active modified PH20 polypeptides.[116]

b) Purported Stability Data is Not Reliable or Probative

The common disclosure reports results in Tables 11 and 12 from two runs of supposed "stability" testing of ~409 single-replacement $PH20_{1-447}$ polypeptides.[117] Table 11 reports the hyaluronidase activity of single-replacement $PH20_{1-447}$ mutants tested at 4° C and 37° C, and in the presence of a preservative (m-cresol),[118] while Table 12 compares relative activities under pairs of these conditions.[119]

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[114] EX1003, ¶ 138.

[115] EX1003, ¶¶ 139, 142.

[116] EX1003, ¶¶ 140, 143.

[117] EX1001, 262:50-264:32 (Tables 11 and 12).

[118] EX1001, 264:34-270:44 (Table 11).

[119] EX1001, 270:45-281:52 (Table 12).

The data in Tables 11 and 12 provides no meaningful insights.[120] For example, it is unsurprising that single-replacement $PH20_{1-447}$ polypeptides showed higher activity at 37° C than at 4° C, given that PH20 exists at that temperature in humans.[121] Testing with a phenolic preservative, on the other hand, showed that only a few mutants were able to resist its effects.[122]

More generally, the examples fail to demonstrate that measured activity data was attributable to improved stability in the PH20 structure, and do not identify to the skilled artisan which multiple substitutions may improve stability.[123] They provide no probative insight regarding multiply-modified PH20 polypeptides.[124]

The values are also largely meaningless, as many of them fall within the huge variability measured for the positive control.[125] The chart below shows

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120 EX1003, ¶ 76.

121 EX1003, ¶ 73; EX1001, 177:48-57.

122 EX1003, ¶ 69.

123 EX1003, ¶¶ 75-76.

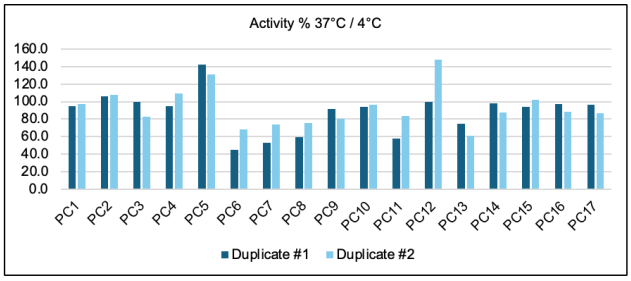
124 *Id*.

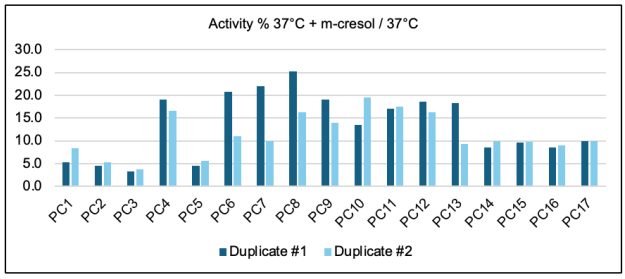
125 EX1003, ¶ 71; EX1001, 281 (Table 12).

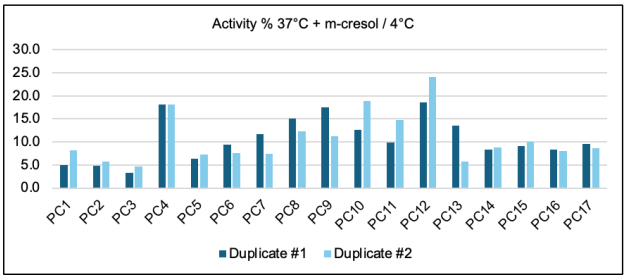
coloring reflecting relative percentage values from 0 to 120% for the positive controls from Tables 11/12 and plots those values below.[126]

Positive Control ("PC") (OHO)	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C+mcr/4 °C
PC1	94.998	5.230	4.970	96.871	8.456	8.190
PC2	105.798	4.480	4.740	108.066	5.246	5.670
PC3	100.000	3.330	3.330	82.778	3.759	4.590
PC4	94.762	19.070	18.070	109.539	16.529	18.110
PC5	142.024	4.480	6.360	130.947	5.595	7.330
PC6	45.115	20.770	9.370	68.017	11.035	7.510
PC7	53.324	21.950	11.710	74.253	9.960	7.400
PC8	59.581	25.240	15.040	75.872	16.231	12.310
PC9	91.844	19.050	17.500	80.371	13.977	11.230
PC10	93.828	13.470	12.630	96.630	19.454	18.800
PC11	57.773	17.040	9.850	83.536	17.573	14.680
PC12	100.000	18.560	18.560	148.226	16.239	24.070
PC13	74.325	18.290	13.600	61.119	9.286	5.680
PC14	98.132	8.480	8.320	87.677	10.006	8.770
PC15	93.817	9.620	9.020	102.223	9.745	9.960
PC16	96.922	8.560	8.300	87.993	9.064	7.980
PC17	96.648	9.910	9.580	86.891	9.938	8.630

KEY
Coloration of Percent (%) Activity Values
n/a
>120
between 100 and 120
between 80 and 100
between 40 and 80
between 20 and 40
between 10 and 20
between 0 and < 10







126 EX1003, ¶ 71, Appendix A-7, A-8.

	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C + m-cresol	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol	% Activity at 37°C+mcr/ 4°C
High	142.02	25.24	18.56	148.23	19.45	24.07
Low	45.12	3.33	3.33	61.12	3.76	4.59
Range	96.91	21.91	15.23	87.11	15.70	19.48
Average	88.17	13.38	10.64	93.00	11.30	10.64
Mean	94.76	13.47	9.58	87.68	9.96	8.63

The table and graphs above show the extensive variability observed for the positive control in the assay being used, with the range in values of almost 100%. As Dr. Hecht observes, the "significant variation raises serious doubts about how probative or instructive the values of individual tested mutants that fall within the range of variability observed for the control can possibly be."[127] The data thus is not only uninformative, it is unreliable.

4. The Common Disclosure's Research Plan Does Not Identify Multiply-Mutated Enzymatically Active PH20 Polypeptides

Instead of describing any multiply-modified PH20 polypeptides that are "active mutants," the common disclosure provides only a prophetic research plan based on iterative rounds of "make-and-test" experiments that were never

[127] EX1003, ¶¶ 70-72; *see also* EX1001, 281:59-282:55 (positive control also varied).

performed. This prophetic method provides absolutely no insights into which multiply-modified PH20 polypeptides are active mutants.[128]

The common disclosure merely outlines ***the idea*** of multiply-modified PH20 polypeptides. It declares that "[a] modified PH20 polypeptide can have up to 150 amino acid replacements," "[t]ypically" contains between 1 and 50 amino acid replacements and "can include any one or more other modifications**,** in addition to at least one amino acid replacement as described herein."[129] In addition to PH20 polypeptides with single amino acid replacements, it contends that a modified PH20 polypeptide "having a sequence of amino acids that exhibits" between 68% and 99% sequence identity with any of unmodified Sequence ID Nos. 74-855 "***can*** exhibit altered, such as improved or increased, properties or activities compared to the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement)."[130]

None of these statements identify ***any*** actual multiply-modified PH20 polypeptides—it does not identify ***any*** sets of specific amino acid substitutions.

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[128] EX1003, ¶¶ 173, 184-85, 190; EX1001, 43:59-61; *see generally id.*, 134:32-135:10, 135:19-136:61, 137:21-141:61.

[129] EX1001, 48:32-39.

[130] EX1001, 100:6-20 (emphasis added).

They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides.

The common disclosure then outlines an "iterative" make-and-test research plan for discovering modified PH20 polypeptides with multiple substitutions that might exhibit hyaluronidase activity.[131] It too is prophetic, and states:

> The method provided herein [] is ***iterative***. In one example, after the method is performed, any modified hyaluronan-degrading enzymes identified as exhibiting stability … ***can be modified or further modified*** to increase or optimize the stability. A secondary library ***can be*** created by introducing additional modifications in a first identified modified hyaluronan-degrading enzyme. … The secondary library ***can be*** tested using the assays and methods described herein.[132]

The guidance in this research plan is effectively meaningless. It says to make mutants, test them to find activity, and keep repeating the process until you find something via screening. It does not indicate that any useful multiply-modified PH20 polypeptides will be found, much less what their specific characteristics or activities are.[133]

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131 EX1003, ¶ 174; EX1001, 135:11-16.

132 EX1001, 141:62-142:7 (emphases added); *see also id.* at 42:40-47.

133 EX1003, ¶¶ 187-90.

The specification also incorrectly portrays the experimental readout—hyaluronidase activity—as a measure of "stability."[134] As Dr. Hecht explains, to assess a protein's stability directly one performs experiments that measure the energy associated with the protein's transition between its folded and unfolded states.[135] Activity may or may not be influenced by stability but is not itself a measure of stability.[136]

An alternative focus is then proposed: mutations can be "targeted near" "critical residues" which supposedly "can be identified because, when mutated, a normal activity of the protein is ablated or reduced."[137] But Tables 5 and 10 show that at least one substitution at each of 405 positions between positions 1 and 444 of $PH20_{1-447}$ resulted in an inactive mutant.[138] In other words, the guidance is to target locations "near" ~90% of the amino acids in $PH20_{1-447}$, which is no different

134 EX1003, ¶¶ 67, 69, 179.

135 EX1003, ¶¶ 63-66.

136 EX1003, ¶ 67.

137 EX1001, 142:8-33; EX1003, ¶¶ 178-79.

138 EX1003, ¶ 180, Appendix A-3.

than targeting every residue in the protein.[139] It is, like the first proposed "iterative" process, meaningless.

These prophetic research plans, based entirely on unfocused, iterative "make-and-test" experiments, provide no direction to the skilled artisan about which of the trillions and trillions of possible multiply-modified PH20 polypeptides are "active mutant" PH20 polypeptides. Instead, they require the skilled artisan to repeat the cycle of mutagenesis iteratively, screening and selecting until 10^{49} to 10^{66} modified PH20 polypeptides are produced and screened for activity.[140] That in no way demonstrates possession of the claimed genus.

5. The Common Disclosure Does Not Identify a Structure-Function Relationship for Multiply-Modified, Enzymatically Active PH20 Polypeptides

The common disclosure does not identify the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20

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139 EX1003, ¶ 180.

140 EX1003, ¶¶ 175-77, 181, 187-88; EX1001, 137:2-7, 136:62-137:19, 140:13-17, 140:28-33; 140:50-64.

polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.[141] Instead, it simply lists single replacements to randomly selected amino acids at random positions that were classified as "active mutants" by a hyaluronidase assay, without further explanation, and nothing is said about the effects (if any) of substitutions on the protein's structure.[142]

The common disclosure also does not identify any ***sets*** of specific amino acid replacements that correlate to structural domains or motifs that positively or negatively influence hyaluronidase activity, much less ***predictably*** increase activity to defined thresholds.[143] Again, it simply reported activity data from testing randomly generated ***single***-replacement $PH20_{1-447}$ mutants.

The common disclosure's empirically identified examples of "active mutant" single-replacement $PH20_{1-447}$ mutants also do not ***by themselves*** identify any "structure-function" relationship between "active mutants" and the set of single-replacement modified $PH20_{1-447}$ polypeptides.[144] And they plainly do not do

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141 EX1003, ¶¶ 139-40, 151.

142 EX1001, 234:2-31; EX1003, ¶¶ 139-40, 142.

143 EX1003, ¶¶ 55, 142-43.

144 EX1003, ¶¶ 61, 143, 157, 159.

so for the much larger genus of modified PH20 polypeptides having varying lengths and between 2 and 22 substitutions, with or without additions or deletions.[145]

Critically, the common disclosure also ***does not even contend*** that a particular amino acid replacement at a particular position that makes a $PH20_{1-447}$ an "active mutant" will make any other modified PH20 polypeptide with that same amino acid replacement (plus between 2 to 22 additional replacements or truncations) an "active mutant."[146] Such an assertion would have no scientific credibility—the activity of a protein such as PH20 is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.[147] Thus, even the inventors did not view their compilation of test results as identifying a structure-function correlation for multiply-modified PH20 polypeptides.

The common disclosure, thus, does not identify to a skilled artisan ***any*** structural features shared by the many, diverse "active mutant" modified PH20

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145 EX1003, ¶ 157.

146 EX1003, ¶¶ 168, 192-93.

147 EX1003, ¶¶ 56-57.

polypeptides within the scope of the claims.[148] As such, it cannot satisfy the written description requirement of § 112(a) as being a disclosure that links a functional property shared by members of the genus to a particular structure ***shared*** by the members of the genus.

6. The Common Disclosure Does Not Describe a Representative Number of Multiply-Modified Enzymatically Active PH20 Polypeptides

The ~2,500 single-replacement $PH20_{1-447}$ polypeptides that are "active mutants" are not examples representative of the claimed genera of claims 1 to 4, much less its various sub-genera.[149]

First, the single-replacement $PH20_{1-447}$ examples are not representative of the trillions and trillions of $PH20_{1-447}$ polypeptides with between ***2 and 22 substitutions*** at any of hundreds of positions within the protein.[150] The latter group of proteins is structurally distinct from single replacement PH20 polypeptides, both as to their sequence and due to the various structures within the folded protein that, when incorporating different amino acid substitutions, may alter their structures

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148 EX1003, ¶ 157.

149 EX1003, ¶¶ 61, 143, 155, 159.

150 *See* § IV.D.1; EX1003, ¶¶ 61, 143, 159.

and their interactions with neighboring residues.[151] The effects of those numerous substitutions on a protein's various secondary structures and structural motifs within the protein is not described in the common disclosure, and the magnitude of concurrent substitutions encompassed by the claims was unknowable in 2011.[152] The overall activity of a protein with multiple substitutions also will not be due to one amino acid, but to the unique structure of each protein that reflects ***the totality*** of effects of those many substitutions.[153]

More specifically, introducing a first amino acid substitution often affects the neighbors of that original/replaced amino acid by, for example, (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).[154] Introducing a second substitution in that region may reverse those interactions (or not) with each neighboring residue, and a third substitution may do the same, up to 22 rounds each potentially impacting each interaction.[155] The data associated with

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151 EX1003, ¶¶ 54-56, 58, 120, 156, 159.

152 EX1003, ¶ 224.

153 EX1003, ¶¶ 36, 61, 140, 143, 151.

154 EX1003, ¶¶ 56-58.

155 EX1003, ¶¶ 58-60, 142.

a single amino acid substitution thus cannot be representative of the properties of any of these downstream, multiply-substituted mutants, which will have an unknowable combination of substitutions that each uniquely impact the properties of the mutated protein.[156]

Enzymatically active single-replacement $PH20_{1-447}$ polypeptides also are not representative of enzymatically active, multiply modified PH20 polypeptides that incorporate changes that alone render PH20 proteins inactive (*e.g.*, truncations terminating below position 429, or single substitutions that render $PH20_{1-447}$ inactive).[157] The reason for this is simple: the active single-replacement $PH20_{1-447}$ polypeptide does not also contain the distinct structural features that render the latter types of PH20 polypeptides enzymatically inactive. For example, an enzymatically active $PH20_{1-447}$ protein with a single amino acid substitution (*e.g.*, L317Q) would not be considered representative of a PH20 that combines that L317Q substitution with truncations at the C terminus ending at positions between 409 to 433 because the common disclosure would have led a skilled artisan to expect that PH20 proteins terminating at those positions would be inactive.[158] A

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156 EX1003, ¶¶ 61, 142-43, 159, 169.

157 EX1003, ¶¶ 161-64.

158 EX1003, ¶¶ 167-69.

skilled artisan could not have predicted—based on the examples in the common specification, all of which are limited to single-replacement $PH20_{1-447}$ polypeptides—whether enzymatic activity could be restored to such severely truncated PH20 mutants, much less the precise additional changes that would do so.[159]

The Patents thus provide a very narrow set of working examples relative to the diversity of modified PH20 polypeptides being claimed.[160] The examples are restricted to ***one type of change*** (a single amino acid replacement) in ***one type of PH20 polypeptide*** (SEQ ID NO: 3).[161] By contrast, the claims encompass changes in 35 different unmodified PH20 sequences, and include, in addition to one identified replacement, anywhere from 1 to 21 (claim 1), 1-16 (claim 3) or 1-20 (claim 4) additional changes.[162] A simple illustration demonstrates how ***non-representative*** the examples are: all of the Patents' examples of single-replacement $PH20_{1-447}$ mutants fit into one box of the array below.

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159 EX1003, ¶ 168.

160 EX1003, ¶ 155.

161 EX1003, ¶¶ 97, 99, 103.

162 EX1003, ¶¶ 115-20.

	Number of Changes																				
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
3																						
32																						
33																						
34																						
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Consequently, the skilled artisan would not have viewed the Patents' examples of individual single amino acid replacements in $PH20_{1-447}$ as

representative of the diversity of modified PH20 polypeptides encompassed by the claims.[163]

7. The Claims Capture Multiply-Modified PH20 Polypeptides the Disclosure Excludes from the Class of Enzymatically Active PH20 Proteins

Patentee's position on the breadth of the claims is unknown. However, by their literal language, the claims capture several sub-genera of "active mutant" modified PH20 polypeptides the common disclosure says caused single-replacement $PH20_{1-447}$ mutants to be rendered inactive (*i.e.*, those with replacements in Tables 5/10 or in PH20 sequences truncated below position 429). Likewise, the claim language captures modified PH20 polypeptides with the six combinations of replacements the common disclosure explicitly says to not make: P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, N333A/N358A and N47A/N131A/N219A.[164] The claims thus improperly capture subject matter the common disclosure affirmatively excluded from the genus of enzymatically active modified PH20 polypeptides having multiple substitutions and other changes.

The common disclosure provides no exemplification of multiply-modified species of PH20 polypeptides that violate these prohibitions in the common

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163 EX1003, ¶ 143.

164 *See* § V.A.2.a; EX1001, 77:31-43.

disclosure.[165] There is no explanation of the types of substitutions that might be made to restore activity that, under the logic of the common disclosure, will result of enzymatically inactive PH20 polypeptides or which the specification teaches ***not*** to make.[166] Yet the claims encompass such proteins. The claims therefore independently violate the written description requirement for the reasons articulated by the Federal Circuit in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998)—if a disclosure "unambiguously limited" the invention, but the claims circumvent that limitation, those claims are "broader than the supporting disclosure" and are unpatentable.

8. The Dependent Claims Lack Written Description

a) Claims 5 and 6 Lack Written Description

Claims 5 and 6 add a purely functional requirement to the genus defined by claim 1: that the modified PH20 polypeptides exhibit increased (>100% (claim 5) or >120% (claim 6)) hyaluronidase activity relative to unmodified $PH20_{1-447}$.

The reasons provided in §§ V.A.1-V.A.7 explaining why claims 1-4 lack written description apply with full force to claims 5 and 6. Stated simply, the common disclosure's recitation of a ***desired*** level of hyaluronidase activity in

[165] EX1003, ¶ 161.

[166] EX1003, ¶ 168.

claims 5 and 6 does not identify ***which*** of the many trillions of PH20 polypeptides having 95% sequence identity with SEQ ID NOS: 3 or 32-66 and one of seven replacements at position 317 will exhibit those functional requirements.[167]

First, the identification of five $PH20_{1-447}$ mutations at position 317 that exhibit 120% or higher activity (Q, I, K, M, R) of unmodified $PH20_{1-447}$ is not representative of each claim's genus of PH20 polypeptides with 2 to 22 additional substitutions and/or truncations.[168] There is no description of multiply-modified PH20 polypeptides with the claimed substitutions at 317, much less one that identifies the 2 to 22 more substitutions and would retain this elevated enzymatic activity.[169] Indeed, the common specification does not identify even one multiply-modified PH20 polypeptide with any level of hyaluronidase activity.[170]

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides and exhibiting the recited >100% or >120% activity.[171] Certainly, the mere presence of a L317Q replacement in a

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167 EX1003, ¶¶ 185, 191-92.

168 EX1001, 237 (Table 9); EX1003, ¶¶ 191-92.

169 EX1003, ¶¶ 140, 190-93.

170 EX1003, ¶¶ 130, 172.

171 EX1003, ¶¶ 157, 190.

multiply-modified PH20 does not dictate such a result, and the common disclosure makes no claim that it does.[172]

Claims 5 and 6 lack written description in the common disclosure.

b) Claim 7 Lacks Written Description

Claim 7 requires the modified PH20 polypeptide of claim 1 to be "soluble."

Claim 7 lacks written description support (i) for the same reasons identified for claim 1, and (ii) because it encompasses modified PH20 polypeptides that the common disclosure suggests would be insoluble.

The common disclosure explains that "a soluble PH20 lacks all or a portion of a glycophosphatidyl anchor (GPI) attachment sequence,"[173] which was known to be hydrophobic.[174] Citing prior art, it identifies the first residue of the GPI sequence in human PH20 as position 456 (position 491 in SEQ ID NO: 6).[175] It

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172 EX1003, ¶¶ 143, 168, 192.

173 EX1001, 46:17-19, 71:63-64; 74:14-26.

174 EX1001, 72:20-32; EX1005, 86:18-22.

175 EX1001, 72:20-32; *also* EX1005, 2:56-61 ("Attempts to make human PH20 DNA constructs that would not introduce a lipid anchor into the polypeptide resulted in either a catalytically inactive enzyme, or an insoluble enzyme") (citing EX1011).

also states that a soluble PH20 "is a polypeptide that is truncated after amino acid 482 of … SEQ ID NO: 6" (*i.e.*, 447 in SEQ ID NO:3)."[176] It thus suggests that human PH20 sequences that terminate below position 448 are soluble and those that terminate above position 456 are insoluble.[177]

Claim 7 encompasses PH20 polypeptides based on SEQ ID NOS:59-66, which terminate between positions at 457 to 464 respectively (*i.e.*, beyond position 456), and does not restrict where in the PH20 polypeptide changes are made, other than the replacement at position 317. Consequently, claim 7 captures modified PH20 polypeptides that, per the common disclosure, ***are not*** "soluble modified PH20 polypeptides" because each contains "all or a portion of" the GPI attachment sequence.[178]

Patentee may contend that some unidentified number of modified PH20 polypeptides based on SEQ ID NOS: 59-66 ***may*** be soluble, citing the common disclosure as suggesting that between 1-10 residues within the GPI anchor "can be retained, provided the polypeptide is soluble."[179] But the common disclosure does

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176 EX1001, 75:4-6; EX1005, 3:57-62.

177 EX1003, ¶¶ 89-90.

178 EX1001, 46:44-50.

179 EX1001, 74:7-13.

not identify ***which*** modified PH20 polypeptides terminating above position 448 (and especially terminating between 457 and 464) ***are*** soluble, provides no examples of such soluble PH20 mutants, and provides no reason to expect that many modified PH20 polypeptides within the claim's scope are soluble.

Thus, claim 7 is unpatentable for lack of written description for this additional, independent reason.

c) Claims 8-10 Lack Written Description

Claims 8-10 employ claim 1's definition of the genus of modified PH20 polypeptides, and do not add requirements that limit the numbers of polypeptides in that genus. Claims 8-10 lack written description for the same reasons as claim 1.

d) Claims 11-13 Lack Written Description

Claims 11-13 employ claim 1's definition of the genus of modified PH20 polypeptides to define pharmaceutical compositions and methods of administering such compositions. Claims 11-13, however, contain no language that identifies ***which*** modified PH20 polypeptides within that immense genus can be used in the claimed methods, and thus do not remedy the § 112 deficiencies of claim 1.[180]

[180] *Idenix*, 941 F.3d at 1155, 1165 (claims directed to method of treatment involving immense genus of modified proteins invalid for lack of written

Because each of claims 11-13 are directed to the same genus of polypeptides that are not adequately described in the written description of the common disclosure, they are unpatentable.

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

"If a patent claims an entire class of … compositions of matter, the patent's specification must enable a person skilled in the art to make and use the ***entire*** class," *i.e.*, "the ***full scope*** of the invention."[181] So, the "more one claims, the more one must enable."[182] "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."[183] "Claims are not enabled when, at the effective filing date

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description and non-enablement); *Boehringer*, PGR2020-00076, Paper 42, at 40-41 (claims to methods of treatment using compositions found to lack written description because specification did not provide an adequate written description of the compositions being administered).

181 *Amgen*, 598 U.S. at 610 (emphases added).

182 *Id.*

183 *Idenix*, 941 F.3d at 1159.

of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation."[184]

Although not required, enablement may be assessed using the *Wands* factors, which consider: "(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention."[185]

Where the scope of the claims is large, there are few working examples disclosed in the patent, and the only guidance to practice "the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims' functional limitations—the asserted claims are not enabled."[186]

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184 *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

185 *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

186 *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, T., sitting by designation) *aff'd* 81 F.4th 1362 (Fed. Cir. 2023).

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the 10^{49}+ PH20 polypeptides having multiple amino acid replacements and/or truncations are "active mutant" PH20 polypeptides within the scope of the claims.[187]

1. Claims 1 to 4 Are Not Enabled

The facts of this case are a textbook example of claims that are not enabled under the reasoning articulated by the Supreme Court in *Amgen*. An analysis of the common disclosure under the Federal Circuit's framework for assessing undue experimentation using the factors in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) also compels the same conclusion.

a) Extreme Scope of the Claims

As explained in § IV.D.1, each of claims 1 to 4 defines an immense and structurally diverse genus of between 10^{49} and 10^{66} modified PH20 polypeptides, which introduces substantial scientific questions that are left unanswered by the common disclosure.

[187] EX1003, ¶¶ 170-71, 190.

The claims encompass many modified PH20 polypeptides that terminate below position 429.[188] The common disclosure and the prior art, however, report that unmodified human PH20 must include residues through position 429 to have hyaluronidase activity.[189] Several of the claims (1-2, 5-12) also encompass modified PH20 polypeptides that, per the common disclosure's guidance, would be expected to be insoluble because they include all or some of the GPI anchor sequence.[190] And, to the extent Patentee contends the claims should be read as covering any polypeptide that falls within the mathematical "sequence identity" boundaries set by the claim language, they would capture modified PH20 polypeptides with 2-22 amino acid replacements the common disclosure instructs "are less tolerant to change or required for hyaluronidase activity"[191] or which the common disclosure affirmatively says to not make.[192]

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188 EX1003, ¶¶ 154, 164.

189 EX1001, 69:53-62; EX1003, ¶¶ 93, 152-53.

190 EX1001, 46:17-19, 71:63-64, 74:7-13, 75:4-6; EX1005, 2:56-61, 3:57-62.

191 EX1001, 79:66-80:1.

192 EX1001, 77:31-43.

In other words, the claims capture a massive genus of modified PH20 polypeptides, most of which would have unknowable properties absent individual production and testing.[193]

Claims that capture a massive and diverse genus of proteins have routinely been found non-enabled. For example, the claims in *Amgen* covered "millions" of different, untested antibodies,[194] while in *Idenix*, a skilled artisan would "understand that 'billions and billions' of compounds literally meet the structural limitations of the claim."[195] In both cases, the enormous claim scope was found non-enabled after being contrasted to the limited working examples in the patent, the existence of unpredictability, and the quantity of experimentation needed to practice the full scope of the claims (*Wands* Factors 1, 3, 4, and 7). And, as the *Idenix* court observed, one cannot rely on the knowledge and efforts of a skilled artisan to try to "fill the gaps in the specification" regarding which of the "many, many thousands" of possible compounds should be selected for screening, and which in this case is impossible.[196]

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193 EX1003, ¶ 158.

194 598 U.S. at 603.

195 941 F.3d at 1157.

196 *Id.* at 1159.

b) Limited Working Examples and Only a Research Plan for Discovering Active Mutant PH20 Polypeptides

The common disclosure provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement $PH20_{1-447}$ polypeptides, of which ~2500 were "active mutants."[197] Those examples are a tiny fraction of the 10^{49} to 10^{66} modified PH20 polypeptides covered by the claims, and provide no guidance that would help a skilled artisan navigate the "trial-and-error" methodology the common disclosure describes using to make modified PH20 polypeptides; indeed, none incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.[198]

The common disclosure provides no credible guidance on the full scope of the genus comprising multiple combinations of changes to PH20 polypeptides.[199] Instead, it describes an explicitly prophetic and "iterative" process for ***discovering*** active mutant PH20 polypeptides. *See* § V.A.4.

The purely prospective research plan in the common disclosure demands that a skilled artisan engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of ***randomized***

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[197] EX1003, ¶ 103.

[198] EX1003, ¶¶ 155, 159, 167.

[199] EX1003, ¶¶ 131, 139.

mutations (up to 21 rounds per starting molecule under the broadest claims) to ***discover*** which of the 10^{49}+ possible modified PH20 polypeptides having 2 to 21 replacements to any of 19 other amino acids in any of 35 starting PH20 sequences might possess hyaluronidase activity.[200]

Second, it provides no meaningful guidance in producing "active mutant" modified PH20 polypeptides:

(i) it does not identify ***any*** specific combination of two or more replacements within any PH20 polypeptide that yield "active mutants";

(ii) it provides no data from testing ***any*** PH20 polypeptide with two or more substitutions;

(iii) it does not identify any regions or residues that are "associated with the activity and/or stability of the molecule" or "'critical residues

[200] EX1003, ¶¶ 188-90; *see also* EX1018, 382 ("combinatorial randomization of only five residues generates a library of 205 possibilities (3.2 x 10^6 mutants), too large a number for manual screening"). Chica also credited a supposed "ground-breaking" advancement in predictive molecular modeling techniques. EX1018, 384, 382. That supposed advancement, however, was later shown to be false. EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

involved in structural folding or other activities' of the molecule" when two or more concurrent replacements have been made.[201]

A skilled artisan could not predict whether a particular multiply-modified PH20 polypeptide will be enzymatically active without making and testing each one.[202]

Regardless of whether individual rounds of "iterative" production and testing might be considered "routine," the process described in the common disclosure is indistinguishable from the "***iterative, trial-and-error process[es]***" that have consistently been found to not enable broad genus claims to modified proteins.[203] Simply put, the common disclosure's prophetic, iterative and labor-intensive process requires making and screening an immense number of modified PH20 polypeptides, before which the skilled artisan will not know which multiply-modified PH20 polypeptides are within the claims' scope.[204]

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201 EX1003, ¶¶ 144, 158, 172, 184-85.

202 EX1003, ¶ 190.

203 *Idenix*, 941 F.3d at 1161-63 (emphasis added); *see also Amgen,* 598 U.S. at 612-15; *Wyeth*, 720 F.3d at 1384-86; *Baxalta*, 597 F. Supp. 3d at 616-19; *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 n.2 (Fed. Cir. 2020).

204 EX1003, ¶¶ 172, 183-85, 189.

c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable

Like any protein, the activity of PH20 can be unpredictably influenced by changes to its amino acid sequence.[205] Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary structures or structural motifs within the protein that are important to its biological activity (*e.g.*, catalysis, ligand binding, etc.).[206]

As explained in § VI, below, by 2011, skilled artisans could have assessed whether certain ***single*** amino acid substitutions at certain positions would be tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.[207] That person, using a rational design approach, would have performed such an assessment by, *inter alia*, analyzing evolutionarily non-conserved positions and evaluating specific changed residues using a PH20 protein structure model using experimental evidence available before 2011 that is not disclosed in or referenced by the common disclosure.[208]

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205 EX1003, ¶ 61.

206 *Id.*

207 EX1003, ¶ 194.

208 EX1003, ¶¶ 20-22, 49, 211-12, 216.

By contrast, the skilled artisan could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011.[209] Introducing ***multiple*** concurrent changes into a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity, and can even introduce new ones into the protein.[210] Replacing multiple amino acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.[211]

The cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure in 2011. For example, the further away the modeled amino acid sequence gets from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model became.[212] In addition, depending on the structural template used to produce the model, regions of the protein not supported by a

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209 EX1003, ¶ 224.

210 EX1003, ¶¶ 59-60.

211 EX1003, ¶ 58.

212 EX1003, ¶¶ 158, 190, 224; EX1004, ¶¶ 163-164.

corresponding structure cannot be reliably used to assess particular changes.[213] And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.[214]

Consequently, a skilled artisan could not have used conventional rational design techniques to identify, much less predict the outcome of attempts to make, the enormous number of PH20 polypeptide sequences that incorporate the myriad possible combinations of between 5 and 22 substitutions the claims encompass.[215] Stated another way, practicing the full scope of the claims would have been well beyond the ability of the skilled artisan's ability to reasonably predict which multiply-modified PH20 polypeptides would be enzymatically active, and, even if possible, doing so would have taken an extreme amount of time and effort even for a small handful of the vast universe of multiply-modified polypeptides within the claims.[216]

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213 EX1003, ¶¶ 158, 224; EX1004, ¶¶ 153-55; EX1012, 4, 8.

214 EX1003, ¶ 51, 190; EX1059, 1225-26; EX1018, 378.

215 EX1003, ¶¶ 61, 158, 224.

216 EX1003, ¶¶ 158, 190.

d) Other Wands *Factors and Conclusion*

The remaining *Wands* factors either support the conclusion that practicing the full scope of the claims would require undue experimentation or are neutral.

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of multiply-changed PH20 polypeptides.[217] Likewise, while there was significant knowledge in the public art about hyaluronidases, there was no solved structure of the PH20 protein, experimental reports generally reported on ***loss of activity*** from mutations, and did not predictably teach how to introduce changes that ***enhanced*** stability or activity. Indeed, the patent disclosure at issue in *Amgen* dates to the same 2011 timeframe as the common disclosure.

Practicing the full scope of claims 1-4 thus would have required a skilled artisan to engage in undue experimentation, which renders those claims non-enabled.

2. The Dependent Claims Are Not Enabled

a) Claims 5 and 6 Are Not Enabled

Claims 5 and 6 require the modified PH20 polypeptides to have specific levels of increased activity (*i.e.*, >100% or >120% of unmodified PH20).

[217] EX1003, ¶¶ 158, 224.

The reasons why claims 1-4 are not enabled (*see* § V.B.1) establish why claims 5 and 6 are also not enabled. Specifically, a skilled artisan could not have predicted which of the trillions of PH20 polypeptides having up to 21 changes in addition to a required change at position 317 would exhibit greater than 100% or 120% of the hyaluronidase activity of an unmodified PH20.[218] Instead, a skilled artisan would need to make-and-test each of those molecules in order to practice the "full scope" of the claims.[219]

b) Claim 7 is Not Enabled

Because claim 7 encompasses a substantial portion of the genus defined by claim 1, it is not enabled for the same reasons that claims 1-4 are not enabled. Additionally, as explained in §§ V.A.8.b, the common disclosure suggests that PH20 polypeptides (modified or unmodified) that extend past position 456 would be "insoluble." Based on it and published literature, a skilled artisan would have expected the presence of the highly hydrophobic GPI sequence would lead to a much greater propensity for the PH20 protein to misfold, to aggregate, and/or to not be successfully expressed from a host cell.[220] The common disclosure

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218 EX1003, ¶¶ 185, 190.

219 *Id.*

220 EX1003, ¶ 196.

reinforces that these problems can occur, but provides no guidance as to how solve them and no examples of modified PH20 polypeptides extending past position 456 that are soluble. Claim 7 is thus not enabled.

c) Claims 8-10 Are Not Enabled

Claims 8-10 employ the genus definition used in claim 1, and do not add requirements that limit the numbers of polypeptides in the claim 1 genus. Claims 8-10 are therefore not enabled for the same reasons as claim 1.

d) Claims 11-13 Are Not Enabled

Claims 11-13 employ the definition of the genus of modified PH20 polypeptides used in claim 1 to define a pharmaceutical composition and methods of administering such composition. None of claims 11-13 limit the number of polypeptides in the claim 1 genus. Claims 11-13 are therefore not enabled for the same reasons as claim 1.[221]

C. Inactive PH20 Polypeptides Are Not Useful and Do Not Remedy the § 112(a) Deficiencies of the Claims

Patentee may contend the claims do not require the modified PH20 polypeptides to be "active mutants." Such a contention, even if accepted, does not solve the written description and enablement problems of the claims.

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[221] *See, e.g.*, *Idenix*, 941 F.3d at 1155, 1165.

First, it ignores that at least a portion of the claimed genus ***does*** require the modified PH20 polypeptides to be an "active mutant." *See* § IV.D.3. Because dependent claims 5 and 6 require the modified PH20 polypeptides to exhibit increased hyaluronidase activity levels (>100% or 120% of unmodified PH20), parent claim 1 necessarily encompasses a sub-genus comprised of "active mutant" modified PH20 polypeptides. A failure to enable or describe a subgenus within the scope of the claims demonstrates that the claim ***as a whole*** is unpatentable for lack of written description and non-enablement.

Second, the common disclosure fails to provide any correlation between changes to PH20 polypeptides and ***either*** active or inactive mutants.[222] Rather, it leaves to the skilled artisan the burdensome task of making and testing, through trial-and-error iteration, each of the 10^{49}+ candidate polypeptides within the claims' scope to determine which exhibit hyaluronidase activity and which are inactive mutants.[223]

Third, the only putative utility identified for "inactive" polypeptides is as "antigens in contraception vaccines."[224] This assertion is not scientifically

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222 EX1003, ¶ 143.

223 EX1003, ¶¶ 173-74, 182-84.

224 EX1001, 75:42-44, 194:28-47.

credible, but regardless, the common disclosure provides no guidance about which epitopes on the PH20 protein must be preserved in an "inactive mutant" (if any) to induce contraceptive antibody production in a human subject.[225] Notably, while the specification cites two studies in guinea pigs,[226] it ignores numerous publications before 2011 that showed that immunizing mammals with PH20 did ***not*** cause contraception.[227] Moreover, Patentee's own clinical studies of the unmodified $PH20_{1-447}$ protein reported in 2018 that, despite producing anti-PH20 antibodies, those anti-PH20 antibodies ***did not affect fertility*** in humans:

> Although some antisperm antibodies are associated with decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex.[228]

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225 EX1003, ¶ 113.

226 EX1001, 194:28-47; EX1022, 1142-43; EX1023, 1133-34.

227 *See* EX1019, 325, 331-33 ("recombinant mPH20 is not a useful antigen for inclusion in immunocontraceptive vaccines that target mice"); EX1020, 179-81 ("immunization [of rabbits] with reproductive antigens … are unlikely to result in reduced fertility …"); EX1021, 30310, 30314 ("PH-20 is not essential for fertilization, at least in the mouse …").

228 EX1024, 87-88; *see also* EX1061, 1154; EX1003, ¶¶ 110-11.

Notably, Patentee reported this clinical result before filing the application that issued as the ’262 Patent.

Even if one considers the unlikely possibility than some epitope on human PH20 might induce contraceptive effects in a human, a skilled artisan could not have reasonably predicted from the common disclosure whether any “inactive mutant” modified PH20 polypeptides would preserve that epitope or induce antibody production that would confer (contrary to Patentee’s clinical evidence) contraceptive effects in humans.[229] Indeed, a skilled artisan would have expected the vast majority of “inactive mutant” PH20 polypeptides would have no utility at all.[230] Consequently, a skilled artisan would not have accepted the common disclosure’s assertion that “inactive mutants” are useful as contraceptive vaccines, particularly in humans.[231]

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[229] EX1003, ¶¶ 112-13.

[230] *Id.*; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App’x. 26, 30 (Fed. Cir. 2007).

[231] EX1003, ¶¶ 112-13; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

Finally, and most significantly, the common disclosure does not identify a single inactive PH20 mutant (with any number of substitutions) that was shown to have contraceptive effect.[232] Therefore, at most, the common disclosure presents only a "research proposal" to discover such "inactive mutants."[233] It does not demonstrate possession of or enable the immense and diverse genus of PH20 polypeptides claimed, regardless of whether the claims are appropriately limited to "active mutants" or, instead, include "inactive mutants."

D. The Original Claims of the '731 Application Do Not Cure the Written Description and Enablement Deficiencies

The specifications of the pre-AIA '731 Application and AIA '262 Patent are substantially identical, and the challenged claims are not supported as § 112(a) requires by either. The claims are both PGR eligible and unpatentable under § 112(a).

The originally-filed claims of the '731 Application employed different claim formats but encompassed an equivalently large genus of multiply-substituted polypeptides. For example, original claim 1 required a "modified PH20

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232 EX1003, ¶ 113.

233 *See Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("[t]he utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research").

polypeptide" with an "amino acid replacement [that] confers … increased stability" and having "85% sequence identity to SEQ ID NO: 3" (claim 3) or between "1 [and] 75 or more amino acid replacements" (claim 4). Dependent claims list positions (claim 12) or replacements (claims 13-16) in those polypeptides. And, while certain claims contemplated 2-3 particular combinations of amino acid replacements (from dozens of locations), the claims also encompassed other unspecified substitutions at unspecified locations.[234]

The original claims provide no additional guidance or insight that would demonstrate written description of or enable the claimed sets of modified PH20 polypeptides. As such, the original claims do not provide § 112 support for the challenged claims.[235]

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[234] EX1026, at 335.

[235] *See, e.g.*, *Ariad Pharms.*, 598 F.3d at 1349 ("original claim language" does not "necessarily disclose[] the subject matter that it claims"); *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993) (original claim amounted to no more than a "wish" or "plan" for obtaining the claimed DNA and "attempt[ed] to preempt the future before it has arrived").

VI. Challenged Claims 1-4 and 7-13 Are Unpatentable Under § 103

As explained in § IV.D.2 above, claims 1-4 each define a genus that includes ***one*** specific modified PH20 polypeptide: L317Q $PH20_{1-447}$. Because that particular modified PH20 polypeptide would have been obvious from the '429 Patent in view of Chao and the knowledge of a skilled artisan before 2011, each of claims 1-4 is unpatentable. Each of claims 7-12 also would have been obvious, as each specifies attributes that are met by the L317Q modified $PH20_{1-447}$ polypeptide, or involve issues taught or suggested by the '429 Patent alone or with other prior art.

A. The Prior Art

The '429 Patent (EX1005) is owned by Patentee, was originally filed in 2003, and issued on Aug 3, 2010.

Chao (EX1006) is an article published in the scientific journal "Biochemistry" in 2007. Chao is not discussed in the common disclosure of the '262 Patent and '731 Application, and was not cited or considered during examination of either.

Knowledge of the skilled artisan relevant to obviousness is described in the testimony of Drs. Hecht (EX1003) and Park (EX1004), and is also documented in the prior art, including Patentee's earlier-published application, WO297 (EX1007).

B. Because L317Q PH20$_{1-447}$ Would Have Been Obvious, Claims 1-4 Are Unpatentable

As explained below, Patentee's '429 Patent would have motivated a skilled artisan to produce modified PH20$_{1-447}$ polypeptides having a single amino acid substitution in a non-essential region of the protein. That person, guided by her familiarity with conventional rational protein design principles and the teachings of the '429 Patent and Chao, would have readily identified single amino acid substitutions in non-essential regions of PH20$_{1-447}$ that would have been tolerated by the enzyme (*i.e.*, the PH20$_{1-447}$ enzyme with that single substitution would be expected to retain its enzymatic activity). One such singly substituted PH20$_{1-447}$ polypeptide would have been L317Q PH20$_{1-447}$, which the skilled artisan would have reasonably expected would retain hyaluronidase activity. Because claims 1-4 each encompass this obvious variant of PH201-447, each is unpatentable.

1. Patentee's '429 Patent Motivates a Skilled Artisan to Make Single Amino Acid Substitutions in Non-Essential Regions of PH20$_{1-447}$

Patentee's '429 Patent, filed in 2003, describes as its invention soluble hyaluronidase glycoproteins ("sHASEGPs") based on PH20 that are enzymatically active at neutral pH.[236] It exemplifies and claims one such "sHASEGP" produced

[236] EX1005, 6:4-10, 10:30-59.

by truncating the human PH20 sequence at position 447 (positions 36-482 of SEQ ID NO: 1).[237]

The ’429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, when combined with other therapeutic agents, and specifically illustrates administering such combinations subcutaneously to treat diseases including cancer.[238] $PH20_{1-447}$ was approved by the FDA as Hylenex® in 2005.[239] The ’429 Patent’s teachings combined with the status of $PH20_{1-447}$ as an approved human therapeutic before 2011 would have induced a skilled artisan to focus on this particular PH20 polypeptide.[240]

Patentee’s ’429 Patent defines sHASEGPs as not only being the wild-type $PH20_{1-447}$ sequence, but as also including “equivalent” proteins “with amino acid substitutions that do not substantially alter activity” of the protein.[241] It then expands on this guidance, explaining:

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237 EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

238 EX1005, 8:25-9:4, 56:36-43, 56:56-57:36, 63:41-61, 74:10-29, 76:19-77:36, 99:28-100:47.

239 EX1049, 1.

240 EX1003, ¶ 195.

241 EX1005, 9:65-10:13; *see also id.* at 18:64-19:6 (“equivalent” proteins).

> Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity …[242]

The '429 Patent also explains that single amino acid substitutions can include "conservative" substitutions in Table 1, but that "[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions."[243]

The '429 Patent thus teaches making a ***particular*** type of modification (a single amino acid substitution) at a ***particular*** location (non-essential regions of PH20) in a ***particular*** PH20 sequence ($PH20_{1-447}$) to yield equivalents of $PH20_{1-447}$ (*i.e.*, those that do not substantially alter the activity or function of $PH20_{1-447}$).[244]

The '429 Patent also motivates skilled artisans to undertake this effort to design and produce such single-amino acid substituted $PH20_{1-447}$ proteins because

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242 EX1005, 16:14-22.

243 EX1005, 16:24-36.

244 EX1003, ¶¶ 202-204; EX1004, ¶ 32.

it assures them their efforts will be successful.[245] As it states, skilled artisans recognized that such "single amino acid substitutions in non-essential regions" of $PH20_{1-447}$ "do not substantially alter biological activity" of $PH20_{1-447}$. As such, a skilled artisan would have expected a $PH20_{1-447}$ mutant with a single amino acid substitution in a non-essential region to have the same utility and therapeutic applications that the '429 Patent identifies for wild-type $PH20_{1-447}$ and other sHASEGPs.[246]

2. Chao Provides Information Useful for Engineering the Changes to $PH20_{1-447}$ that the '429 Patent Suggests

In 2011, a skilled artisan looking to implement the '429 Patent's suggestion to make a single-amino acid modification in a non-essential region of $PH20_{1-447}$ would have recognized this type of change could best be accomplished using conventional rational design techniques, which involves determining (i) which regions are non-essential in PH20, and (ii) which single amino acids to substitute into positions in those non-essential regions.[247]

The '429 Patent was written eight years before 2011. Given that, a skilled artisan would have looked for additional published insights into the structure of

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245 EX1003, ¶¶ 203-204.

246 EX1003, ¶¶ 199, 203, 218.

247 EX1003, ¶¶ 209-10.

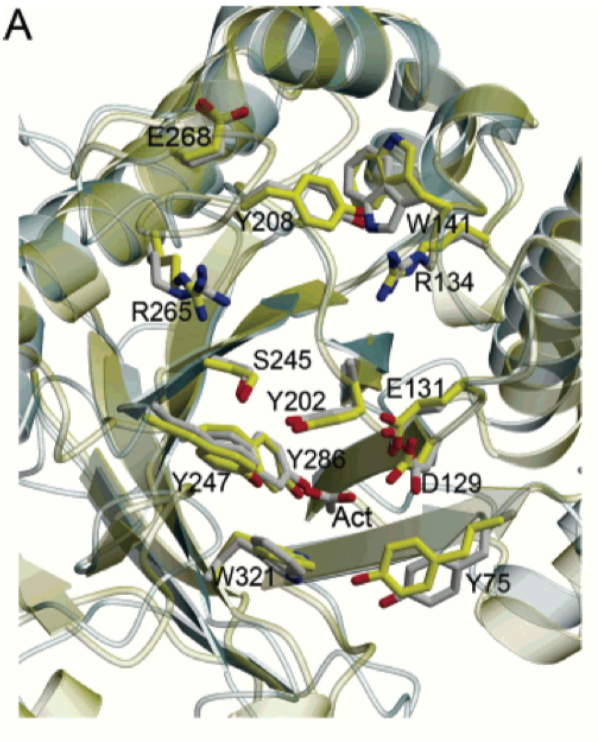
human hyaluronidase enzymes like PH20.[248] That would have led the person directly to Chao (EX1006), which reported an experimentally determined structure for human HYAL1, and provided new insights into the shared characteristics of human hyaluronidase enzymes.[249]

First, by superimposing the HYAL1 and bee venom hyaluronidase structures, Chao showed that human and non-human hyaluronidases share a highly conserved catalytic active site structure and identified residues within this catalytic site that interact with the HA substrate.[250]

[248] EX1003, ¶¶ 86, 205; EX1004, ¶ 88.

[249] EX1003, ¶¶ 86, 205-207; EX1004, ¶ 88; EX1006, 6912-17.

[250] EX1006, 6917 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1004, ¶¶ 89-91; EX1003, ¶¶ 81-82.



The ’429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20.[251] It also taught that hyaluronidase domains share similarity among and between species, including certain residues in conserved motifs necessary for enzymatic activity.[252]

Second, using an alignment of five human hyaluronidases, Chao identified predicted secondary structures in the proteins (*e.g.*, β-sheets, α-helices) (Figure 3, below), as well as, invariant conserved positions (blue), residues involved in

[251] EX1005, 4:12-22, 86:49-53, 88:14-24.

[252] EX1005, 2:6-67, 4:11-22.

catalysis (red), conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).[253]

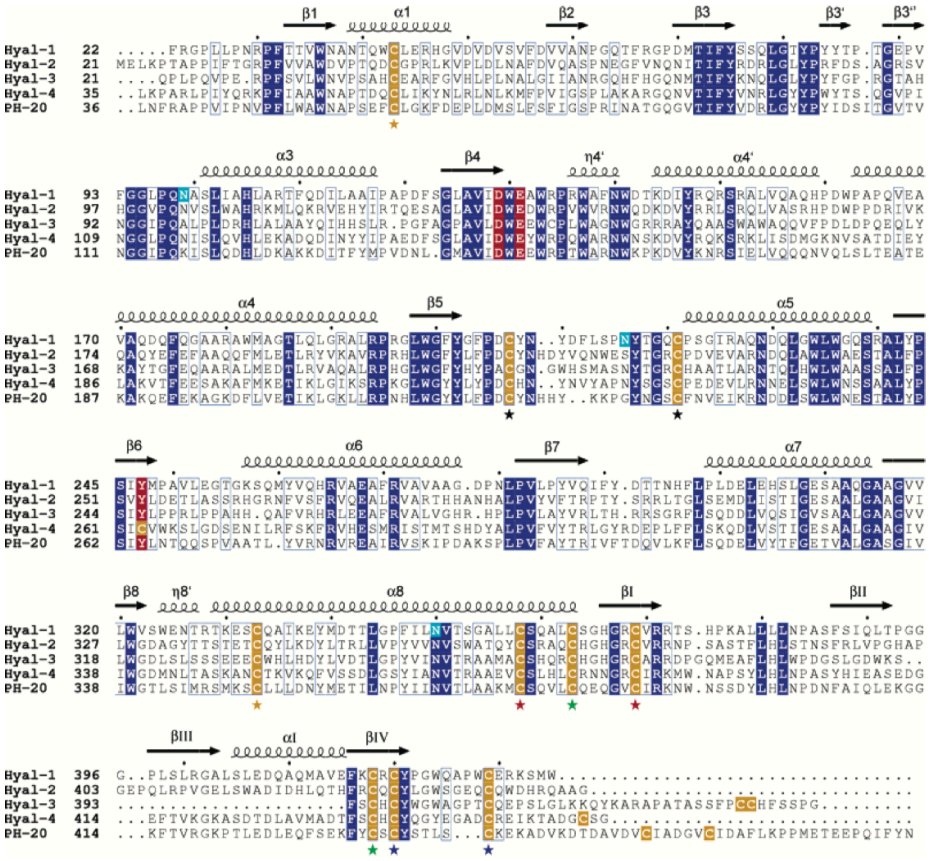


FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative replacements are blocked in blue. Pairs of cysteine residues that form disulfide bonds are indicated by stars with matching colors. Secondary structure units are labeled as in Figure 2B.

Third, Chao reported the presence of "a novel, EGF-like domain" in the C-terminal region of human hyaluronidases that was "closely associated" with the

253 EX1006, 6916; EX1003, ¶ 83; EX1004, ¶ 92.

catalytic domain (discussed above, § V.A.2.c), and identified a characteristic pattern for the Hyal-EGF domain in PH20 at positions 337-409.[254]

3. A Skilled Artisan Would Have Identified L317Q as Being in a Non-Essential Region of $PH20_{1-447}$ in 2011

To implement the '429 Patent's suggestion to produce modified $PH20_{1-447}$ polypeptides with single amino acid substitutions in non-essential regions that retain hyaluronidase activity, the skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011.[255] The person would have done that using conventional sequence alignment tools in conjunction with the information in the '429 Patent and in Chao, as well as information publicly known in 2011.[256]

The multiple sequence alignment identifies the non-essential regions in PH20—they are the sequences between essential residues containing positions at which variations occur at a frequency above ~5% (illustrated in Chao for five homologous human hyaluronidase sequences below).[257]

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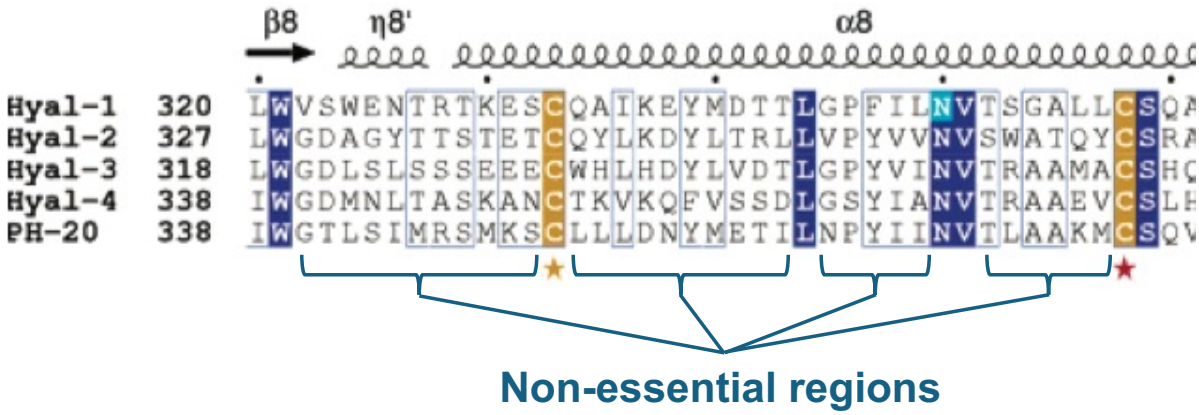
254 EX1006, 6912; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84-85.

255 EX1003, ¶¶ 208-210; EX1004, ¶¶ 22, 25-30, Appendix D-3.

256 EX1003, ¶¶ 20-21, 209-211; EX1004, ¶¶ 22-24; EX1017, 224-26.

257 EX1004, ¶¶ 31-32, Appendix D-2; EX1003, ¶ 211; EX1006, 6916.

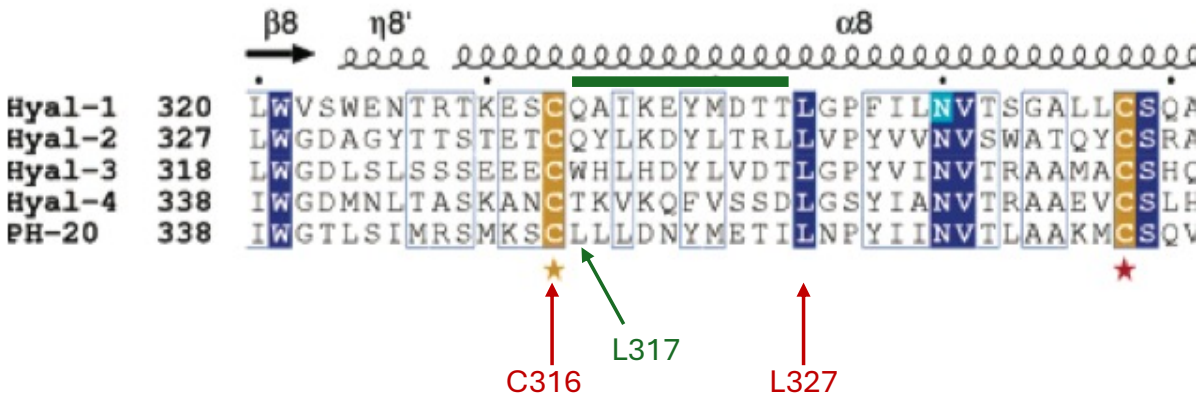


Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps. He first identified 88 homologous hyaluronidase protein sequences that had been published by December 29, 2011.[258] Dr. Park then prepared a multiple-sequence alignment of the 88 homologous proteins, similar to what Chao did with the five human hyaluronidases, and from that alignment identified essential (Appendix D-3) and non-essential (Appendix D-2) residues.[259]

[258] EX1004, ¶¶ 27, 145-148; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

[259] EX1004, ¶¶ 28-32, 149-150, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

Position 317 is within a non-essential region of $PH20_{1-447}$, which is shown not only by Dr. Park's analysis, but also by Chao's Figure 3; both report the same bounding essential residues (*i.e.*, C316 and L327) (below).[260]



Thus, following the guidance and information in the '429 Patent and Chao, and assessing information publicly available in December 2011 using conventional sequence analysis tools, a skilled artisan would have readily identified position 317 as a position in a non-essential region $PH20_{1-447}$.[261]

4. A Skilled Artisan Would Have Found Glutamine to Be Suggested as an Obvious Single Amino Acid Substitution at Position 317 of $PH20_{1-447}$

The multiple-sequence alignment reveals a second powerful insight: it identifies ***which*** amino acids have been tolerated at specific positions in the amino

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260 EX1003, ¶ 213; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.

261 EX1003, ¶ 216; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

acid sequence of homologous, stable and active naturally occurring hyaluronidase enzymes.[262] This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms those variations in the sequences of a protein that do not yield stable and active forms of the protein.[263] Thus, a skilled artisan can readily compile a list of the specific amino acids that have been tolerated at positions within non-essential regions of PH20 using a multiple-sequence alignment of homologous hyaluronidase enzymes.[264]

Dr. Park did this; he used the alignment he produced of the 88 hyaluronidase proteins known by December 2011 to identify and calculate the frequency of

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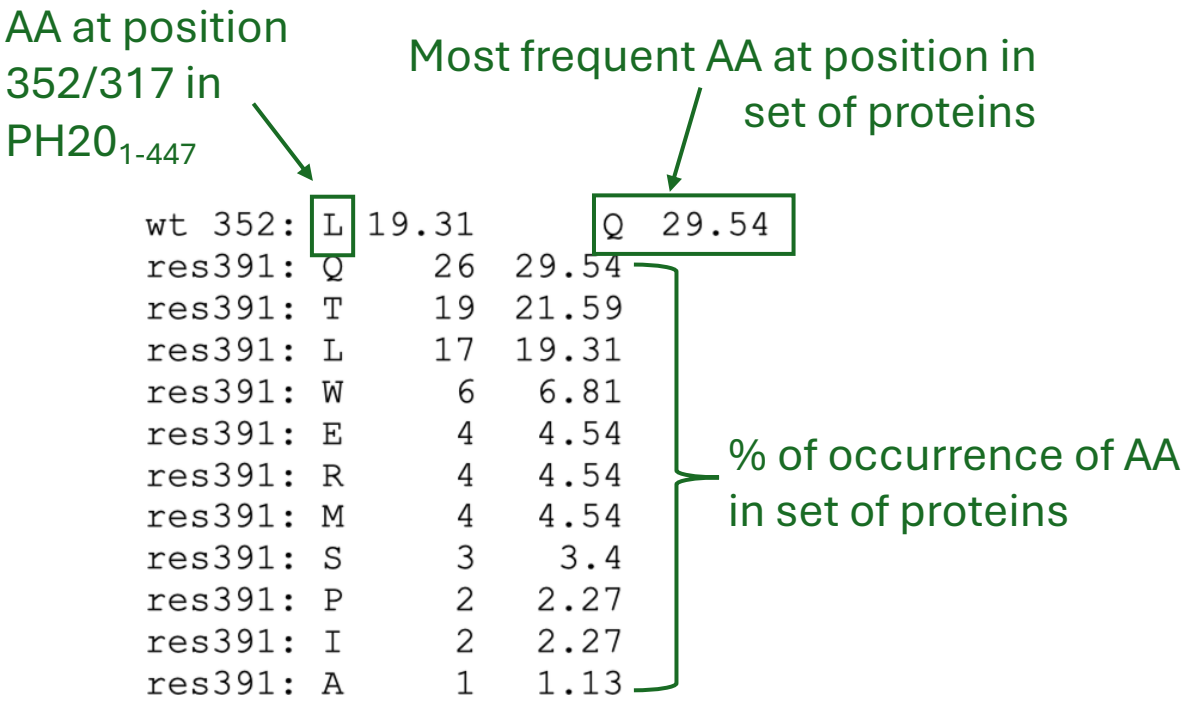
[262] EX1003, ¶¶ 20, 49, 210, 214, 216; EX1004, ¶¶ 21-22.

[263] EX1003, ¶¶ 20, 210; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 ("Evolution provides a tremendously useful model for protein design. … By considering the common features of the sequences of these proteins, it is possible to deduce the key elements that determine protein structure and function—even in absence of any explicit structural information."); EX1014, 351.

[264] EX1003, ¶¶ 214, 216; EX1004, ¶¶ 21-22.

occurrence of each different amino acid that occurs at positions corresponding to each position in the non-essential regions of $PH20_{1-447}$.[265]

The amino acids appearing at positions corresponding to 317 in PH20 in the 88 naturally occurring hyaluronidase enzymes known by 2011 are shown below.[266] The wild-type residue at position 317 in PH20 is leucine (L), which occurs in ~19% of the proteins (including PH20). The most prevalent amino acid found at position 317 in this set of homologous sequences is glutamine (Q) (~30%), which is present in 26 different hyaluronidase proteins.



[265] EX1004, ¶¶ 30-32, 41-43, Appendix D-1.

[266] EX1003, ¶ 214; EX1004, ¶¶ 43, 106, 112, Appendix D-1.

Several amino acids other than leucine occur with significant frequency at positions corresponding to 317 in PH20 in these known, homologous hyaluronidase enzymes.[267] A skilled artisan would have believed those amino acids would be the obvious choices to assess as single amino acid substitution for position 317 of $PH20_{1-447}$.[268]

More directly, a skilled artisan would have had specific reasons to substitute glutamine (Q) for leucine (L)at position 317 as a single amino acid substitution in a non-essential region of $PH20_{1-447}$.

First, glutamine is the most prevalent amino acid found at positions corresponding to 317 in PH20: it occurs in nearly 30% of the 88 homologous hyaluronidase enzymes known by 2011 (26 different naturally occurring hyaluronidase enzymes) and in 2 of the 5 human hyaluronidases.[269] The high frequency with which glutamine occurs in this position makes it an obvious candidate for being substituted at position 317 of PH20, as glutamine is tolerated at that position in many naturally occurring hyaluronidase enzymes.[270]

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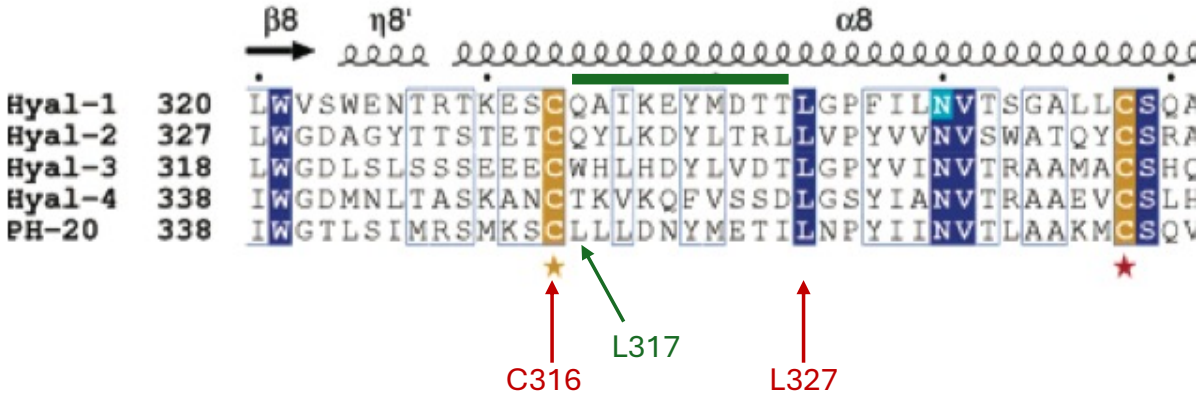
267 EX1004, ¶ 106.

268 EX1003, ¶¶ 210, 214, 216-17; EX1004, ¶¶ 41-42, 106.

269 EX1004, ¶¶ 43, 106, 112; EX1003, ¶ 214.

270 EX1003, ¶¶ 214, 216-17; EX1004, ¶ 112.

Second, glutamine was known to have a high helix propensity, meaning it is favored in sequences that form α-helix secondary structures.[271] Chao identified the "α8" helix sequence as one such α-helix forming sequence in PH20, and position 317 of PH20 is in the middle of that α8 helix sequence (below).[272] Given its high propensity for supporting α-helix secondary structures, a skilled artisan would have viewed glutamine as a logical (and thus obvious) substitution for leucine at position 317, given its location within the α8 helix sequence in $PH20_{1-447}$.[273]



For all of the reasons above, a skilled person would have found it obvious change the leucine (L) at position 317 to glutamine (Q) in $PH20_{1-447}$.[274]

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271 EX1050, 422-24, Table 2; EX1003, ¶ 215; EX1004, ¶¶ 69-70, 115.

272 EX1006, 6916, Figure 3; EX1003, ¶ 192, 215; EX1004, ¶¶ 32, 108.

273 EX1003, ¶ 215; EX1004, ¶¶ 32, 108, 115, 119.

274 EX1003, ¶¶ 213-216.

5. A Skilled Artisan Would Have Reasonably Expected the L317Q Substitution in $PH20_{1-447}$ to Yield an Enzymatically Active PH20 Protein

a) Patent Owner Cannot Contradict Its Past Representations to the PTO

Replacing the leucine (L) at position 317 with glutamine (Q) yields a $PH20_{1-447}$ with a single amino acid substitution in a non-essential region of the polypeptide.[275] In its '429 Patent, Patentee stated:

> Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.[276]

Patentee also secured claims in the '429 patent to modified $PH20_{1-447}$ proteins with at least one substitution (*e.g.*, claim 1), even though it provided no examples of any PH20 proteins with any substitutions. Patentee, thus, made and relied on its affirmative statements that a skilled artisan would have expected ***any*** single amino acid substitution in ***any*** non-essential position of $PH20_{1-447}$ to not substantially affect the biological activity of the enzyme, and particularly ones listed in Table 1. Patentee should not be permitted to change its position now and contend that a skilled artisan would not have reasonably expected that making the

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[275] *See* § VI.B.3; EX1003, ¶¶ 213-14; EX1004, ¶ 32.

[276] EX1005, 16:17-20.

L317Q substitution in $PH20_{1-447}$ would yield an enzyme with substantially the same activity as unmodified $PH20_{1-447}$.

b) Skilled Artisans Would Reasonably Expect L317Q to be Tolerated in $PH20_{1-447}$

Independently, a skilled artisan would have reasonably expected that the L317Q substitution in $PH20_{1-447}$ would not substantially alter the biological activity (hyaluronidase activity) of $PH20_{1-447}$.

Both experts noted that many naturally occurring homologous hyaluronidase proteins contain glutamine at the position corresponding to position 317 in PH20.[277] The high frequency of occurrence of glutamine at positions equivalent to 317 in naturally-occurring hyaluronidases, including in 2 of 4 human homologs of PH20 (Chao), along with glutamine's high helix propensity, would have led a skilled artisan to reasonably expect the L317Q substitution would be tolerated in $PH20_{1-447}$.[278]

c) A PH20 Structural Model Confirms that $PH20_{1-447}$ Would Tolerate Glutamine at 317

Dr. Park further assessed whether a variety of single amino acid substitutions in $PH20_{1-447}$ would be tolerated, such as the L317Q substitution, using

[277] EX1003, ¶ 214; EX1004, ¶ 112.

[278] EX1003, ¶¶ 217-218; EX1006, 6916.

a PH20 protein structural model generated by SWISS-MODEL from Chao's HYAL1 structure as the template, as would have been done in 2011 by a skilled artisan.[279]

Dr. Park explains that the PH20 model he used was reliable in the region of position 317 of PH20 based on QMEAN values,[280] and would be very similar to a PH20 model generated by SWISS-MODEL in 2011 (*e.g.*, because it used 165 conserved positions in the backbone of the two proteins).[281]

Dr. Park also devised a consistent, objective methodology for assessing substitutions using the $PH20_{1-447}$ model.[282] Factors he considered included, *inter alia*, the number of neighboring residues at position 317 (*i.e.*, those within 5 Å), the various types of possible interactions between neighbors (*e.g.*, hydrophobic,

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279 EX1004, ¶¶ 39-40, 151-52; EX1003, ¶¶ 221, 223; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

280 EX1004, ¶¶ 153-55 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

281 EX1004, ¶¶ 156-57, 161; EX1038, 3382-4; EX1017, 229-230; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

282 EX1004, ¶¶ 102-103; *see generally id.* at § IV.C (description of Dr. Park's methodology).

charged, van der Walls, steric, etc.), and solvent accessibility.[283] Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*, hydrophobic-hydrophilic, effects on secondary structures, size related issues such as steric clashes or creation/filling of "holes" in the structure).[284]

Dr. Park assessed the environment of position 317 visually by comparing the wild-type with the version incorporating substituted amino acids at position 317 using functionality within the viewer (PyMol) and as a modeled sequence generated from the $PH20_{1-447}$ sequence incorporating the single substitution in SWISS-MODEL.[285] Again, these technologies were available in 2011.[286] He used his methodology to assess numerous substitutions representing diverse interactions, and confirmed that it provided a consistent, objective and unbiased evaluation of substitutions throughout the protein.[287]

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283 EX1004, ¶¶ 44-47, 53-60, 65-85, Appendix D-5; EX1035, 1408, Table 2; EX1043, 2, Table 1.

284 EX1004, ¶¶ 62-63, 85.

285 EX1004, ¶¶ 61, 107, 111, 167-68; EX1003, ¶¶ 22, 49, 221, 223.

286 EX1004, ¶¶ 151, 156-57, 165, 167-69; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4.

287 EX1004, ¶¶ 102-103.

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed (below).[288]

Score	***Expected Impact***	***Expected Toleration***
1	Significantly Destabilized	Likely Not Tolerated
2	Neutral or Minor Impacts	Tolerated
3	Improved Stability	Tolerated

Dr. Park assigned a score of 2 for the L317Q substitution in $PH20_{1-447}$, indicating that the substitution would not be expected to significantly impact stability.[289] He observed that in the wild-type environment, position 317 is a significantly solvent exposed position on helix 8 of PH20, that many different types of amino acids occur at this position in homologous proteins (*e.g.*, polar and non-polar, varying sizes), and that the neighboring residues at position 317 are both hydrophilic and hydrophobic, collectively indicating that many different amino acids would likely be tolerated at this position.[290]

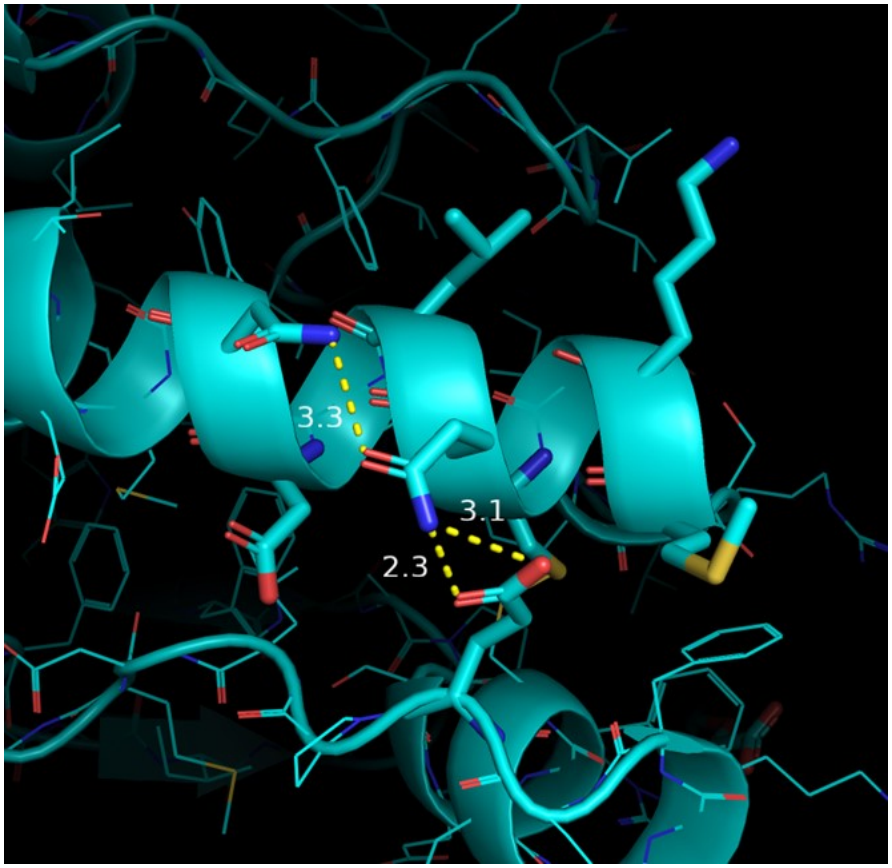
Dr. Park also identified several reasons why glutamine would be tolerated at position 317 of PH20, including that it is a hydrophilic residue and has a high helix

[288] EX1004, ¶¶ 85-87.

[289] EX1004, ¶ 119, Appendix C.

[290] EX1004, ¶¶ 108-110.

propensity, making it compatible with the environment at position 317.[291] He also observed that glutamine in position 317 may form hydrogen bonds with nearby residues (E31, N321), which could enhance stability around this position (below), which could offset reduced hydrophobic contacts from replacing the wild-type leucine residue.[292] Overall, Dr. Park found that the L317Q substitution would have a neutral or slightly positive effect on the stability of the protein.[293]



[291] EX1004, ¶¶ 113, 115.

[292] EX1004, ¶ 116.

[293] EX1004, ¶ 119.

Dr. Park's visualization-based assessment is a technique that was prevalent in 2011.[294] Similarly, his technique of assessing interactions between neighbors and assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications (*e.g.*, Dr. Moult's group used this technique to assess substitutions caused by single-nucleotide polymorphisms, and classified the net effects on a 3-point scale).[295]

Dr. Hecht reviewed Dr. Park's analysis and conclusions, and agreed with both.[296] Through his own assessment, he observed that glutamine would be likely tolerated at position 317. For example, he explained that glutamine's hydrophilic character would be compatible with the high solvent accessibility of position 317,

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294 EX1017, 228 ("… a structural biologist's intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this."); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 22, 49, 221, 223.

295 EX1004, ¶¶ 48-52; EX1031, 439, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 223.

296 EX1003, ¶ 225.

and that its high helix propensity would be favorable to the α-helix structure that includes position 317.[297]

The common disclosure defines an "active mutant" as a modified PH20 polypeptide with as little as 40% of the activity of unmodified $PH20_{1-447}$.[298] Drs. Hecht and Park each independently concluded that the L317Q substitution would have been tolerated by $PH20_{1-447}$, meaning it would exhibit comparable hyaluronidase activity to unmodified $PH20_{1-447}$ (*i.e.*, activity well above 40%).[299] A skilled artisan considering the L317Q substitution in $PH20_{1-447}$ thus would have reasonably expected that it would exhibit at least 40% of the activity of unmodified $PH20_{1-447}$.[300]

Based on the '429 Patent, Chao, and information available in 2011, the L317Q $PH20_{1-447}$ mutant polypeptide would have been obvious to a skilled artisan in 2011. And because claims 1-4 each encompass the single-replacement modified L317Q $PH20_{1-447}$ polypeptide, each claim is unpatentable.

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297 EX1003, ¶¶ 226-227.

298 EX1001, 75:33-38; *also id.* at 79:15-19.

299 EX1003, ¶¶ 225-27, 229; EX1004, ¶¶ 112-119.

300 EX1003, ¶ 229.

C. Dependent Claims 7-13 Are Obvious

None of the dependent claims define subject matter that is independently patentable from claims 1-4. For the reasons below, each would have been obvious to a skilled artisan.

1. Claim 7

Claim 7 requires the modified PH20 polypeptide to be "a soluble PH20 polypeptide."

The '429 Patent identifies that $PH20_{1-447}$ exists as a soluble form of the PH20 protein because it omits the C-terminal residues above position 448 (483) containing the GPI anchor sequence.[301] A skilled artisan would believe that changing leucine to glutamine at position 317 would not change the solubility of the $PH20_{1-447}$ as it would not meaningfully alter the structure of the protein.[302]

2. Claims 8-10

Claims 8-10 require the modified PH20 polypeptide to "comprise[] one or more post-translational modifications" including glycosylation (claims 8-9) and be a "glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues" (10).

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301 EX1005, 3:57-62; 87:52-88:24.

302 EX1003, ¶¶ 196, 218.

The ’429 Patent teaches (i) that human PH20 must be glycosylated to exhibit activity, and (ii) expression of $PH20_{1-447}$ in mammalian (CHO) host cells that yield active forms of $PH20_{1-447}$.[303] It further teaches that “N- and O-linked glycans are attached to polypeptides through asparagine-N-acetyl-D-glucosamine … linkages,” and claims PH20 polypeptides (including $PH20_{1-447}$) having asparagine-linked sugar moieties.[304] Frost reports that the recombinant production of $PH20_{1-447}$ in CHO cells “resulted in a 447 amino acid 61 kDA glycoprotein with a properly processed amino terminus and 6 N-linked glycosylation sites.”[305]

Based on the ’429 Patent and knowledge in the art, a skilled artisan would have found it obvious to produce L317Q $PH20_{1-447}$ in a CHO cell, and that doing so causes six N-linked glycosylation sites to be glycosylated.[306]

3. Claims 11-13

Claim 11 specifies a pharmaceutical composition comprising any modified PH20 polypeptide in the genus of claim 1. Claims 12 and 13 concern methods of

303 EX1005, 95:13-30; 40:41-51, 89:53-91:67; 88:5-9.

304 EX1005, 3:27-35, claims 1, 6.

305 EX1013, 432.

306 EX1003, ¶¶ 197-98, 200-201.

administering the compositions of claim 11 (claim 12) and doing so subcutaneously (13).

The ’429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*, $PH20_{1-447}$), alone or in combination with other therapeutic agents including antibodies, small molecule drugs, and agents used in treating cancer.[307] It similarly describes and claims methods of administering them subcutaneously via formulations that combine an enzymatically active hyaluronidase protein with the other therapeutic agent, which together enable “spreading” of the therapeutic agent after injection.[308]

A skilled artisan would have appreciated that a single-replacement $PH20_{1-447}$ polypeptide with comparable hyaluronidase activity to $PH20_{1-447}$ (such as the L317Q mutant) would be equivalently useful in the therapeutic compositions, methods of administration, and methods of treatment described in the ’429 Patent

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307 EX1005, 8:60-9:4, 54:52-55:35, 56:28-57:21, 55:61-56:9, 56:66-57:21, 73:4-74:29, claims 14, 29, 33.

308 EX1005, 8:25-38, 56:28-56, 57:22-36, 58:59-59:12, 63:40-64:4, 76:18-77:37, claim 27.

for $PH20_{1-447}$.[309] Indeed, in the '429 Patent, Patentee secured claims encompassing pharmaceutical compositions containing certain modified PH20 polypeptides and chemotherapeutic agents despite the absence of any exemplification.[310] Claims 11-13 also impose no restrictions on the makeup of the pharmaceutical composition. A skilled artisan would have found such agents and methods of administration and treatment to have been obvious from the '429 Patent for the above reasons.[311]

D. There Is No Nexus Between the Claims and Any Evidence of Putative Secondary Indicia

Well-established law holds that evidence of secondary indicia cannot support non-obviousness if it does not have nexus to the claims. A key question in a nexus analysis is whether such evidence is commensurate with the scope of the claims. The answer here is a definitive no.

Patentee is likely to dispute that the L317Q $PH20_{1-447}$ is obvious because it is reported to have unexpectedly high hyaluronidase activity as a single substitution mutant. Demonstrating that result for one mutant out of the ~10^{49}-10^{66} modified PH20 polypeptides encompassed by the claims, however, utterly fails to establish a nexus between that evidence and the claims. As explained above, the single-

309 EX1003, ¶¶ 199, 203, 217-18, 229.

310 EX1005, claims 29, 30, 50.

311 EX1003, ¶¶ 199, 203.

substitution L317Q $PH20_{1-447}$ is not representative of the numerous, structurally different proteins that are encompassed by the claims, particularly those that would be expected to be inactive. *See* § V.A.2. No evidence or explanation is provided in the common disclosure that resolves this confusion.

Petitioner submits that if Patentee advances evidence or arguments concerning a nexus, consideration of that issue should be deferred until after institution. Petitioner otherwise reserves its right to contest such evidence.

VII. The Board Should Not Exercise Its Discretion Under § 324(a) or § 325(d)

No litigation involving the ’262 Patent is pending, making discretionary denial unwarranted under the factors in *Apple Inc. v. Fintiv, Inc.,* IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020).

The examination record also does not warrant the Board exercising its discretion to not institute. As explained in § IV.C, while an obviousness rejection was imposed, it was based on different prior art than that used in the grounds, and Patentee overcome the rejection by a claim amendment.[312] The present obviousness grounds also are based in part on Chao (EX1006), which was not cited or considered during examination, employ a different rationale than that used

[312] EX1002, 530-31, 532-33.

during examination,[313] and are supported by evidence not available to the Examiner (*e.g.*, expert testimony of Drs. Hecht and Park).

Also, while an indefiniteness rejection was imposed due to a typographical error,[314] the Examiner erred by not rejecting the claims for lack of written description and non-enablement. *See* §§ V.A and IV.B.

There is thus no proper basis for the Board to exercise its discretion to not institute trial.

VIII. CONCLUSION

For the foregoing reasons, the challenged claims are unpatentable.

Dated: December 10, 2024

Respectfully Submitted,

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313 *Supra* § IV.C; EX1002, 489-91.

314 EX1002, 489, 509, 530.

EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,152,262
1002	File History of U.S. Patent No. 12,152,262
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Brandon & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '262 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," Methods in Enzymology, 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," Protein Eng'g & Design, Ch. 10, 223-237 (2010)
1018	Chica et al., "Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design," Curr. Opin. Biotechnol., (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," Reprod., 127:325-334 (2004)
1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," Am. J. Reprod. Immunol., (3):174-82 (2002)
1021	Baba et al., "Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg," J. Biol. Chem., 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," Biol Reprod., 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 56(5):1133-41 (1997)
1024	Rosengren et al., "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects," BioDrugs, 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	[Reserved]
1028	[Reserved]
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," FEBS Letters, 3:545-548 (1993)

No.	Exhibit Description
1030	Sills, "Retraction," Science, 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," J. Mol. Biol., 353:459-473 (2005)
1032	Wang & Moult, "SNPs, Protein Structure, and Disease," Hum. Mutation, 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," Structure, 8:1025-1035 (2000)
1034	"Negative Results," Nature: Editorials, 453:258 (2008)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," Protein Sci., 12:1406-1417 (2003)
1036	Hayden, "Chemistry: Designer Debacle," Nature, 453:275-278 (2008)
1037	Benkert et al., "Toward the Estimation of the Absolute Quality of Individual Protein Structure Models," Bioinformatics, 27:343-350 (2010)
1038	Schwede et al., "SWISS-MODEL: An Automated Protein Homology-Modeling Server," Nucleic Acids Rsch., 31:3381-3385 (2003)
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007).
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," PNAS, 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," PNAS, 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," Nature Comm., 14 (2023)
1043	Sievers et al., "Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega," Molecular Sys. Biology, 7.1 (2011)
1044	Mihel, "PSAIA – Protein Structure and Interaction Analyzer," BMC Structural Biology, 8:21 (2008)

No.	Exhibit Description
1045	Redline Comparison of the ’731 and ’262 Specifications
1046	Beasley & Hecht, “Protein Design: The Choice of *de Novo* Sequences,” J. Biological Chemistry, 272:2031-2034 (1997)
1047	Xiong et al., “Periodicity of Polar and Nonpolar Amino Acids is the Major Determinant of Secondary Structure in Self-Assembling Oligomeric Peptides,” PNAS, 92: 6349-6353 (1995)
1048	Hayden, “Key Protein-Design Papers Challenged,” Nature, 461:859 (2009)
1049	KEGG, *DRUG: Hyaluronidase (human recombinant)*, available at: https://www.genome.jp/entry/D06604
1050	Pace & Scholtz, “A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins,” Biophysical J. 75:422-427 (1998)
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
1057	Ph20_pre2011.aln-clustal_num
1058	Ph20_pre2011 Alignment html
1059	Leisola & Turunen, “Protein Engineering: Opportunities and Challenges,” Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	Hecht et al., “De Novo Proteins from Designed Combinatorial Libraries,” Protein Sci., 13:1711-1723 (2004)
1061	Rosengren et al., “Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration,” AAPS J., 17:1144-1156 (2015)
1062	[Reserved]
1063	[Reserved]

No.	Exhibit Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with L317Q Mutation
1071	Swiss Model Printout of PH20 Model with L317R Mutation
1072	Swiss Model Printout of PH20 Model with L317M Mutation
1073	Swiss Model Printout of PH20 Model with L317S Mutation
1074	Swiss Model Printout of PH20 Model with L317I Mutation

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,605 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

Dated: December 10, 2024

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 10th day of December, 2024, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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Paper No. 1

Filed: November 26, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00004
U.S. Patent No. 12,018,298

PETITION FOR POST GRANT REVIEW

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I. Introduction

Petitioner Merck Sharp & Dohme LLC ("Merck") requests post grant review of claims 1-22 of U.S. Patent No. 12,018,298 ("'298 Patent").

The '298 Patent claims are unpatentable for three independent reasons.

The first two are linked to the extreme breadth of the claims, which encompass between 10^{49} and 10^{66} different mutated forms of an enzymatically active human hyaluronidase protein called PH20. That breadth results from the unconstrained language in claims 1 to 4, which each define a genus of PH20 polypeptides that ***requires one*** amino acid substitution at position 313, but then ***permits*** (via sequence identity language) up to 16, 20, 21, or 22 additional substitutions at ***any*** of between 430 and 465 positions of PH20, and to ***any*** of 19 other amino acids. The scale of this genus is unfathomable. The weight of a set of one molecule of each polypeptide in one genus exceeds that of the Earth, and practicing the claims' full scope using the patent's iterative methodology would require many lifetimes of "making-and-testing" by a skilled artisan.

These immensely broad claims, measured against the common disclosure of the '298 Patent and its ultimate parent '731 Application,[1] utterly fail to satisfy the written description and enablement requirements of § 112(a). That deficiency

[1] 13/694,731 ('731 Application) (EX1026).

renders every claim of the ’298 Patent unpatentable. It also precludes those claims from a valid § 120 benefit claim to the ’731 Application, the only non-provisional application filed before March 16, 2013, thus making the ’298 Patent PGR eligible.

First, regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by enzymatically active, multiply-modified PH20 polypeptides within each claimed genus. The disclosed examples also are plainly not representative of that gargantuan and structurally diverse genus: every disclosed mutant has only ***one*** amino acid substitution in ***one*** PH20 sequence (1-447), while the claims encompass myriad structural variants of PH20, resulting from incorporation of innumerable, ***undescribed*** combinations of 5, 10, 15 or 20+ substitutions anywhere in the PH20 sequence. The claims even capture mutated PH20 polypeptides the disclosure says to exclude, such as those which rendered PH20 inactive with a single mutation, or truncated forms the disclosure and prior art describe as inactive. The disclosure is nothing more than a research plan, lacking any blaze marks, while the claims improperly seek to capture any enzymatically active, multiply-mutated PH20 polypeptides that might be discovered now or in the future.

Second, regarding enablement, the common disclosure has equally fatal problems. It neither describes nor characterizes ***any*** modified PH20 with 2 or more substitutions that is enzymatically active, much less affirmatively guides the

selection of ***which*** combinations of substitutions yield such proteins. And the only disclosed process for making PH20 mutants with multiple substitutions is a prophetic, "iterative" research plan that explicitly requires the same type of 2011-era "trial-and-error" experiments the Supreme Court recently found incapable of enabling a large genus of diverse polypeptides.[2] Indeed, to practice the full scope of the claims would require scientists to repeat this "make-and-test" methodology innumerable times until they had made and tested between 10^{49} and 10^{66} unique proteins. That is far more than undue experimentation—it is impossible.

Finally, claims 1-4 and 7-22 are also independently unpatentable because each captures a ***single*** PH20 mutant with a ***single*** amino acid substitution at position 313 (from methionine (M) to lysine (K)) ("M313K $PH20_{1-447}$"). But Patentee's earlier '429 Patent (EX1005)[3] makes that mutant obvious, along with methods of making and using it. In particular, it directs artisans to make single amino acid substitutions in non-essential regions of the $PH20_{1-447}$ sequence, and then explicitly claimed them. Implementing that guidance in 2011 would have led the skilled artisan to an intervening publication—Chao (EX1006)—that is ignored in Patentee's 2011-era disclosure and was never cited to the Office during

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[2] *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023).

[3] U.S. Patent No. 7,767,429.

examination. The collective guidance of the '429 Patent and Chao (i) readily identifies position 313 as being in a non-essential region of PH20, and (ii) motivates the skilled artisan to substitute lysine at that position—the most commonly occurring amino acid in that position in known, homologous hyaluronidases. And the skilled artisan would have reasonably expected M313K $PH20_{1-447}$ to retain the enzymatic activity of its parent because that is precisely what the '429 Patent says ("Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity").[4] A skilled artisan, in 2011, would have considered M313K $PH20_{1-447}$ to be ***one*** obvious PH20 mutant in the claimed genus.

The evidence demonstrates the '298 Patent claims are unpatentable. The Board should institute post grant review.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the '298 Patent's issuance. Petitioner certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '298 Patent.

[4] EX1005, 16:17-22.

The ’298 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

A patent is PGR eligible if it issued from an application filed after March 16, 2013 “if the patent contains … at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought.” *See Inguran, LLC v. Premium Genetics (UK) Ltd.*, Case PGR2015-00017, Paper 8 at 16-17 (P.T.A.B. Dec. 22, 2015); *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17 at 8 (P.T.A.B. Jan. 29, 2016); *Collegium Pharm., Inc. v. Purdue Pharma L.P.*, 2021 WL 6340198, at *14-18 (P.T.A.B. Nov. 19, 2021) (same) *aff’d Purdue Pharma L.P. v. Collegium Pharm., Inc.*, 86 F.4th 1338, 1346 (Fed. Cir. 2023); *Intex Recreation Corp. v. Team Worldwide Corp.*, 2020 WL 2071543, at *26 (P.T.A.B. Apr. 29, 2020) (same).

The ’298 Patent claims benefit under 35 U.S.C. § 120 and/or § 121 to seventeen earlier-filed non-provisional applications. Only one—U.S. Application No. 13/694,731 (the ’731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to and incorporates by reference the disclosures of two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011),

as well as WO 01/3087 ("WO087"). The '731 application alters several passages of the provisional disclosures, adds new examples and tested mutants and makes other changes.[5]

The disclosure of the '731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '298 Patent (§§ V.A, V.B). The same is true for the '298 Patent, whose disclosure is substantively identical to the '731 Application.[6] The '298 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the '731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

Merck Sharp & Dohme LLC is the real party-in-interest for this Petition.

2. Related Proceedings

PGR2025-00003 is a related proceeding.

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[5] EX1026, 153:15-163:26, 324-34, 19:25-26, 28; EX1051; EX1052.

[6] References to the "common disclosure" are to the shared disclosure of the '298 Patent and the '731 Application (EX1026). Citations are to the '298 Patent, and EX1015 correlates citations to the '731 Application.

3. Counsel and Service Information

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III. Grounds

The grounds advanced in this Petition are:

(a) Claims 1-22 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.

(b) Claims 1-22 are unpatentable under 35 U.S.C. § 112 as not being enabled.

(c) Claims 1-4 and 7-22 are unpatentable as obvious under 35 U.S.C. § 103 based on the ’429 Patent (EX1005), Chao (EX1006) and knowledge held by a person of ordinary skill in the art.

Petitioner’s grounds are supported by the evidence submitted with this Petition, including testimony from Dr. Michael Hecht (EX1003) and Dr. Sheldon Park (EX1004).

In this Petition, “PH20” refers to the human PH20 hyaluronidase protein. The full-length form of the protein (SEQ ID NO: 6) includes a 35 amino acid

signal sequence, while mature forms of PH20 omit those 35 residues and have positions that differ from SEQ ID NO: 6 by 35 residues.[7] The annotation "$PH20_{1-n}$" is used to refer to a sequence of 1-n residues in PH20 (*e.g.*, $PH20_{1-447}$ is SEQ ID NO: 3), and "AxxxB" is used to identify the position of a substitution ("M313K").

IV. Background on the '298 Patent

A. Field of the Patent

The '298 Patent concerns the human PH20 hyaluronidase enzyme, and structurally altered forms of that protein that retain enzymatic activity.[8]

1. Protein Structures

Proteins are comprised of sequences of amino acids. The activity of a protein, however, derives from its unique, three-dimensional shape—its structure.[9] That, in turn, is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary structures and structural motifs, which are packed into compact domains that define the protein's overall structure (tertiary structure).[10]

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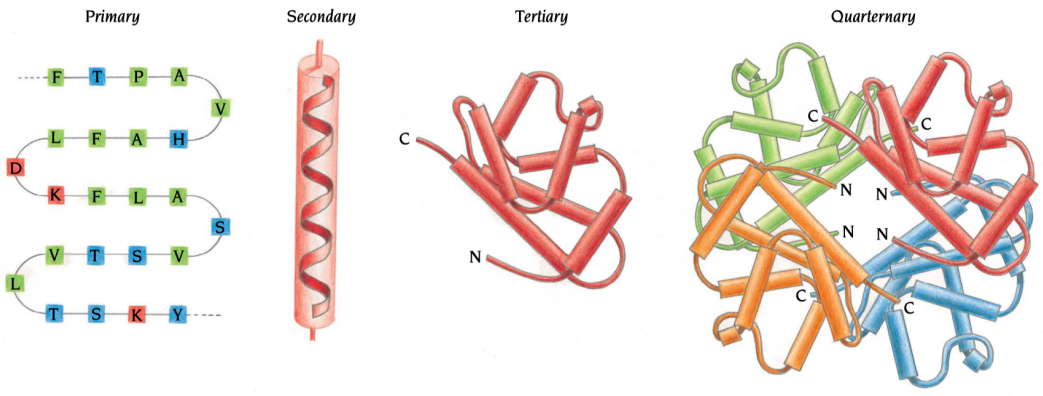
[7] EX1003, ¶ 15.

[8] EX1001, 2:50-54.

[9] EX1003, ¶ 36.

[10] EX1014, 3-4, 24-32, Figure 1.1; EX1039, 136-37 (Figure 3-11); EX1003, ¶¶ 36-40.



For example, secondary structures, such as α-helices or β-strands, are formed and stabilized by different but characteristic patterns of amino acids (below).[11]

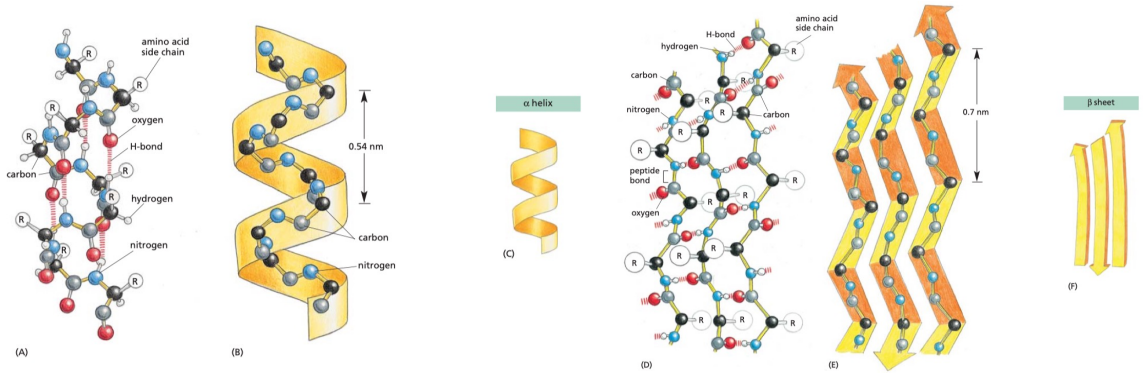


Figure 3–7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT>
(A, B, and C) The α helix. The N–H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N–H groups point up in this diagram and that all of the C=O groups point down (toward the C-terminus); this gives a polarity to the helix, with the C-terminus having a partial negative and the N-terminus a partial positive charge. (D, E, and F) The β sheet. In this example, adjacent peptide chains run in opposite (antiparallel) directions. Hydrogen-bonding between peptide bonds in different strands holds the individual polypeptide chains (strands) together in a β sheet, and the amino acid side chains in each strand alternately project above and below the plane of the sheet. (A) and (D) show all the atoms in the polypeptide backbone, but the amino acid side chains are truncated and denoted by R. In contrast, (B) and (E) show the backbone atoms only, while (C) and (F) display the shorthand symbols that are used to represent the α helix and the β sheet in ribbon drawings of proteins (see Panel 3–2B).

[11] EX1039, 134; EX1014, 14-22, Figures 2.2, 2.5, Table 2.1; EX1047, 2031-32; EX1003, ¶¶ 40-43.

Intervening sequences between those characteristic sequences are important too; they direct and facilitate positioning and arrangement of the various secondary structures into structural motifs and the protein's tertiary structure.[12]

Changes to a protein's amino acid sequence can affect the folding, formation and stability of these various structures that define the protein's overall shape. For example, changing even a single residue known to be critical to the protein's structure or activity can render a protein inactive.[13]

In 2011, making many concurrent changes to a protein's sequence was highly unpredictable, which can cause myriad effects on the protein's structure, especially when they are in or affect the same region(s) of the protein.[14] For example, introducing numerous changes in a protein's sequence can disrupt the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of secondary structures, while changes to intervening sequences can disrupt folding and positioning of the secondary structures and

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12 EX1003, ¶¶ 44-46; EX1014, 21-22.

13 EX1003, ¶¶ 54, 150; EX1004, ¶¶ 20, 25.

14 EX1003, ¶ 158.

structural motifs into the protein's tertiary structure.[15] Multiple changes introduced at different regions of the amino acid sequence also can cause unfavorable spatial interactions that destabilize or impair folding.[16] In 2011, predicting the possible effects of the myriad interactions that may be disrupted by multiple concurrent substitutions was beyond the capacity of skilled artisans and the computational tools available at that time.[17]

2. Hyaluronidase Enzymes

PH20 is one of five structurally similar hyaluronidase proteins in humans and is homologous—evolutionarily related to—hyaluronidases in many species.[18] It breaks down hyaluronan ("HA") by selectively hydrolyzing glycosidic linkages in it.[19] The human PH20 protein exists naturally as a GPI anchored protein, but a

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15 EX1003, ¶¶ 55-56, 142; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

16 EX1003, ¶¶ 57-59.

17 EX1003, ¶¶ 50, 158, 190, 224; EX1004, ¶¶ 166-68.

18 EX1007, 10:18-30; EX1006, 6911, 6916 (Figure 3); EX1003, ¶¶ 33, 77.

19 EX1003, ¶ 77; EX1008, 819.

truncation at the C-terminal region of PH20 yields a soluble, neutral active form of the enzyme.[20]

Various groups before 2011 had identified various essential residues in PH20. These included several in the catalytic site of the protein, a conserved structure shared by many species.[21] Mutating certain residues in or near the catalytic site can abolish the enzymatic activity of hyaluronidases.[22] Conserved cysteine residues that stabilize the protein structure are another example,[23] as are conserved asparagine residues involved in glycosylation, which was known to be important for PH20 activity.[24]

In 2007, Chao reported an experimentally determined structure of the human HYAL1 hyaluronidase, and used an alignment of the five human hyaluronidases to

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20 EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 89, 196; EX1029, 546, Figure 1.

21 EX1006, 6914-16, Figure 3; EX1007, 35:28-36:10; EX1011, 810-14; EX1008, 824-25; EX1009, 6912-17.

22 EX1011, 812-14; EX1010, 9435-39, Table 1.

23 EX1006, 6914-16, Figure 3; EX1011, 810-11; EX1005, 88:21-22.

24 EX1005, 7:9-27; EX1007, 36:12-20; EX1010, 9433, 9435-40.

illustrate shared secondary structures and conserved residues in these proteins.[25] Among its findings was that human hyaluronidases contain a unique structure—the Hyal-EGF domain.[26] Using its sequence analysis, an earlier structure of bee venom hyaluronidase and a computer model of the protein structures, it analyzed the catalytic site of HYAL1 and identified residues in it that interact with HA.[27]

3. Engineering Proteins in 2011

In 2011, skilled artisans used two general approaches to engineer changes into proteins.[28] "Rational design" employed computational tools like sequence alignments and protein structure models to study the protein sequence and structure. Using known sequence-structure relationships for the protein, artisans then selected where and what changes to introduce into the protein sequence.[29] For example, sequences of naturally occurring proteins homologous to the one being studied would be compiled and compared in a "multiple-sequence alignment"

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25 EX1006, 6914-18.

26 EX1006, 6916-18; EX1010, 9439-40; EX1003, ¶¶ 84-86; EX1004, ¶¶ 97-99.

27 EX1006, 6912-13, 6916-18, Figures 2C, 4A; EX1033, 1028-29, 1035; EX1010, 9434, 9436, Figure 1.

28 EX1003, ¶ 47.

29 EX1016, 181-82; EX1017, 223, 236; EX1003, ¶¶ 48-50.

("MSA").[30] The MSA identifies conserved ("essential") positions with no or little amino acid variation and positions where different amino acids occur ("non-essential" residues).[31] A structural model of the protein using its sequence but based on a suitable known structure of a homologous protein was then used to visualize locations within the protein's structure to identify and assess interactions of the amino acids at that position.[32] In 2011, skilled artisans could assess, with varying amounts of effort, the effects of changing one or a few amino acids, but predicting the effects of many concurrent changes was not possible, given the escalating complexity of predicting numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.[33]

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30 EX1017, 224-27; EX1016, 181-86 (Figure 1); EX1003, ¶¶ 48-50; EX1004, ¶¶ 22-23, 29.

31 EX1003, ¶¶ 209-210; EX1004, ¶¶ 21-22, 25, 30-31; EX1016, 181-84; EX1017, 224-25; EX1014, 351.

32 EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶¶ 37, *also id.* 33-36; EX1003, ¶¶ 219, 221.

33 EX1003, ¶¶ 50, 158; EX1004, ¶¶ 167-168.

"Directed evolution" techniques arose due to the limits of rational design.[34] It uses "trial-and-error" experiments to find mutants with randomly distributed changes that exhibit desired properties, but requires creation and screening of large libraries of mutants, each with one amino acid randomly changed at one position in its sequence.[35] Importantly, until a desired mutant is made, tested and found, whether it exists and its sequence are unknown.[36] Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale of experimentation this approach requires.[37] The '298 Patent embodies this approach.[38]

B. Person of Ordinary Skill in the Art

The '298 Patent claims priority to two provisional applications filed in 2011. § II.A. Its claims, however, are not entitled to those dates or the filing date of the '731 Application (December 28, 2012), as they are not supported as § 112(a) requires by those earlier-filed applications. *See* §§ V.A, V.B. The prior art of the

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[34] EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

[35] EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

[36] EX1003, ¶ 184.

[37] EX1003, ¶¶ 52-53.

[38] EX1003, ¶¶ 138, 173, 186.

grounds, however, was published by December 2011, and the obviousness grounds thus use that date to assess the knowledge and perspectives of the skilled artisan.

In 2011, a person of ordinary skill in the art would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).[39]

C. Prosecution History

In the sole Office action issued during examination of the ’298 Patent, three rejections were imposed, none of which is relevant to the grounds. First, a dependent claim to soluble PH20 polypeptides was rejected for failing to further limit an independent claim.[40] Patentee mooted the rejection by cancelling the

[39] EX1003, ¶ 13.

[40] EX1002, 436-39.

claim.[41] Second, claims to pharmaceutical compositions were rejected as indefinite,[42] which Patentee overcame by amendments specifying the composition is "formulated in the same composition or … in a separate composition."[43] Third, non-statutory double patenting rejections were imposed over U.S. Patent 10,865,400 in view of US 20100143457 A1 ("Wei"),[44] which Patentee overcame with terminal disclaimers.[45]

The claims were allowed without further rejections.[46]

D. The Challenged Claims

The terms used in the claims are either expressly defined in the specification of the common disclosure or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition. A clear understanding of the ***breadth*** of the claims, however, is important to assessing the grounds. Specifically, each claim captures a massive

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41 EX1002, 555-57.

42 EX1002, 440.

43 EX1002, 531, 555-57.

44 EX1002, 440-48.

45 EX1002, 557.

46 EX1002, 551-60.

genus of structurally distinct mutant PH20 polypeptides that is neither adequately described in nor enabled by the common disclosure of the '731 Application and the '298 Patent.

1. The Claims Encompass a Staggering Number of Modified PH20 Polypeptides

Claim 1 defines an incredibly broad and diverse genus of "modified PH20 polypeptides," which are defined as "a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement … in its sequence of amino acids compared to a reference unmodified PH20 polypeptide."[47]

Claim 1 specifies the modified PH20 polypeptides in its genus:

- ***must*** contain ***one*** amino acid replacement at position 313 (*i.e.*, from M to any of K, A, H, L, P, R, or Y); and
- ***may*** contain ***additional*** modifications, provided each polypeptide retains ***at least 95% sequence identity*** to one of the 35 unmodified sequences (SEQ ID NOs: 3 or 32-66), ranging in length from 430 (SEQ ID NO: 32) to 465 residues (SEQ ID NO: 35).

Claim 2 requires position 313 to be to K. Claims 3 and 4 restrict claim 1's genus by specifying each polypeptide has: (i) 96% sequence identity to SEQ ID NO: 35 ($PH20_{1-433}$), or (ii) 95% sequence identity to SEQ ID NO: 32 ($PH20_{1-430}$).

[47] EX1001, 47:15-20.

The specification explains that "sequence identity can be determined by standard alignment programs …"[48] It then provides an example, explaining a polypeptide that is "'at least 90% identical' refers to percent identities from 90 to 100% relative to the reference polypeptide" where "no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides."[49] Per claim 1, "terminal gaps" are "treated as non-identical" residues.

The specification further explains that "differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence" and that "[d]ifferences are defined as [] amino acid substitutions, insertions or deletions."[50] Also, "amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids" (*e.g.*, 10-18 of the 19 alternative amino acids).[51] Consistent with these passages, no language in the claims restricts ***where*** substitutions can occur

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48 EX1001, 58:45-47.

49 EX1001, 59:13-22.

50 EX1001, 59:23-31; *see also id.* at 3:36-37; 46:20-24, 33-35.

51 EX1001, 135:52-59; *see also id.* at 141:2-4.

within the sequence of the modified PH20 polypeptides, or ***which*** of 19 other amino acids can be substituted at those positions.

The parameters in claims 1-4 cause them to encompass an immense number of distinct polypeptides, each with a unique amino acid sequence.[52] In particular, it permits the modified PH20 polypeptides to contain between 17 and 23 total changes but requires only one change: a substitution at position 313, with either 7 alternatives (claim 1) or one alternative ("K") (claims 2, 3, 4). Based on Dr. Park's calculations, each claim's parameters capture an immense number of distinct polypeptides (below).[53]

Claim	**SEQ ID** / % Identity	PH20 length	# Changes	Pos. 313 Choices	Add'l Changes	# Distinct Polypeptides
1	**3** / 95%	447	22	7	21	2.35×10^{63}
	66 / 95%	465	23	7	22	2.63×10^{66}
2	**3** / 95%	447	22	1	21	3.76×10^{62}
3	**35** / 96%	433	17	7	16	1.53×10^{49}
4	**32** / 95%	430	21	7	20	4.40×10^{59}

2. The Claims Encompass One Particular PH20 Mutant: M313K $PH20_{1-447}$

The structural parameters used in claims 1-4 also cause them to capture a ***single*** modified PH20 polypeptide with ***one*** replacement. That is the $PH20_{1-447}$

[52] EX1003, ¶¶ 120, 122.

[53] EX1004, ¶¶ 174-177, Appendix F.

protein (SEQ ID NO: 3), in which the methionine (M) at position 313 is changed to lysine (K) ("M313K PH20$_{1-447}$"). This single-replacement M313K PH20$_{1-447}$ mutant is: (i) 99.7% identical to SEQ ID NO: 3 (1 change / 447 residues), (ii) 96.5% identical to SEQ ID NO: 35 (15 changes / 433 residues), and (iii) 95.9% identical to SEQ ID NO: 32 (18 changes / 430 residues).[54]

3. The Claims Are Restricted to One of Two Alternative Embodiments in the Patents: "Active Mutants"

When a specification discloses alternative embodiments, the language used in the claims may cause them to be limited to only one.[55] That is the case here: the specification describes two mutually exclusive categories of "modified PH20 polypeptides" (*i.e.*, "active mutants" vs. "inactive mutants") but the claims are limited to one of them: "active mutants."

According to the specification:

- "***Active mutants***" are modified PH20 polypeptides that "exhibit at least 40% of the hyaluronidase activity of the corresponding PH20

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54 EX1003, ¶ 136.

55 *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008).

polypeptide not containing the amino acid modification (e.g., amino acid replacement)."[56]

- "***Inactive mutants***" are modified PH20 polypeptides that "generally exhibit less than 20% … of the hyaluronidase activity of a wildtype or reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7."[57]

It then classifies mutants into tables of "active" and "inactive" mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).[58]

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[56] EX1001, 74:11-16; *see also id.* at 77:61-65 ("active mutants" "can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide …").

[57] EX1001, 117:44-53. *See also id*. at 255:26-30 (mutants exhibiting <20% hyaluronidase activity "were rescreened to confirm that the dead mutants are inactive" in Table 10).

[58] EX1001, 79:25-80:26 (Table 3 "Active Mutants"); 232:40-42 (Table 9 "Active Mutants"); 118:44-67 (Table 5 "Inactive Mutants"), 255:53-56 ("reconfirmed inactive mutants are set forth in Table 10."); EX1003 ¶¶ 98, 104-105, 107, 126-28.

The common disclosure reports no examples of a modified PH20 with two replacements.[59] More directly, it reports no examples of a $PH20_{1-447}$ that was made and tested and which incorporated: (i) a mutation listed in Tables 3 and 9 ("active mutants"), and (ii) a mutation listed in Tables 5 and 10 that yielded an "inactive mutant" (Tables 5 and 10).

The specification also portrays "active" and "inactive" mutants as having distinct utilities requiring mutually exclusive properties.

- "Active mutants" are portrayed as being therapeutically useful ***because they possess hyaluronidase activity***. For example, the specification explains that ***due to*** having hyaluronidase activity, "the modified PH20 polypeptides can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents."[60]
- "Inactive mutants" are portrayed as being therapeutically useful ***because they lack hyaluronidase activity***. Their only identified utility

[59] *E.g.*, EX1003, ¶¶ 141, 172.

[60] EX1001, 179:53-59; *see also id*. at 2:67-3:3, 71:64-72:11, 179:53-193:14.

> is "as antigens in contraception vaccines," which is implausible (*see* § V.C) but ostensibly requires them to lack activity.[61]

Notably, the specification does not portray "active mutants" as having contraceptive utility even though they may differ by only one amino acid from an inactive mutant, and instead proposes using them ***in combination*** with contraceptive agents.[62]

The claim language reinforces that they are limited to the "active mutant" embodiment.

First, every claim requires each modified PH20 polypeptide in its scope to have one of seven replacements at position 313 that yielded an "active mutant" as a single-replacement $PH20_{1\text{-}447}$ polypeptide (*i.e.*, M313K, M313A, M313H, M313L,

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[61] EX1001, 71:24-26; *see also id.* at 193:15-16, 74:20-22, 193:14-33 (for "contraception" "the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.").

[62] EX1001, 156:1-14 ("co-formulations containing a modified PH20 polypeptide and a therapeutic agent that is … a contraceptive agent …"); EX1003, ¶ 113; EX1060, 1711.

M313P, M313R, or M313Y). These mutants are listed in Table 3 and reported as having >40% activity in Table 9.[63]

Second, claims 5 and 6 restrict the genus of active mutants in claim 1 (*i.e.*, those with at least 40% activity) to active mutant modified PH20 polypeptides that have at least 100% or 120% of the activity of unmodified PH20, respectively.

Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one modification," but can also "have up to 150 changes, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity.***"[64] This aligns with the specification's prophetic methodology for discovering PH20 polypeptides with multiple changes, which starts with one substitution that yields an "active mutant," randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity.[65] This tracks the claims, which require one substitution and permit others.

Patentee may contend the claims should be read as encompassing both alternative embodiments (*i.e.*, "active" and "inactive" mutants). Reading the claims in that manner is incorrect. It also exacerbates the § 112 problems, as every

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63 EX1001, 85 (Table 3), 235 (Table 9).

64 EX1001, 47:15-30; *see also id*. at 46:38-42, 74:36-39, 75:32-39.

65 EX1001, 140:36-47; *see also id*. at 41:17-24.

claim still necessarily includes (and thus must describe and enable) the full sub-genus of "active mutants" defined by claims 5 and 6.[66]

V. All Challenged Claims Are Unpatentable Under § 112 and None Are Entitled to Benefit to Any Pre-March 13, 2013 Application

Claims 1-22 are unpatentable because each lacks written description in and was not enabled by the common disclosure of the '298 Patent and the '731 Application in 2011.

As explained in § IV.D.1, the claim language defines enormous genera: between 10^{49} and 10^{66} distinct polypeptides. To illustrate the real-world absurdity of those claims, consider what practicing claim 1's full scope requires. Excluding single-replacement $PH20_{1-447}$ mutants, and only focusing on mutants with multiple substitutions in $PH20_{1-447}$, a skilled artisan would need to make-and-test ~10^{63} mutants having between 2 and 22 substitutions. Producing only one molecule of each—each must be made and tested to see if it is active or inactive—would require consuming an aggregate mass (~1.37 x 10^{27} kg) that exceeds the mass of the Earth (~6 x 10^{24} kg).[67] Testing every polypeptide within the claims' scope in search of "active mutants" is impossible—literally.

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66 EX1003, ¶ 135.

67 EX1003, ¶¶ 123, 189; *see also, e.g.*, EX1039, 136-37 (cell theoretically can make 10^{390} forms of a polypeptide with 300 amino acids).

In support of that broad scope, the '298 Patent and the '731 Application provide only a meager disclosure: ***singly***-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones. The patent provides ***nothing*** that demonstrates possession of the vast remainder of multiply-modified polypeptides in the claims' scope or which enables a skilled artisan to practice that full-range of structurally diverse mutant polypeptides without undue experimentation.

A. Claims 1 to 4 Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.[68] "To fulfill the written description requirement, a patent owner 'must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent."[69] If the claims define a genus, the written description must "show that one has truly invented a genus …,"

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[68] *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

[69] *Idenix Pharm., LLC v. Gilead Scis., Inc.,* 941 F.3d 1149, 1163 (Fed. Cir. 2019).

"[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus."[70]

"[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus."[71] "One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent … [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus."[72]

A disclosure that fails to "provide sufficient blaze marks to direct a POSA to the specific subset" of a genus with the claimed function or characteristic does not satisfy § 112(a).[73] And "merely drawing a fence around the outer limits of a

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70 *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1300 (Fed. Cir. 2014).

71 *Idenix*, 941 F.3d at 1164.

72 *AbbVie*, 759 F.3d at 1299-1300.

73 *Idenix*, 941 F.3d at 1164.

purported genus" is insufficient.[74] Instead, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."[75]

Three cases applying these principles are particularly relevant here. First, in *AbbVie*, the Federal Circuit affirmed a finding that the disclosure of 300 examples of IL-12 antibodies was not representative of the functionally defined genus of antibodies, explaining:

> Although the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.[76]

The court also criticized what that patentee cited to support the non-exemplified portion of the claim scope, portraying it as "only a research plan, leaving it to others to explore the unknown contours of the claimed genus" and being a "trial and error approach."[77] Both criticisms are particularly relevant to the present

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74 *Ariad*, 598 F.3d at 1350-54.

75 *Ariad*, 598 F.3d at 1349.

76 *AbbVie*, 59 F.3d at 1300-1301.

77 *Id.*

disclosure, which exemplifies only single-substitution PH20 mutants and otherwise provides only a research plan, yet claims all multiply-modified PH20 mutants with 2 to 22 additional substitutions.

Second, in *Idenix,* the court considered claims to methods of treatment using a broad genera of compounds defined by formulas analogous to the challenged claims here: "eighteen position-by-position formulas describing 'principal embodiments' of compounds that may treat HCV," each with "more than a dozen options" at each position (totaling "more than 7,000 unique configurations").[78] The court criticized the specification's failure to indicate which of the thousands of compounds would be effective, and found that "providing lists or examples of supposedly effective nucleosides," without "explain[ing] what makes them effective, or why" deprives a skilled artisan "of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result" because they "fail to provide sufficient blaze marks to direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV." Again, that logic resonates strongly with the deficiencies of the common disclosure here.

[78] *Idenix*, 941 F.3d at 1158-64.

Finally, the Board in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found*., PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) considered sequence homology claims. Specifically, the claims used "90% sequence homology" language to capture "a broad genus of amino acid sequence homologues" but (like here) imposed no restrictions on where particular amino acids replacements could be made, thus causing the claim "to cover, at minimum, thousands of amino acid sequences."[79] The Board found the specification's failure to "explain what, if any, structural features exist (e.g., remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification" fatal, and that the homology limitation "serves to merely draw a fence around the outer limits of a purported genus [which] is not an adequate substitute for describing a variety of materials constituting the genus" for purposes of section 112(a).[80]

The deficiencies of claims 1 to 4 dwarf those identified in these three cases. The present claims define much larger, much less predictable and much more diverse genera of modified PH20 polypeptides, and the common disclosure is far

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79 *Boehringer*, at 16. The claims at issue encompassed both compositions containing the protein, and methods of using the protein. *Id.* at 6.

80 *Id.* at 35-36.

more limited. As explained below, the common disclosure neither discloses a representative number of species within each immense claimed genus, nor identifies sufficient structural features common to the members of each claimed genus. It thus falls woefully short of demonstrating possession of the genera of modified PH20 polypeptides defined by claims 1 to 4 of the '298 Patent.

1. The Claims Define a Massive and Diverse Genus of Enzymatically Active PH20 Polypeptides

The incredible breadth of the genus defined by claims 1 to 4 has been described above. *See* § IV.D.1. The genera of each claim are also incredibly diverse in their structures and functions.

Most significantly, the use of a ***maximum*** sequence identity boundary with no condition or restrictions other than one required substitution means the claims capture mutants with 2 substitutions, 3 substitutions and so on up to a number set by the boundary (*i.e.*, 17 for claim 3, 21 for claim 4, and 23 for claim 1). The substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, and arranged in any manner. They capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with 22

substitutions mixing polar, charged, aliphatic and aromatic residues together in any manner.[81]

There is more. Each claim also encompasses substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 35 alternative sequences ranging from 430 to 465 residues. They also encompass varying lengths due to the sequence identity language, as the claims encompass both "additions" and "deletions." To illustrate, if one makes the M313K substitution and makes 5 more substitutions to SEQ ID NO: 32, claim 4's parameters would capture that mutant as well as one that also deletes 14 more residues from the C terminus. But, as explained in § V.A.2.c, removing that many residues from the C-terminus of the wild-type PH20 makes it inactive, and nothing in the common disclosure shows (much less suggests) that adding the M313K mutant (plus up to 5 other substitutions) will restore activity to that C-terminally truncated mutant. Patentee nonetheless claims all these polypeptides too.[82]

2. The Claims Capture Modified PH20 Polypeptides the Common Disclosure Says to Avoid or Not Make

The claims' unconstrained sequence identity language causes them to capture three categories of PH20 mutants a skilled artisan would understand the

[81] EX1003, ¶¶ 119-20.

[82] EX1003, ¶¶ 164-67.

disclosure to be saying to avoid or not make. Each category raises unique questions relative to the remainder of the genus, and are thus "sub-genera" of PH20 mutants that are not representative of other "sub-genera" within the claimed genera. But instead of providing guidance that navigates this confusing landscape, the patent simply instructs the skilled artisan "to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein."[83] In other words, it directs the skilled artisan to blindly make-and-test all such candidate mutants using trial-and-error experimentation.[84]

a) Multiply-Modified PH20 Mutants to Not Make

The common disclosure affirmatively addresses only six, specific modified PH20 polypeptides with more than one identified (*i.e.*, position and amino acid) substitution, but that guidance is to ***not make those polypeptides***:

> [W]here the modified PH20 polypeptide contains only two amino acid replacements, the amino acid replacements are ***not*** P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A or N333A/N358A. In a further example, where the modified PH20 polypeptide

[83] EX1001, 76:65-77:3.

[84] EX1003, ¶ 193.

> contains only three amino acid replacements, the amino acid replacements are ***not*** N47A/N131A/N219A.[85]

Notably, the common disclosure provides ***no explanation*** why these particular combinations of replacements should be avoided, and provides no data testing their activity or other characteristics.[86] Further, none (P13A, N47A, N131A, N219A, N333A, N358A, L464W) are included in Tables 5 and 10, which are single-replacements that rendered $PH20_{1-447}$ an "inactive mutant." Indeed, one (N219A) yielded a $PH20_{1-447}$ with increased activity (129%) as a single replacement.[87] Instead, the skilled artisan is left to discover this information themself. And nothing in the claim language excludes these combinations.

b) Substitutions to Avoid in Active Mutants

The common disclosure indicates that active mutant modified PH20 polypeptides should not incorporate specific amino acid substitutions that rendered $PH20_{1-447}$ inactive, stating:

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85 EX1001, 76:10-22 (emphases added).

86 EX1003, ¶¶ 146-47.

87 EX1001, 245 (Table 9).

> ***To retain hyaluronidase activity***, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.[88]

It identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10 that are made at other positions.[89]

Notably, the common disclosure does not condition this observation on single-replacement $PH20_{1-447}$ mutants, and as such, it clearly conveys to a skilled artisan that modified PH20 polypeptides with "hyaluronidase activity" do not include, and should not be modified to contain, the amino acid replacements listed in Tables 5 and 10, and that is true regardless of the length or the number of additional amino acid substitutions in the PH20 polypeptide.[90]

The skilled artisan also would find no description of, much less guidance concerning, ***which*** of these identified substitutions that did render $PH20_{1-447}$ inactive should be incorporated into enzymatically active multiply-modified PH20

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88 EX1001, 78:45-47 (emphases added).

89 EX1001, 78:47-79:20 ("For example, generally modifications are not made at a position corresponding to position …").

90 EX1003, ¶¶ 148-51.

polypeptides (and what other substitutions should be combined with them).[91] Instead, by stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that the ***claimed*** enzymatically active multiply-modified PH20 polypeptides do not contain them. And again, nothing in the claim language operates to exclude such combinations.

c) PH20 with Significant C-terminal Truncations Can Lose Activity

The common disclosure describes no multiply-modified "active mutant" PH20 polypeptides having fewer than 447 residues (or even an unmodified PH20 with such lengths) and provides no guidance about making enzymatically active mutants based on PH20 sequences ending before position 447 and containing 2 or more substitutions.[92]

This omission creates significant uncertainty, because both the common disclosure and the prior art report that PH20 polypeptides with fewer than 442 residues significantly ***reduce or eliminate*** hyaluronidase activity in unmodified PH20 polypeptides. For example, Patentee's prior art '429 Patent reported that

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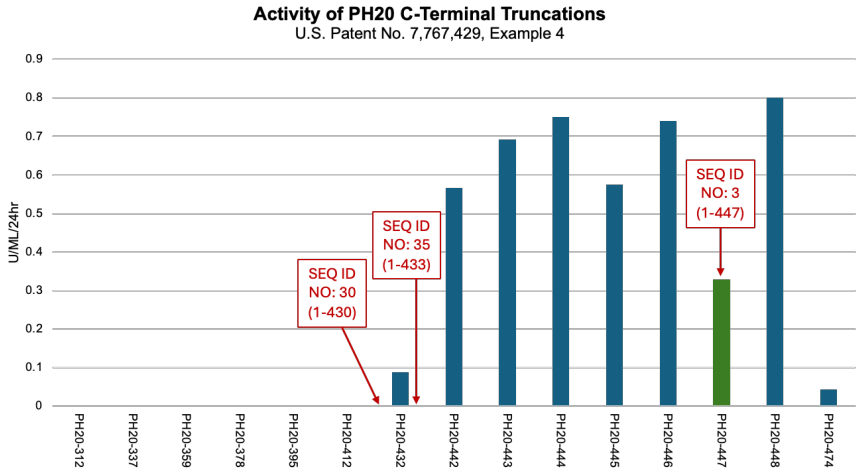
91 EX1003, ¶¶ 151, 161-62, 169.

92 EX1003, ¶¶ 97, 167-69.

PH20 with fewer than 432 residues lacked hyaluronidase activity, while those with between 432 and 448 residues had widely varying activities (below):[93]



Position (w/leader)	Mutant	U/ML/24hr	Normalized to PH20(1-447)
347	PH20-312	0	0.00
372	PH20-337	0	0.00
394	PH20-359	0	0.00
413	PH20-378	0	0.00
430	PH20-395	0	0.00
447	PH20-412	0	0.00
467	**PH20-432**	**0.089**	**27.05**
477	PH20-442	0.567	172.34
478	PH20-443	0.692	210.33
479	PH20-444	0.75	227.96
480	PH20-445	0.575	174.77
481	PH20-446	0.74	224.92
482	**PH20-447**	**0.329**	**100.00**
483	PH20-448	0.8	243.16
509	PH20-474	0.044	13.37

The ’429 Patent also reported that “a very narrow range spanning … [437-447] … defined the minimally active domain” of human PH20, and elsewhere observed this “minimally active” human PH20 domain contains at least residues 1-

93 EX1005, 87:52-88:24 (activity of $PH20_{1-442}$ “decreased to approximately 10% of that found” in the $PH20_{1-447}$ polypeptides); EX1013, Figure 2, 430-32 (“soluble hyaluronidase activity could be recovered in the conditioned medium from deletion mutants terminating after amino acids 477 – 483 [442-448]” but “[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA”).

429.[94] The common disclosure concurs, stating that PH20 polypeptides must extend to at least position 429 to exhibit hyaluronidase activity:

> A mature PH20 polypeptide … containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue ***464*** of SEQ ID NO: 6 [position ***429*** without signal] … ***is the minimal sequence required for hyaluronidase activity***.[95]

Before 2011, the C-terminal region of PH20 was known to contain a unique domain linked to a characteristic pattern of sequences first reported in 2007 by Chao ("Hyal-EGF").[96] In PH20, the Hyal-EGF domain is found at positions 337-409, and it was shown in 2009 to be essential to hyaluronidase activity.[97]

The C-terminus of PH20 is illustrated below, showing (i) the location where SEQ ID NOS: **3** (447), **32** (430) and **35** (433) terminate (arrows), (ii) the "minimally active domain" at 437-447 in green, and (iii) residues below position

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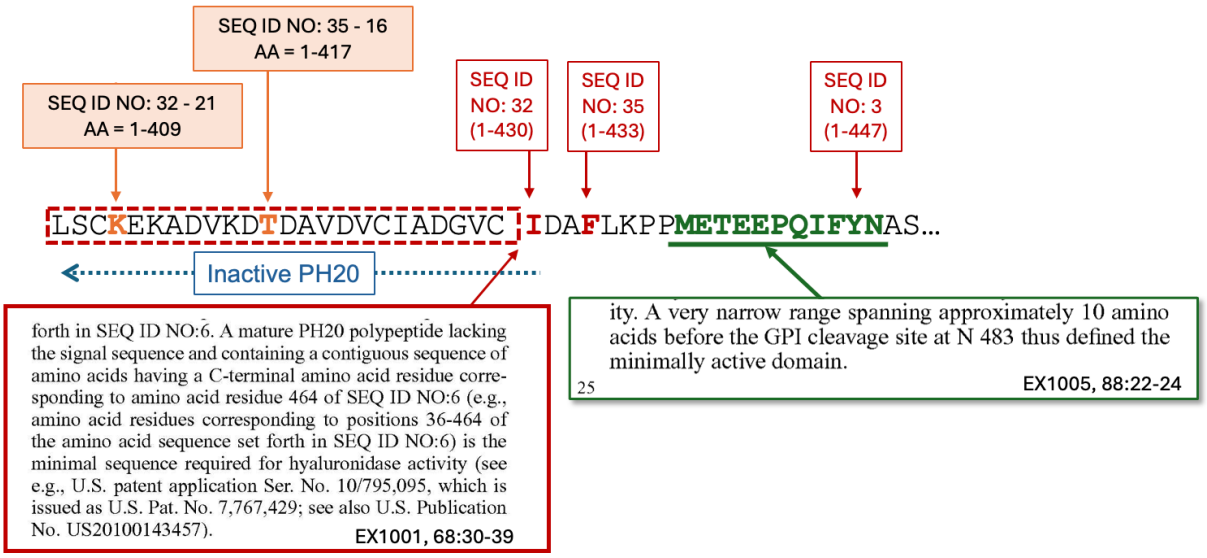
94 EX1005, 6:65-7:7 ("… sHASEGP from amino acids 36 to Cys 464 [429] … comprise the minimally active human sHASEGP hyaluronidase domain").

95 EX1001, 68:30-39 (emphases added).

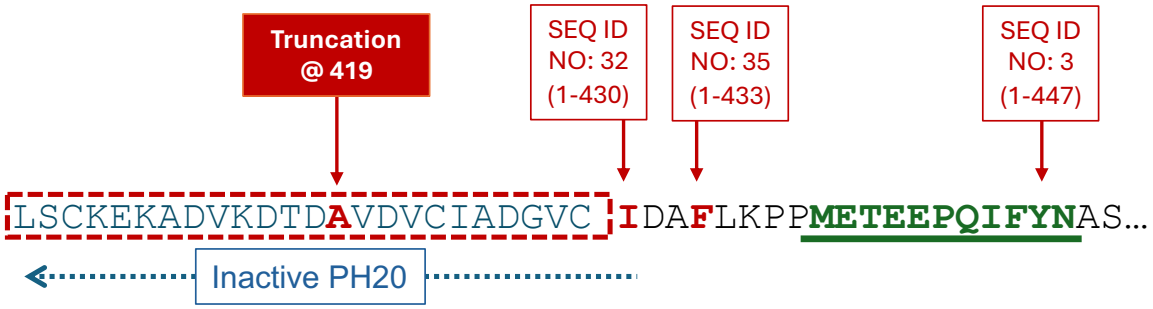
96 EX1006, 6912; EX1003, ¶¶ 84-96, 153.

97 EX1004, ¶ 97-99; EX1010, 9438; EX1003, ¶¶ 95-97.

429 in a red dashed box.[98] Positions that truncate 21 and 16 residues from SEQ ID NOS: 32 and 35 are also shown ending before position 429.



From the prior art and the common disclosure, a skilled artisan in 2011 would believe that C-terminal deletions yielding PH20 polypeptides that terminate before position 430 would be inactive, yet the claims expressly encompass truncations down to and beyond position 419.[99]



98 EX1003, ¶ 153.

99 EX1003, ¶¶ 160-65.

The common disclosure provides no examples of (and provides zero guidance concerning producing) such C-terminally truncated PH20 mutants that are enzymatically active, thus ignoring the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433.[100] And, again, the mathematical boundaries of the claims explicitly encompass modified PH20 polypeptides with these types of truncations.

3. Empirical Results from Testing Single-Replacement Modified PH20 Does Not Identify Multiply-Modified Enzymatically Active PH20 Polypeptides

The empirical results reported in the common disclosure provide no predictive guidance to a skilled artisan about the structural features of the vast genus of amino acid changes that can be combined to form multiply-modified PH20 polypeptides.

a) Data Showing Most Single-Replacements Were Inactive or Less Active Is Not Probative of Multiple-Replacement Mutants

The common disclosure reports results from testing a portion of a randomly generated library of ~6,743 single-replacement $PH20_{1-447}$ polypeptides.[101] It explains the mutants were generated with a mutagenesis process which substituted

[100] EX1003, ¶¶ 143, 159, 167-69.

[101] EX1001, 133:5-16, 200:31-33, 200:11-17.

one of ~15 amino acids into random positions in $PH20_{1-447}$ "such that each member contained a single amino acid change."[102] Approximately 5,917 were tested, while ~846 were uncharacterized.[103] More than half (~57%) of these mutants were classified as "inactive mutants," while ~30% (1335) were reported to have less activity than unmodified $PH20_{1-447}$ (20%-100%).[104] In other words, ~87% of the single-replacement $PH20_{1-447}$ polypeptides had ***less*** activity than unmodified $PH20_{1-447}$.[105]

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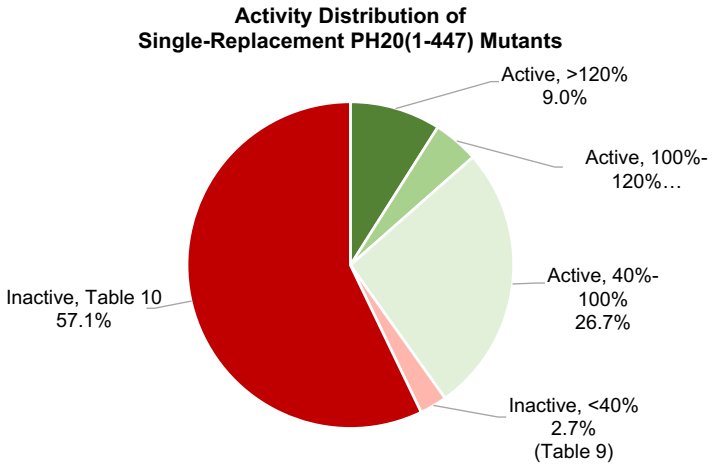
[102] EX1001, 200:11-20.

[103] EX1003, ¶¶ 103-104. The common disclosure reports inconsistent numbers of tested mutants and classifications of mutants. Table 3 lists 2,516 single-replacement $PH20_{1-447}$ mutants as "active mutants," but Table 9 identifies only 2,376 mutants that exhibit >40% hyaluronidase activity. Likewise, Tables 5 and 10 list 3,368 and 3,380 $PH20_{1-447}$ "inactive mutants," respectively. The discrepancies are not explained.

[104] EX1003, ¶ 105.

[105] *Id.*

Activity vs. Unmodified PH20	Number	% of Tested (5916)
Active Mutants (Table 9)		
>120%	532	9.0%
100%-120%	267	4.5%
40%-100%	1577	26.7%
Inactive Mutants (Table 9)		
<40%	160	2.7%
Inactive Mutants (Table 10)		
Table 10 'inactive mutants"	3,380	57.1%



The measured activity of single-replacement $PH20_{1-447}$ mutants shows no trends or correlations even for single-replacement $PH20_{1-447}$ polypeptides.[106]

Moreover, there are numerous examples in the dataset where the effects of introducing different amino acids into a single position in $PH20_{1-447}$ resulted in (i) increased activity, (ii) decreased activity, or (iii) inactive mutants (below).[107]

106 EX1003, ¶¶ 106, 142-43.

107 Data from Tables 3, 5, 9, 10.

Position	Inactive	Decreased Activity	Increased Activity
008	P	L, M	I
067	R	L, Y	V
092	H	M, T	C, L, V
165	C	A, R, Y	D, F, N, S, V, W
426	K, S	E, G, N, Q, Y	P

The data on activities of tested single-replacement $PH20_{1-447}$ mutants is not analyzed or explained in the common disclosure—it is simply presented. There is no attempt to extrapolate its results to particular combinations of substitutions in PH20 polypeptides, or to even assess the impact the single substitution had on the protein's structure.[108] The quality of the data is also questionable: no control values are reported or statistical assessments.[109] The only realistic takeaway from the data is that most of the tested, random single-substitution mutants impaired PH20's activity.[110] Unlike single substitutions, multiple concurrent mutations can cause complex and unpredictable effects on a protein's structure and resulting function.[111] The patent's empirical set of test results provides no insights of value to a skilled artisan attempting to identify which of the many possible mutants with

[108] EX1003, ¶ 139.

[109] EX1003, ¶ 106.

[110] EX1003, ¶ 138.

[111] EX1003, ¶¶ 139, 142.

different sets of 2-22 substitutions will be enzymatically active modified PH20 polypeptides.[112]

b) Purported Stability Data is Not Reliable or Probative

The common disclosure reports results in Tables 11 and 12 from two runs of supposed "stability" testing of ~409 single-replacement $PH20_{1-447}$ polypeptides. Table 11 reports the hyaluronidase activity of single-replacement $PH20_{1-447}$ mutants tested at 4° C and 37° C, and in the presence of a preservative (m-cresol),[113] while Table 12 compares relative activities under pairs of these conditions.[114]

The data in Tables 11 and 12 provides no meaningful insights.[115] For example, it is unsurprising that single-replacement $PH20_{1-447}$ polypeptides showed higher activity at 37° C than at 4° C, given that PH20 exists at that temperature in

[112] EX1003, ¶¶ 140, 143.

[113] EX1001, 263:41-270:20 (Table 11).

[114] EX1001, 270:21-281:29 (Table 12).

[115] EX1003, ¶ 76.

humans.[116] Testing with a phenolic preservative, on the other hand, showed that only a few mutants were able to resist its effects.[117]

More generally, the examples fail to demonstrate that measured activity data was attributable to improved stability in the PH20 structure, and do not identify to the skilled artisan which multiple substitutions may improve stability.[118] They provide no probative insight regarding multiply-modified PH20 polypeptides.[119]

The values are also largely meaningless, as many of them fall within the huge variability measured for the positive control.[120] The chart below shows coloring reflecting relative percentage values from 0 to 120% for the positive controls from Tables 11/12 and plots those values below.[121]

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116 EX1003, ¶ 73.

117 EX1003, ¶ 69.

118 EX1003, ¶¶ 75-76.

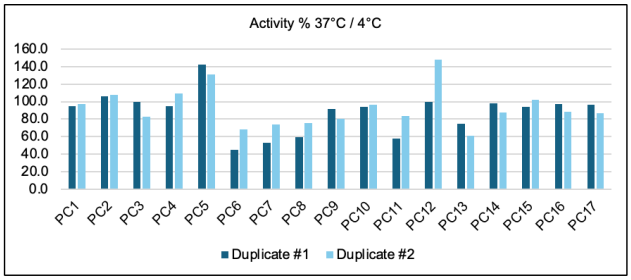
119 *Id*.

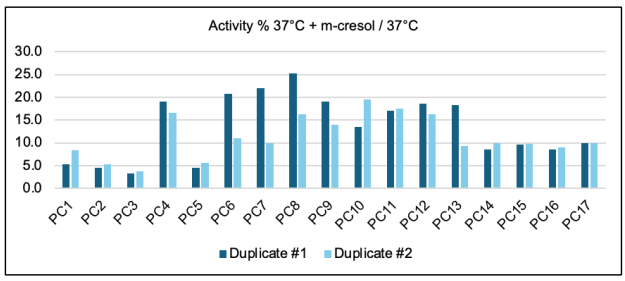
120 EX1003, ¶ 71; EX1001, 281 (Table 12).

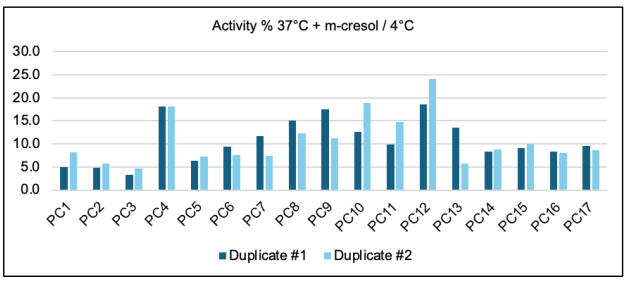
121 EX1003, ¶ 71, Appendix A-7, A-8.

Positive Control ("PC") (OHO)	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C+mcr/4°C
PC1	94.998	5.230	4.970	96.871	8.456	8.190
PC2	105.798	4.480	4.740	108.066	5.246	5.670
PC3	100.000	3.330	3.330	82.778	3.759	4.590
PC4	94.762	19.070	18.070	109.539	16.529	18.110
PC5	142.024	4.480	6.360	130.947	5.595	7.330
PC6	45.115	20.770	9.370	68.017	11.035	7.510
PC7	53.324	21.950	11.710	74.253	9.960	7.400
PC8	59.581	25.240	15.040	75.872	16.231	12.310
PC9	91.844	19.050	17.500	80.371	13.977	11.230
PC10	93.828	13.470	12.630	96.630	19.454	18.800
PC11	57.773	17.040	9.850	83.536	17.573	14.680
PC12	100.000	18.560	18.560	148.226	16.239	24.070
PC13	74.325	18.290	13.600	61.119	9.286	5.680
PC14	98.132	8.480	8.320	87.677	10.006	8.770
PC15	93.817	9.620	9.020	102.223	9.745	9.960
PC16	96.922	8.560	8.300	87.993	9.064	7.980
PC17	96.648	9.910	9.580	86.891	9.938	8.630

KEY
Coloration of Percent (%) Activity Values
n/a
>120
between 100 and 120
between 80 and 100
between 40 and 80
between 20 and 40
between 10 and 20
between 0 and < 10







	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C + m-cresol	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol	% Activity at 37°C+mcr/4°C
High	142.02	25.24	18.56	148.23	19.45	24.07
Low	45.12	3.33	3.33	61.12	3.76	4.59
Range	96.91	21.91	15.23	87.11	15.70	19.48
Average	88.17	13.38	10.64	93.00	11.30	10.64
Mean	94.76	13.47	9.58	87.68	9.96	8.63

The table and graphs above show the extensive variability observed for the positive control in the assay being used, with the range in values of almost 100%. As Dr. Hecht observes, the "significant variation raises serious doubts about how probative or instructive the values of individual tested mutants that fall within the range of variability observed for the control can possibly be," meaning the data not only is uninformative, it is unreliable.[122]

4. The Common Disclosure's Research Plan Does Not Identify Multiply-Mutated Enzymatically Active PH20 Polypeptides

Instead of describing any multiply-modified PH20 polypeptides that are "active mutants," the common disclosure provides only a prophetic research plan based on iterative rounds of "make-and-test" experiments that were never

[122] EX1003, ¶¶ 70-72.

performed. This prophetic method provides absolutely no insights into which multiply-modified PH20 polypeptides are active mutants.[123]

The common disclosure merely outlines ***the idea*** of multiply-modified PH20 polypeptides. It declares that "[a] modified PH20 polypeptide can have up to 150 amino acid replacements," "[t]ypically" contains between 1 and 50 amino acid replacements and "can include any one or more other modifications**,** in addition to at least one amino acid replacement as described herein."[124] In addition to PH20 polypeptides with single amino acid replacements, it contends that a modified PH20 polypeptide "having a sequence of amino acids that exhibits" between 68% and 99% sequence identity with any of unmodified Sequence ID Nos. 74-855 "***can*** exhibit altered, such as improved or increased, properties or activities compared to the corresponding PH20 polypeptide not containing the amino acid modification (e.g., amino acid replacement)."[125]

None of these statements identify ***any*** actual multiply-modified PH20 polypeptides—it does not identify ***any*** sets of specific amino acid substitutions.

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123 EX1003, ¶¶ 173, 184-85, 190.

124 EX1001, 47:20-27.

125 EX1001, 98:53-67 (emphasis added).

They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides.

The common disclosure then outlines an "iterative" make-and-test research plan for discovering modified PH20 polypeptides with multiple substitutions that might exhibit hyaluronidase activity. It too is prophetic, and states:

> The method provided herein [] is ***iterative***. In one example, after the method is performed, any modified hyaluronan-degrading enzymes identified as exhibiting stability … ***can be modified or further modified*** to increase or optimize the stability. A secondary library ***can be*** created by introducing additional modifications in a first identified modified hyaluronan-degrading enzyme. … The secondary library ***can be*** tested using the assays and methods described herein.[126]

The guidance in this research plan is effectively meaningless. It says to make mutants, test them to find activity, and keep repeating the process until you find something via screening. It does not indicate that any useful multiply-modified PH20 polypeptides will be found, much less what their specific characteristics or activities are.[127]

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[126] EX1001, 140:35-47 (emphases added); *see also id.* at 41:17-24.

[127] EX1003, ¶¶ 187-90.

The specification also incorrectly portrays the experimental readout—hyaluronidase activity—as a measure of "stability."[128] As Dr. Hecht explains, to assess a protein's stability directly one performs experiments that measure the energy associated with the protein's transition between its folded and unfolded states.[129] Activity may or may not be influenced by stability but is not itself a measure of stability.[130]

An alternative focus is then proposed: mutations can be "targeted near" "critical residues" which supposedly "can be identified because, when mutated, a normal activity of the protein is ablated or reduced."[131] But Tables 5 and 10 show that at least one substitution at each of 405 positions between positions 1 and 444 of $PH20_{1-447}$ resulted in an inactive mutant.[132] In other words, the guidance is to target locations "near" ~90% of the amino acids in $PH20_{1-447}$, which is no different

[128] EX1003, ¶¶ 67, 69, 179.

[129] EX1003, ¶¶ 63-66.

[130] EX1003, ¶ 67.

[131] EX1001, 140:48-141:6.

[132] EX1003, ¶ 180, Appendix A-3.

than targeting every residue in the protein.[133] It is, like the first proposed "iterative" process, meaningless.

These prophetic research plans, based entirely on unfocused, iterative "make-and-test" experiments, provide no direction to the skilled artisan about which of the trillions and trillions of possible multiply-modified PH20 polypeptides are "active mutant" PH20 polypeptides. Instead, they require the skilled artisan to repeat the cycle of mutagenesis iteratively, screening and selecting until 10^{49} to 10^{66} modified PH20 polypeptides are produced and screened for activity.[134] That in no way demonstrates possession of the claimed genus.

5. The Common Disclosure Does Not Identify a Structure-Function Relationship for Multiply-Modified, Enzymatically Active PH20 Polypeptides

The common disclosure does not identify the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are

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133 EX1003, ¶ 180.

134 EX1003, ¶¶ 175-77, 181, 187-88.

responsible for the measured change in hyaluronidase activity.[135] Instead, it simply lists single replacements made across effectively the entire protein sequence that incorporate randomly selected amino acids being classified as "active mutants" in a hyaluronidase assay, without further explanation, and nothing is said about the effects (if any) of substitutions on the protein's structure.[136]

The common disclosure also does not identify any ***sets*** of specific amino acid replacements that correlate to structural domains or motifs that positively or negatively influence hyaluronidase activity, much less ***predictably*** increase activity to defined thresholds.[137] Again, it simply reported activity data from testing randomly generated ***single***-replacement $PH20_{1-447}$ mutants.

The common disclosure's empirically identified examples of "active mutant" single-replacement $PH20_{1-447}$ mutants also do not ***by themselves*** identify any "structure-function" relationship between "active mutants" and the set of single-replacement modified $PH20_{1-447}$ polypeptides.[138] And they plainly do not do so for the much larger genus of modified PH20 polypeptides having varying

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135 EX1003, ¶¶ 139-40, 151.

136 EX1001, 232:40-67; EX1003, ¶¶ 139-40, 142.

137 EX1003, ¶¶ 55, 142-43.

138 EX1003, ¶¶ 61, 143, 157, 159.

lengths and between 2 and 22 substitutions, with or without additions or deletions.[139]

Critically, the common disclosure also ***does not even contend*** that a particular amino acid replacement at a particular position that makes a $PH20_{1-447}$ an "active mutant" will make any other modified PH20 polypeptide with that same amino acid replacement (plus between 2 to 22 additional replacements or truncations) an "active mutant."[140] Such an assertion would have no scientific credibility—the activity of a protein such as PH20 is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.[141] Thus, even the inventors did not view their compilation of test results as identifying a structure-function correlation for multiply-modified PH20 polypeptides.

The common disclosure, thus, does not identify to a skilled artisan ***any*** structural features shared by the many, diverse "active mutant" modified PH20 polypeptides within the scope of the claims.[142] As such, it cannot satisfy the

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139 EX1003, ¶ 157.

140 EX1003, ¶¶ 168, 192-93.

141 EX1003, ¶¶ 56-57.

142 EX1003, ¶ 157.

written description requirement of § 112(a) as being a disclosure that links a functional property shared by members of the genus to a particular structure ***shared*** by the members of the genus.

6. The Common Disclosure Does Not Describe a Representative Number of Multiply-Modified Enzymatically Active PH20 Polypeptides

The ~2,500 single-replacement $PH20_{1-447}$ polypeptides that are "active mutants" are not examples representative of the claimed genera of claims 1 to 4, much less its various sub-genera.[143]

First, the single-replacement $PH20_{1-447}$ examples are not representative of the trillions and trillions of $PH20_{1-447}$ polypeptides with between ***2 and 22 substitutions*** at any of hundreds of positions within the protein.[144] The latter group of proteins is structurally distinct from single replacement PH20 polypeptides, both as to their sequence and due to the various structures within the folded protein that, when incorporating different amino acid substitutions, may alter their structures and their interactions with neighboring residues.[145] The effects of those numerous substitutions on a protein's various secondary structures and structural motifs

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143 EX1003, ¶¶ 61, 143, 155, 159.

144 *See* § IV.D.1; EX1003, ¶¶ 61, 143, 159.

145 EX1003, ¶¶ 54-56, 58, 120, 156, 159.

within the protein is not described in the common disclosure, and the magnitude of concurrent substitutions encompassed by the claims was unknowable in 2011.[146] The overall activity of a protein with multiple substitutions also will not be due to one amino acid, but to the unique structure of each protein that reflects ***the totality*** of effects of those many substitutions.[147]

More specifically, introducing a first amino acid substitution often affects the neighbors of that original/replaced amino acid by, for example, (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).[148] Introducing a second substitution in that region may reverse those interactions (or not) with each neighboring residue, and a third substitution may do the same, up to 22 rounds each potentially impacting each interaction.[149] The data associated with a single amino acid substitution thus cannot be representative of the properties of any of these downstream, multiply-substituted mutants, which will have an

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146 EX1003, ¶ 224.

147 EX1003, ¶¶ 36, 61, 140, 143, 151.

148 EX1003, ¶¶ 56-58.

149 EX1003, ¶¶ 58-60, 142.

unknowable combination of substitutions that each uniquely impact the properties of the mutated protein.[150]

Single-replacement $PH20_{1-447}$ polypeptides are also not representative of multiply-modified PH20 polypeptides that incorporate structural modifications that rendered the wild-type protein inactive, including polypeptides (i) with truncations terminating below position 429, and (ii) which incorporated a single substitution at a position that rendered $PH20_{1-447}$ inactive.[151] Single-replacement $PH20_{1-447}$ polypeptides are not representative of those sub-genera of mutants because they do not have the additional structural features that are distinct from those in the wild-type sequence and that impart detrimental effects. For example, a single-replacement, active $PH20_{1-447}$ polypeptide would not be considered representative of a PH20 with multiple substitutions and a sequence with 409 to 433 residues (which would still be in the claims' scope).[152] A skilled artisan could not have predicted—based on the disclosed data, all of which are in a $PH20_{1-447}$ sequence—whether a severely truncated mutant could be further modified to restore

[150] EX1003, ¶¶ 61, 142-43, 159, 169.

[151] EX1003, ¶¶ 161-64.

[152] EX1003, ¶¶ 167-69.

hyaluronidase activity, much less what additional substitutions would restore activity.[153]

The Patents thus provide a very narrow set of working examples relative to the diversity of modified PH20 polypeptides being claimed.[154] The examples are restricted to ***one type of change*** (a single amino acid replacement) in ***one type of PH20 polypeptide*** (SEQ ID NO: 3).[155] By contrast, the claims encompass changes in 35 different unmodified PH20 sequences, and include, in addition to one identified replacement, anywhere from 1 to 21 (claim 1), 1-16 (claim 3) or 1-20 (claim 4) additional changes.[156] A simple illustration demonstrates how ***non-representative*** the examples are: all of the Patents' examples of single-replacement $PH20_{1\text{-}447}$ mutants fit into one box of the array below.

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153 EX1003, ¶ 168.

154 EX1003, ¶ 155.

155 EX1003, ¶¶ 97, 99, 103.

156 EX1003, ¶¶ 115-20.

	Number of Changes																				
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
3																						
32																						
33																						
34																						
35																						
36																						
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Consequently, the skilled artisan would not have viewed the Patents' examples of individual single amino acid replacements in $PH20_{1-447}$ as

representative of the diversity of modified PH20 polypeptides encompassed by the claims.[157]

7. The Claims Capture Multiply-Modified PH20 Polypeptides the Disclosure Excludes from the Class of Enzymatically Active PH20 Proteins

Patentee's position on the breadth of the claims is unknown. However, by their literal language, the claims capture several sub-genera of "active mutant" modified PH20 polypeptides the common disclosure says caused single-replacement $PH20_{1-447}$ mutants to be rendered inactive (*i.e.*, those with replacements in Tables 5/10 or in PH20 sequences truncated below position 429). Likewise, the claim language captures modified PH20 polypeptides with the six combinations of replacements the common disclosure explicitly says to not make: P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, N333A/N358A and N47A/N131A/N219A.[158] The claims thus improperly capture subject matter the common disclosure affirmatively excluded from the genus of enzymatically active modified PH20 polypeptides having multiple substitutions and other changes.

The common disclosure provides no exemplification of multiply-modified species of PH20 polypeptides that violate these prohibitions in the common

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157 EX1003, ¶ 143.

158 *See* § V.A.2.a; EX1001, 76:10-22.

disclosure.[159] There is no explanation of the types of substitutions that might be made to restore activity that, under the logic of the common disclosure, will result in enzymatically inactive PH20 polypeptides or which the specification teaches ***not*** to make.[160] Yet the claims encompass such proteins. The claims therefore independently violate the written description requirement for the reasons articulated by the Federal Circuit in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998)—if a disclosure "unambiguously limited" the invention, but the claims circumvent that limitation, those claims are "broader than the supporting disclosure" and are unpatentable.

8. The Dependent Claims Lack Written Description

a) Claims 5 and 6 Lack Written Description

Claims 5 and 6 add a purely functional requirement to the genus defined by claim 1: that the modified PH20 polypeptides exhibit increased (>100% (claim 5) or >120% (claim 6)) hyaluronidase activity relative to unmodified $PH20_{1-447}$.

The reasons provided in §§ V.A.1-V.A.7 explaining why claims 1-4 lack written description apply with full force to claims 5 and 6. Stated simply, the common disclosure's recitation of a ***desired*** level of hyaluronidase activity in

[159] EX1003, ¶ 161.

[160] EX1003, ¶ 168.

claims 5 and 6 does not identify ***which*** of the many trillions of PH20 polypeptides having 95% sequence identity with SEQ ID NOS: 3 or 32-66 and one of seven replacements at position 313 will exhibit those functional requirements.[161]

First, the identification of four $PH20_{1-447}$ mutations at position 313 that exhibit 120% or higher activity (A, H, K, R) of unmodified $PH20_{1-447}$ is not representative of each claim's genus of PH20 polypeptides with 2 to 22 additional substitutions and/or truncations.[162] There is no description of multiply-modified PH20 polypeptides with the claimed substitutions at 313, much less one that identifies the 2 to 22 more substitutions and would retain this elevated enzymatic activity.[163] Indeed, the common specification does not identify even one multiply-modified PH20 polypeptide with any level of hyaluronidase activity.[164]

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides and exhibiting the recited >100% or >120% activity.[165] Certainly, the mere presence of a M313K replacement in a

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161 EX1003, ¶¶ 185, 191-92.

162 EX1001, 235 (Table 9); EX1003, ¶¶ 191-92.

163 EX1003, ¶¶ 140, 190-93.

164 EX1003, ¶¶ 130, 172.

165 EX1003, ¶¶ 157, 190.

multiply-modified PH20 does not dictate such a result, and the common disclosure makes no claim that it does.[166]

Claims 5 and 6 lack written description in the common disclosure.

b) Claims 7-9 Lack Written Description

Claims 7-9 employ claim 1's definition of the genus of modified PH20 polypeptides, and do not add requirements that limit the numbers of polypeptides in that genus. Claims 7-9 lack written description for the same reasons as claim 1.

c) Claims 10-21 Lack Written Description

Claims 10-21 employ claim 1's definition of the genus of modified PH20 polypeptides to define nucleotides, host cells, pharmaceutical compositions, methods of administering such compositions, and specify methods for using compositions containing modified PH20 polypeptides within that genus for treating cancer, including with anticancer drugs. Claims 10-21, however, contain no language that identifies ***which*** modified PH20 polypeptides within that immense genus can be used in the claimed methods, and thus do not remedy the § 112 deficiencies of claim 1.[167] Because each of claims 10-21 are directed to the same

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166 EX1003, ¶¶ 143, 168, 192.

167 *Idenix*, 941 F.3d at 1155, 1165 (claims directed to method of treatment involving immense genus of modified proteins invalid for lack of written

genus of polypeptides that are not adequately described in the written description of the common disclosure, they are unpatentable.

d) Claim 22 Lacks Written Description

Claim 22 defines a method of producing a genus of PH20 polypeptides that employs the same genus definition as claim 1, and thus lacks written description for the same reasons.

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

"If a patent claims an entire class of … compositions of matter, the patent's specification must enable a person skilled in the art to make and use the ***entire*** class," *i.e.*, "the ***full scope*** of the invention."[168] So, the "more one claims, the more one must enable."[169] "It is the specification, not the knowledge of one skilled in

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description and non-enablement); *Boehringer*, PGR2020-00076, Paper 42, at 40-41 (because "the Specification does not provide an adequate written description of the composition of claim 1… we find that claims 12-16 [directed to methods of treatment using the compositions] lack written description for at least the same reasons").

[168] *Amgen*, 598 U.S. at 610 (emphases added).

[169] *Id.*

the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."[170] "Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation."[171]

Although not required, enablement may be assessed using the *Wands* factors, which consider: "(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention."[172]

Where the scope of the claims is large, there are few working examples disclosed in the patent, and the only guidance to practice "the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those

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170 *Idenix*, 941 F.3d at 1159.

171 *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

172 *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

satisfying the claims' functional limitations—the asserted claims are not enabled."[173]

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the 10^{49}+ PH20 polypeptides having multiple amino acid replacements and/or truncations are "active mutant" PH20 polypeptides within the scope of the claims.[174]

1. Claims 1 to 4 Are Not Enabled

The facts of this case are a textbook example of claims that are not enabled under the reasoning articulated by the Supreme Court in *Amgen*. An analysis of the common disclosure under the Federal Circuit's framework for assessing undue experimentation using the factors in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) also compels the same conclusion.

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[173] *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, T., sitting by designation) *aff'd* 81 F.4th 1362 (Fed. Cir. 2023).

[174] EX1003, ¶¶ 170-71, 190.

a) Extreme Scope of the Claims

As explained in § IV.D.1, each of claims 1 to 4 defines an immense and structurally diverse genus of between 10^{49} and 10^{66} modified PH20 polypeptides, which introduces substantial scientific questions that are left unanswered by the common disclosure.

The claims encompass many modified PH20 polypeptides that terminate below position 429.[175] The common disclosure and the prior art, however, report that unmodified human PH20 must include residues through position 429 to have hyaluronidase activity.[176] Several of the claims (1-2, 5-22) also encompass modified PH20 polypeptides that, per the common disclosure's guidance, would be expected to be insoluble because they include all or some of the GPI anchor sequence.[177] And, to the extent Patentee contends the claims should be read as covering any polypeptide that falls within the mathematical "sequence identity" boundaries set by the claim language, they would capture modified PH20 polypeptides with 2-22 amino acid replacements the common disclosure instructs

[175] EX1003, ¶¶ 154, 164.

[176] EX1001, 68:30-39; EX1003, ¶¶ 93, 152-53.

[177] EX1001, 45:5-7, 70:39-40, 72:50-56, 73:47-49; EX1005, 2:56-61, 3:57-62.

"are less tolerant to change or required for hyaluronidase activity"[178] or which the common disclosure affirmatively says to not make.[179]

In other words, the claims capture a massive genus of modified PH20 polypeptides, most of which would have unknowable properties absent individual production and testing.[180]

Claims that capture a massive and diverse genus of proteins have routinely been found non-enabled. For example, the claims in *Amgen* covered "millions" of different, untested antibodies,[181] while in *Idenix*, a skilled artisan would "understand that 'billions and billions' of compounds literally meet the structural limitations of the claim."[182] In both cases, the enormous claim scope was found non-enabled after being contrasted to the limited working examples in the patent, the existence of unpredictability, and the quantity of experimentation needed to practice the full scope of the claims (*Wands* Factors 1, 3, 4, and 7). And, as the *Idenix* court observed, one cannot rely on the knowledge and efforts of a skilled

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178 EX1001, 78:45-47.

179 EX1001, 76:10-22.

180 EX1003, ¶ 158.

181 598 U.S. at 603.

182 941 F.3d at 1157.

artisan to try to "fill the gaps in the specification" regarding which of the "many, many thousands" of possible compounds should be selected for screening, and which in this case is impossible.[183]

b) Limited Working Examples and Only a Research Plan for Discovering Active Mutant PH20 Polypeptides

The common disclosure provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement $PH20_{1-447}$ polypeptides, of which ~2500 were "active mutants."[184] Those examples are a tiny fraction of the 10^{49} to 10^{66} modified PH20 polypeptides covered by the claims, and provide no guidance that would help a skilled artisan navigate the "trial-and-error" methodology the common disclosure describes using to make modified PH20 polypeptides; indeed, none incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.[185]

The common disclosure provides no credible guidance on the full scope of the genus comprising multiple combinations of changes to PH20 polypeptides.[186]

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183 *Id.* at 1159.

184 EX1003, ¶ 103.

185 EX1003, ¶¶ 155, 159, 167.

186 EX1003, ¶¶ 131, 139.

Instead, it describes an explicitly prophetic and "iterative" process for ***discovering*** active mutant PH20 polypeptides. *See* § V.A.4.

The purely prospective research plan in the common disclosure demands that a skilled artisan engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of ***randomized*** mutations (up to 21 rounds per starting molecule under the broadest claims) to ***discover*** which of the 10^{49}+ possible modified PH20 polypeptides having 2 to 21 replacements to any of 19 other amino acids in any of 35 starting PH20 sequences might possess hyaluronidase activity.[187]

Second, it provides no meaningful guidance in producing "active mutant" modified PH20 polypeptides:

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[187] EX1003, ¶¶ 188-90; *see also* EX1018, 382 (noting that "combinatorial randomization of only five residues generates a library of 205 possibilities (3.2 x 106 mutants), too large a number for manual screening"). Chica also credited a supposed "ground-breaking" advancement in predictive molecular modeling techniques. EX1018, 384, 382. That supposed advancement, however, was later shown to be false. EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

(i) it does not identify ***any*** specific combination of two or more replacements within any PH20 polypeptide that yield "active mutants";

(ii) it provides no data from testing ***any*** PH20 polypeptide with two or more substitutions;

(iii) it does not identify any regions or residues that are "associated with the activity and/or stability of the molecule" or "'critical residues involved in structural folding or other activities' of the molecule" when two or more concurrent replacements have been made.[188]

A skilled artisan could not predict whether a particular multiply-modified PH20 polypeptide will be enzymatically active without making and testing each one.[189]

Regardless of whether individual rounds of "iterative" production and testing might be considered "routine," the process described in the common disclosure is indistinguishable from the "***iterative, trial-and-error process[es]***" that have consistently been found to not enable broad genus claims to modified

[188] EX1003, ¶¶ 144, 158, 172, 184-85.

[189] EX1003, ¶ 190.

proteins.[190] Simply put, the common disclosure's prophetic, iterative and labor-intensive process requires making and screening an immense number of modified PH20 polypeptides, before which the skilled artisan will not know which multiply-modified PH20 polypeptides are within the claims' scope.[191]

c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable

Like any protein, the activity of PH20 can be unpredictably influenced by changes to its amino acid sequence.[192] Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary structures or structural motifs within the protein that are important to its biological activity (*e.g.*, catalysis, ligand binding, etc.).[193]

As explained in § VI, below, by 2011, skilled artisans could have assessed whether certain ***single*** amino acid substitutions at certain positions would be

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190 *Idenix*, 941 F.3d at 1161-63 (emphasis added); *see also Amgen,* 598 U.S. at 612-15; *Wyeth*, 720 F.3d at 1384-86; *Baxalta*, 597 F. Supp. 3d at 616-19; *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 n.2 (Fed. Cir. 2020).

191 EX1003, ¶¶ 172, 184-85, 189.

192 EX1003, ¶ 61.

193 *Id.*

tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.[194] That person, using a rational design approach, would have performed such an assessment by, *inter alia*, analyzing evolutionarily non-conserved positions and evaluating specific changed residues using a PH20 protein structure model using experimental evidence available before 2011 that is not disclosed in or referenced by the common disclosure.[195]

By contrast, the skilled artisan could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011.[196] Introducing ***multiple*** concurrent changes into a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity, and can even introduce new ones into the protein.[197] Replacing multiple amino acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.[198]

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194 EX1003, ¶ 194.

195 EX1003, ¶¶ 20-22, 49, 211-12, 216.

196 EX1003, ¶ 224.

197 EX1003, ¶¶ 59-60.

198 EX1003, ¶ 58.

The cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure in 2011. For example, the further away the modeled amino acid sequence gets from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model became.[199] In addition, depending on the structural template used to produce the model, regions of the protein not supported by a corresponding structure cannot be reliably used to assess particular changes.[200] And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.[201]

Consequently, a skilled artisan could not have used conventional rational design techniques to identify, much less predict the outcome of attempts to make, the enormous number of PH20 polypeptide sequences that incorporate the myriad possible combinations of between 5 and 22 substitutions the claims encompass.[202] Stated another way, practicing the full scope of the claims would have been well

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199 EX1003, ¶¶ 158, 190, 224; EX1004, ¶¶ 167-168.

200 EX1003, ¶¶ 158, 224; EX1004, ¶¶ 157-59; EX1012, 4, 8.

201 EX1003, ¶ 51, 190; EX1059, 1225-26; EX1018, 378.

202 EX1003, ¶¶ 61, 158, 224.

beyond the ability of the skilled artisan's ability to reasonably predict which multiply-modified PH20 polypeptides would be enzymatically active, and, even if possible, doing so would have taken an extreme amount of time and effort even for a small handful of the vast universe of multiply-modified polypeptides within the claims.[203]

d) Other Wands *Factors and Conclusion*

The remaining *Wands* factors either support the conclusion that practicing the full scope of the claims would require undue experimentation or are neutral.

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of multiply-changed PH20 polypeptides.[204] Likewise, while there was significant knowledge in the public art about hyaluronidases, there was no solved structure of the PH20 protein, experimental reports generally reported on ***loss of activity*** from mutations, and did not predictably teach how to introduce changes that ***enhanced*** stability or activity. Indeed, the patent disclosure at issue in *Amgen* dates to the same 2011 timeframe as the common disclosure.

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[203] EX1003, ¶¶ 158, 190.

[204] EX1003, ¶¶ 158, 224.

Practicing the full scope of claims 1-4 thus would have required a skilled artisan to engage in undue experimentation, which renders those claims non-enabled.

2. The Dependent Claims Are Not Enabled

a) Claims 5 and 6 Are Not Enabled

Claims 5 and 6 require the modified PH20 polypeptides to have specific levels of increased activity (*i.e.*, >100% or >120% of unmodified PH20).

The reasons why claims 1-4 are not enabled (*see* § V.B.1) establish why claims 5 and 6 are also not enabled. Specifically, a skilled artisan could not have predicted which of the trillions of PH20 polypeptides having up to 21 changes in addition to a required change at position 313 would exhibit greater than 100% or 120% of the hyaluronidase activity of an unmodified PH20.[205] Instead, a skilled artisan would need to make-and-test each of those molecules in order to practice the "full scope" of the claims.[206]

b) Claims 7-9 Are Not Enabled

Claims 7-9 employ the genus definition used in claim 1, and do not add requirements that limit the numbers of polypeptides in the claim 1 genus. Claims 7-9 are therefore not enabled for the same reasons as claim 1.

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[205] EX1003, ¶¶ 185, 190.

[206] *Id.*

c) Claims 10-21 Are Not Enabled

Claims 10-21 employ the definition of the genus of modified PH20 polypeptides used in claim 1 to define nucleotides, host cells, and PH20-based pharmaceutical compositions and methods of administering them or using them to treat cancer. None of claims 10-21 limit the number of polypeptides in the claim 1 genus. Claims 10-21 are therefore not enabled for the same reasons as claim 1.[207]

d) Claim 22 Is Not Enabled

Claim 22 defines a method of producing a genus of PH20 polypeptides that employs the same genus definition in claim 1. Claim 22 is not enabled for the same reasons as claim 1.

C. Inactive PH20 Polypeptides Are Not Useful and Do Not Remedy the § 112(a) Deficiencies of the Claims

Patentee may contend the claims do not require the modified PH20 polypeptides to be "active mutants." Such a contention, even if accepted, does not solve the written description and enablement problems of the claims.

First, it ignores that at least a portion of the claimed genus ***does*** require the modified PH20 polypeptides to be an "active mutant." *See* § IV.D.3. Because dependent claims 5 and 6 require the modified PH20 polypeptides to exhibit increased hyaluronidase activity levels (>100% or 120% of unmodified PH20),

[207] *See, e.g.*, *Idenix*, 941 F.3d at 1155, 1165.

parent claim 1 necessarily encompasses a sub-genus comprised of "active mutant" modified PH20 polypeptides. A failure to enable or describe a subgenus within the scope of the claims demonstrates that the claim ***as a whole*** is unpatentable for lack of written description and non-enablement.

Second, the common disclosure fails to provide any correlation between changes to PH20 polypeptides and ***either*** active or inactive mutants.[208] Rather, it leaves to the skilled artisan the burdensome task of making and testing, through trial-and-error iteration, each of the 10^{49}+ candidate polypeptides within the claims' scope to determine which exhibit hyaluronidase activity and which are inactive mutants.[209]

Third, the only putative utility identified for "inactive" polypeptides is as "antigens in contraception vaccines."[210] This assertion is not scientifically credible, but regardless, the common disclosure provides no guidance about which epitopes on the PH20 protein must be preserved in an "inactive mutant" (if any) to induce contraceptive antibody production in a human subject.[211] Notably, while

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208 EX1003, ¶ 143.

209 EX1003, ¶¶ 173-74, 182-84.

210 EX1001, 74:20-22, 193:14-33.

211 EX1003, ¶ 113.

the specification cites two studies in guinea pigs,[212] it ignores numerous publications before 2011 that showed that immunizing mammals with PH20 did ***not*** cause contraception.[213] Moreover, Patentee's own clinical studies of the unmodified $PH20_{1-447}$ protein reported in 2018 that, despite producing anti-PH20 antibodies, those anti-PH20 antibodies ***did not affect fertility*** in humans:

> Although some antisperm antibodies are associated with decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex.[214]

Notably, Patentee reported this clinical result almost seven years before filing the application that issued as the '298 Patent.

Even if one considers the unlikely possibility than some epitope on human PH20 might induce contraceptive effects in a human, a skilled artisan could not

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212 EX1001, 193:14-33; EX1022, 1142-43; EX1023, 1133-34.

213 *See* EX1019, 325, 331-33 ("recombinant mPH20 is not a useful antigen for inclusion in immunocontraceptive vaccines that target mice"); EX1020, 179-81 ("immunization [of rabbits] with reproductive antigens … are unlikely to result in reduced fertility …"); EX1021, 30310, 30314 ("PH-20 is not essential for fertilization, at least in the mouse …").

214 EX1024, 87-88; *see also* EX1061, 1154; EX1003, ¶¶ 110-11.

have reasonably predicted from the common disclosure whether any "inactive mutant" modified PH20 polypeptides would preserve that epitope or induce antibody production that would confer (contrary to Patentee's clinical evidence) contraceptive effects in humans.[215] Indeed, a skilled artisan would have expected the vast majority of "inactive mutant" PH20 polypeptides would have no utility at all.[216] Consequently, a skilled artisan would not have accepted the common disclosure's assertion that "inactive mutants" are useful as contraceptive vaccines, particularly in humans.[217]

Finally, and most significantly, the common disclosure does not identify a single inactive PH20 mutant (with any number of substitutions) that was shown to have contraceptive effect.[218] Therefore, at most, the common disclosure presents

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[215] EX1003, ¶¶ 112-13.

[216] *Id.*; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App'x. 26, 30 (Fed. Cir. 2007).

[217] EX1003, ¶¶ 112-13; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005) (implausible scientific statements not entitled to weight).

[218] EX1003, ¶ 113.

only a "research proposal" to discover such "inactive mutants."[219] It does not demonstrate possession of or enable the immense and diverse genus of PH20 polypeptides claimed, regardless of whether the claims are appropriately limited to "active mutants" or, instead, include "inactive mutants."

D. The Original Claims of the '731 Application Do Not Cure the Written Description and Enablement Deficiencies

The specifications of the pre-AIA '731 Application and AIA '298 Patent are substantially identical, and the challenged claims are not supported as § 112(a) requires by either. The claims are both PGR eligible and unpatentable under § 112(a).

The originally-filed claims of the '731 Application employed different claim formats but encompassed an equivalently large genus of multiply-substituted polypeptides. For example, original claim 1 required a "modified PH20 polypeptide" with an "amino acid replacement [that] confers … increased stability" and having "85% sequence identity to SEQ ID NO: 3" (claim 3) or between "1 [and] 75 or more amino acid replacements" (claim 4). Dependent claims list positions (claim 12) or replacements (claims 13-16) in those

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[219] *See Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("[t]he utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research").

polypeptides. And, while certain claims contemplated 2-3 particular combinations of amino acid replacements (from dozens of locations), the claims also encompassed other unspecified substitutions at unspecified locations.[220]

The original claims provide no additional guidance or insight that would demonstrate written description of or would enable the claimed sets of modified PH20 polypeptides. As such, the original claims do not provide § 112 support for the challenged claims.[221]

VI. Challenged Claims 1-4 and 7-22 Are Unpatentable Under § 103

As explained in § IV.D.2 above, claims 1-4 each define a genus that includes ***one*** specific modified PH20 polypeptide: M313K $PH20_{1-447}$. Because that particular modified PH20 polypeptide would have been obvious from the '429 Patent in view of Chao and the knowledge of a skilled artisan before 2011, each of claims 1-4 is unpatentable. Each of claims 7-22 also would have been obvious, as

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[220] EX1026, at 335.

[221] *See, e.g.*, *Ariad Pharms.*, 598 F.3d at 1349 ("original claim language" does not "necessarily disclose[] the subject matter that it claims"); *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993) (original claim amounted to no more than a "wish" or "plan" for obtaining the claimed DNA and "attempt[ed] to preempt the future before it has arrived").

each specifies attributes that are met by the M313K modified $PH20_{1-447}$ polypeptide, or involve issues taught or suggested by the '429 Patent alone or with other prior art.

A. The Prior Art

The '429 Patent (EX1005) is owned by Patentee, was originally filed in 2003, and issued on Aug 3, 2010.

Chao (EX1006) is an article published in the scientific journal "Biochemistry" in 2007. Chao is not discussed in the common disclosure of the '298 Patent and '731 Application, and was not cited or considered during examination of either.

Knowledge of the skilled artisan relevant to obviousness is described in the testimony of Drs. Hecht (EX1003) and Park (EX1004), and is also documented in the prior art, including Patentee's earlier-published application, WO297 (EX1007).

B. Because M313K $PH20_{1-447}$ Would Have Been Obvious, Claims 1-4 Are Unpatentable

As explained below, Patentee's '429 Patent would have motivated a skilled artisan to produce modified $PH20_{1-447}$ polypeptides having a single amino acid substitution in a non-essential region of the protein. That person, guided by her familiarity with conventional rational protein design principles and the teachings of the '429 Patent and Chao, would have readily identified single amino acid substitutions in non-essential regions of PH20 that would be tolerated by the PH20

protein, such that the PH20 with the substitution would be expected to substantially retain its enzymatic activity. This process would have led the skilled artisan to identify M313K as one such single-amino acid substitution in $PH20_{1-447}$ that would be expected to retain hyaluronidase activity. Because claims 1-4 each encompass this obvious variant of $PH20_{1-447}$, each is unpatentable.

1. Patentee's '429 Patent Motivates a Skilled Artisan to Make Single Amino Acid Substitutions in Non-Essential Regions of $PH20_{1-447}$

Patentee's '429 Patent, filed in 2003, describes as its invention soluble hyaluronidase glycoproteins ("sHASEGPs") based on PH20 that are enzymatically active at neutral pH.[222] It exemplifies and claims one such "sHASEGP" produced by truncating the human PH20 sequence at position 447 (positions 36-482 of SEQ ID NO: 1).[223]

The '429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, when combined with other therapeutic agents, and specifically illustrates administering such combinations subcutaneously to treat

[222] EX1005, 6:4-10, 10:30-59.

[223] EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

diseases including cancer.[224] A $PH20_{1-447}$ was approved by the FDA as Hylenex® in 2005.[225]

The '429 Patent's teachings combined with the status of $PH20_{1-447}$ as an approved human therapeutic before 2011 would have induced a skilled artisan to focus on this particular PH20 polypeptide.[226]

Patentee's '429 Patent defines sHASEGPs as not only being the wild-type $PH20_{1-447}$ sequence, but as also including "equivalent" proteins "with amino acid substitutions that do not substantially alter activity" of the protein.[227] It then expands on this guidance, explaining:

> Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in

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224 EX1005, 8:25-9:4, 56:36-43, 56:56-57:36, 63:41-61, 74:10-29, 76:19-77:36, 99:28-100:47.

225 EX1049, 1.

226 EX1003, ¶ 195.

227 EX1005, 9:65-10:13; *see also id.* at 18:64-19:6 ("equivalent" proteins).

> non-essential regions of a polypeptide do not substantially alter biological activity …[228]

The ’429 Patent explains that single amino acid substitutions can include “conservative” substitutions in Table 1, but that “[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions.”[229] Notably, however, lysine is specifically identified as one of the exemplified “conservative” substitutions that Table 1 of the ’429 Patent suggests for methionine in these non-essential positions of PH20.[230]

The ’429 Patent thus teaches making a ***particular*** type of modification (a single amino acid substitution) at a ***particular*** location (non-essential regions of PH20) in a ***particular*** PH20 sequence ($PH20_{1-447}$) to yield equivalents of $PH20_{1-447}$ (*i.e.*, those that do not substantially alter the activity or function of $PH20_{1-447}$).[231]

The ’429 Patent also motivates skilled artisans to undertake this effort to design and produce such single-amino acid substituted $PH20_{1-447}$ proteins because

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228 EX1005, 16:14-22.

229 EX1005, 16:24-36.

230 *Id.*; EX1003, ¶ 204.

231 EX1003, ¶¶ 202-204; EX1004, ¶ 32.

it assures them their efforts will be successful.[232] As it states, skilled artisans recognized that such "single amino acid substitutions in non-essential regions" of $PH20_{1-447}$ "do not substantially alter biological activity" of $PH20_{1-447}$. As such, a skilled artisan would have expected a $PH20_{1-447}$ mutant with a single amino acid substitution in a non-essential region to have the same utility and therapeutic applications that the '429 Patent identifies for wild-type $PH20_{1-447}$ and other sHASEGPs.[233]

2. Chao Provides Information Useful for Engineering the Changes to $PH20_{1-447}$ that the '429 Patent Suggests

In 2011, a skilled artisan looking to implement the '429 Patent's suggestion to make a single-amino acid modification in a non-essential region of $PH20_{1-447}$ would have recognized this type of change could best be accomplished using conventional rational design techniques, which involves determining (i) which regions are non-essential in PH20, and (ii) which single amino acids to substitute into positions in those non-essential regions.[234]

The '429 Patent was written eight years before 2011. Given that, a skilled artisan would have looked for additional published insights into the structure of

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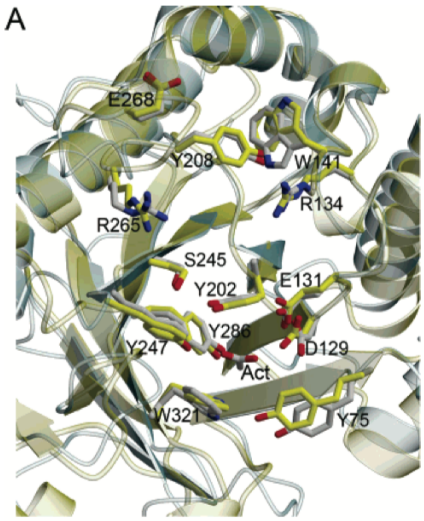
232 EX1003, ¶¶ 203-204.

233 EX1003, ¶¶ 199, 203, 218.

234 EX1003, ¶¶ 209-10.

human hyaluronidase enzymes like PH20.[235] That would have led the person directly to Chao (EX1006), which reported an experimentally determined structure for human HYAL1, and provided new insights into the shared characteristics of human hyaluronidase enzymes.[236]

First, by superimposing the HYAL1 and bee venom hyaluronidase structures, Chao showed that human and non-human hyaluronidases share a highly conserved catalytic active site structure and identified residues within this catalytic site that interact with the HA substrate.[237]



235 EX1003, ¶¶ 86, 205; EX1004, ¶ 88.

236 EX1003, ¶¶ 86, 205-207; EX1004, ¶ 88; EX1006, 6912-17.

237 EX1006, 6917 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1004, ¶¶ 89-91; EX1003, ¶¶ 81-82.

The ’429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20.[238] It also taught that hyaluronidase domains share similarity among and between species, including certain residues in conserved motifs necessary for enzymatic activity.[239]

Second, using an alignment of five human hyaluronidases, Chao identifies predicted secondary structures in the proteins (*e.g.*, β-sheets, α-helices) (Figure 3, below), as well as, invariant conserved positions (blue), residues involved in catalysis (red), conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).[240]

[238] EX1005, 4:12-22, 86:49-53, 88:14-24.

[239] EX1005, 2:6-67, 4:11-22.

[240] EX1006, 6916; EX1003, ¶ 83; EX1004, ¶¶ 92.

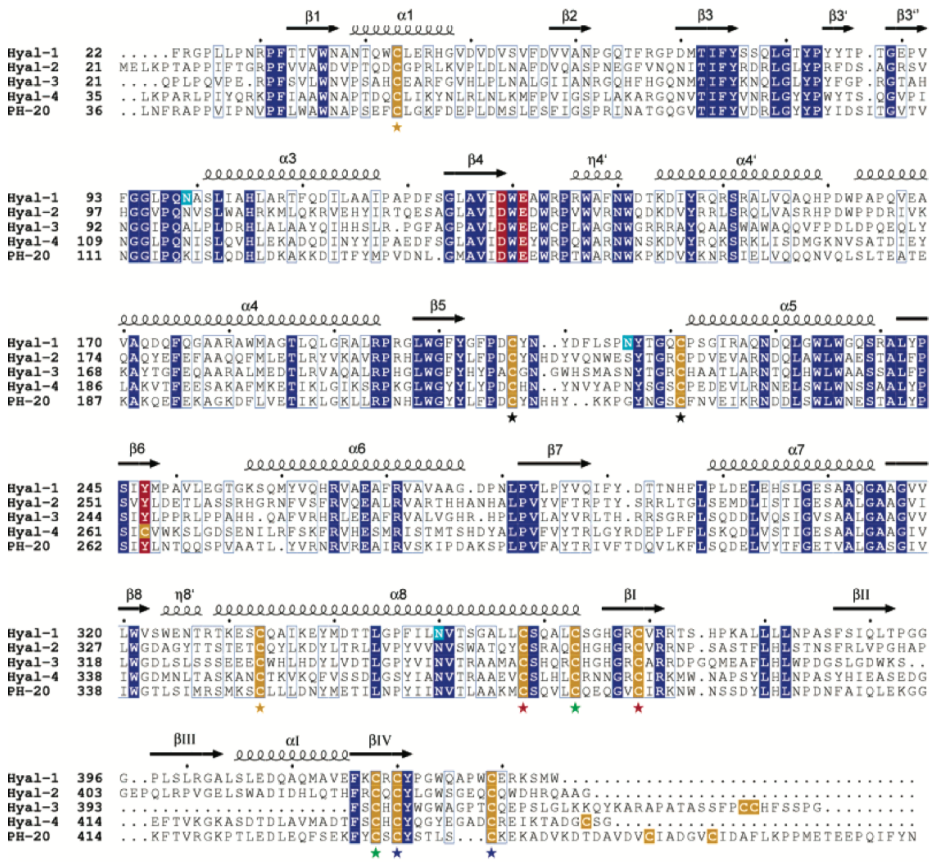


FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative replacements are blocked in blue. Pairs of cysteine residues that form disulfide bonds are indicated by stars with matching colors. Secondary structure units are labeled as in Figure 2B.

Third, Chao reported the presence of "a novel, EGF-like domain" in the C-terminal region of human hyaluronidases that was "closely associated" with the catalytic domain (discussed above, § V.A.2.cV.A.2.c). Of note here, Chao identifies a characteristic pattern for the Hyal-EGF domain in PH20 (at 337-409).[241]

241 EX1006, 6912; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84-85.

3. A Skilled Artisan Would Have Identified M313K as Being in a Non-Essential Region of $PH20_{1-447}$ in 2011

To implement the '429 Patent's suggestion to produce modified $PH20_{1-447}$ polypeptides with single amino acid substitutions in non-essential regions that retain hyaluronidase activity, the skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011.[242] The person would have done that using conventional sequence alignment tools in conjunction with the information in the '429 Patent and in Chao, as well as information publicly known in 2011.[243]

The multiple sequence alignment identifies the non-essential regions in PH20—they are the sequences between essential residues containing positions at which variations occur at a frequency above ~5% (illustrated in Chao for five homologous human hyaluronidase sequences below).[244]

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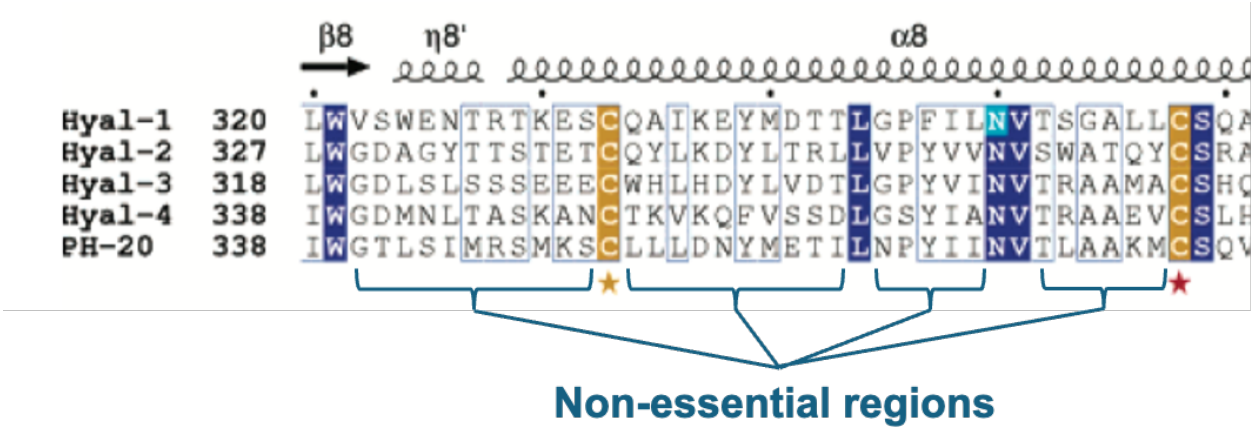
[242] EX1003, ¶¶ 208-210; EX1004, ¶¶ 22, 25-30, Appendix D-3.

[243] EX1003, ¶¶ 20-21, 209-211; EX1004, ¶¶ 22-24; EX1017, 224-26.

[244] EX1004, ¶¶ 31-32, Appendix D-2; EX1003, ¶ 211; EX1006, 6916.

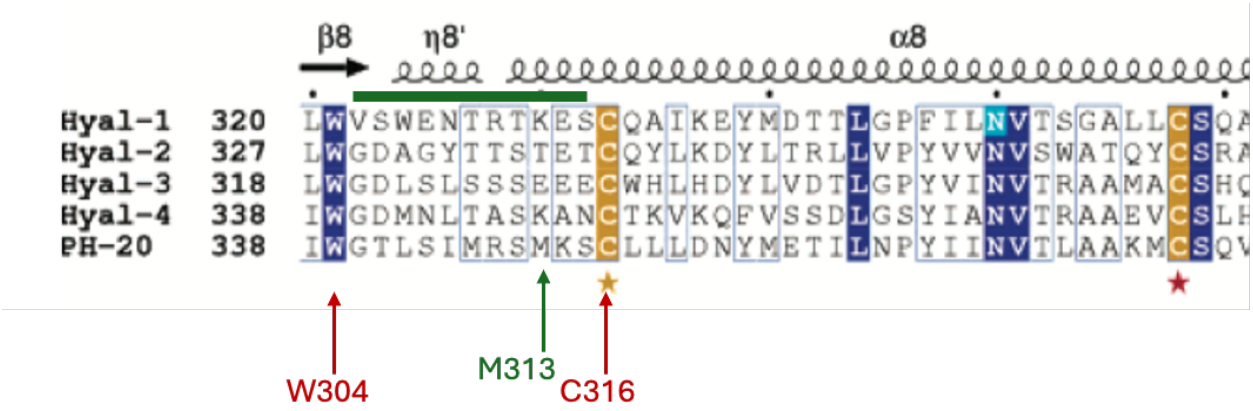


Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps on a set of 88 homologous hyaluronidase protein sequences he identified that had been published by December 29, 2011.[245] Dr. Park then prepared a multiple-sequence alignment of these 88 homologous proteins, similar to what Chao did with the five human hyaluronidases, and from that alignment identified essential (Appendix D-3) and non-essential (Appendix D-2) residues.[246]

[245] EX1004, ¶¶ 27, 149-152; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

[246] EX1004, ¶¶ 28-32, 153-154, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

Position 313 is within a non-essential region of $PH20_{1-447}$, which is shown not only by Dr. Park's analysis, but also by Chao's Figure 3; both report the same bounding essential residues (*i.e.*, W304 and C316) (below).[247]



Thus, following the guidance and information in the '429 Patent and Chao, and assessing information publicly available in December 2011 using conventional sequence analysis tools, a skilled artisan would have readily identified position 313 as a position in a non-essential region $PH20_{1-447}$.[248]

4. A Skilled Artisan Would Have Found Lysine to Be Suggested as an Obvious Single Amino Acid Substitution at Position 313 of $PH20_{1-447}$

The multiple-sequence alignment reveals a second powerful insight: it identifies ***which*** amino acids have been tolerated at specific positions in the amino

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247 EX1003, ¶ 213; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.

248 EX1003, ¶ 216; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

acid sequence of homologous, stable and active naturally occurring hyaluronidase enzymes.[249] This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms those variations in the sequences of a protein that do not yield stable and active forms of the protein.[250] Thus, a skilled artisan can readily compile a list of the specific amino acids that have been tolerated at positions within non-essential regions of PH20 using a multiple-sequence alignment of homologous hyaluronidase enzymes.[251]

Dr. Park did this; he used the alignment he produced of the 88 hyaluronidase proteins known by December 2011 to identify and calculate the frequency of

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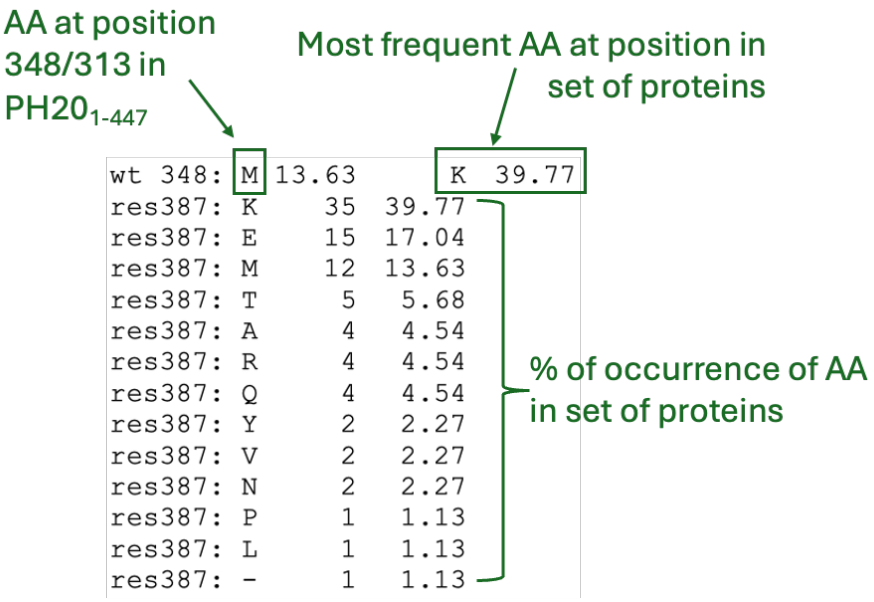
[249] EX1003, ¶¶ 20, 49, 210, 214, 216; EX1004, ¶ 21-22.

[250] EX1003, ¶¶ 20, 210; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 ("Evolution provides a tremendously useful model for protein design. … By considering the common features of the sequences of these proteins, it is possible to deduce the key elements that determine protein structure and function—even in absence of any explicit structural information."); EX1014, 351.

[251] EX1003, ¶¶ 214, 216; EX1004, ¶ 21-22.

occurrence of each different amino acid that occurs at positions corresponding to each position in the non-essential regions of $PH20_{1-447}$.[252]

The amino acids appearing at position 313 of PH20 in the corresponding positions of the 88 naturally occurring hyaluronidase enzymes known by 2011 are shown below.[253] The wild-type residue at position 313 in PH20 is methionine (M), which occurs in ~14% of the proteins (including PH20). As shown, the most prevalent amino acid found at position 313 in this set of homologous sequences is lysine (K) (~40%), which is present in 35 different hyaluronidase proteins.



Several amino acids other than methionine occur with significant frequency at a position corresponding to 313 in PH20 in known, homologous hyaluronidase

252 EX1004, ¶¶ 30-32, 41-43, Appendix D-1.

253 EX1003, ¶ 214; EX1004, ¶¶ 43, 113, Appendix D-1.

enzymes.[254] A skilled artisan would have believed those amino acids would be the obvious choices to assess as single amino acid substitution for position 313 of $PH20_{1-447}$.[255]

More directly, a skilled artisan would have had specific reasons to substitute lysine (K) for methionine (M) at position 313 as a single amino acid substitution in a non-essential region of $PH20_{1-447}$.

First, lysine is the most prevalent amino acid at the position corresponding to position 313 in PH20 in the set of 88 homologous hyaluronidase enzymes known in 2011—it occurs in nearly 40% of those proteins (35 different naturally occurring hyaluronidase enzymes) and in 2 of the 5 human hyaluronidases.[256] The high frequency with which lysine occurs in this position makes it an obvious candidate for being incorporated into position 313 of PH20, as it is tolerated in many naturally occurring hyaluronidase enzymes.[257]

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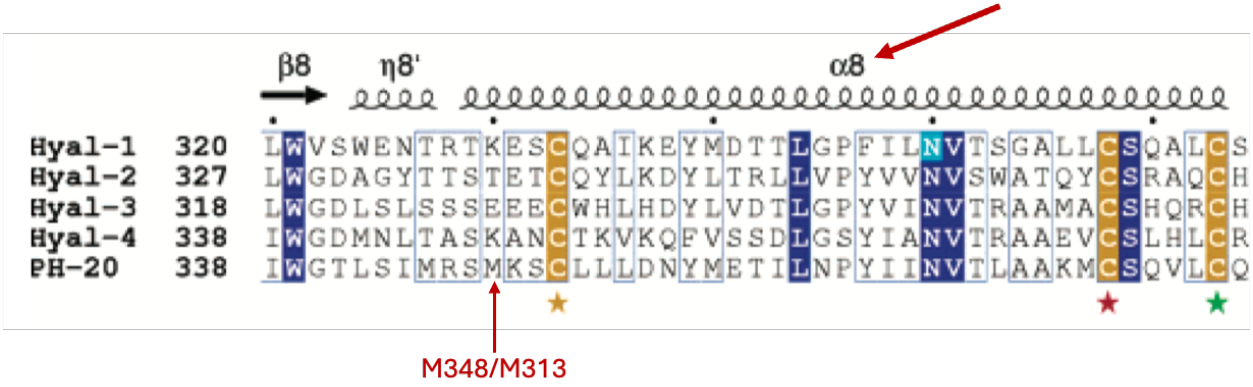
254 EX1004, ¶ 106.

255 EX1003, ¶¶ 210, 214, 216-17; EX1004, ¶¶ 41-42 106.

256 EX1004, ¶¶ 43, 106, 113; EX1003, ¶ 214.

257 EX1003, ¶¶ 214, 216-17; EX1004, ¶ 113.

Second, lysine was known to have a high helix propensity, meaning it is favored in sequences that form α-helix secondary structures.[258] Chao identified the "α8" helix sequence as one such α-helix forming sequence in PH20, and position 313 of PH20 is at the beginning of that α8 helix sequence (below).[259] Given its high propensity for supporting α-helix secondary structures, a skilled artisan would have viewed lysine as a logical (and thus obvious) substitution for methionine at position 313, given its location within the α8 helix sequence in $PH20_{1-447}$.[260]



Third, the '429 Patent specifically identifies lysine as an example of a conservative amino acid substitution for methionine in non-essential regions of

[258] EX1050, 422-24, Table 2; EX1003, ¶¶ 215; EX1004, ¶¶ 69-70, 117.

[259] EX1006, 6916, Figure 3; EX1003, ¶ 192, 215; EX1004, ¶¶ 32, 108.

[260] EX1003, ¶ 215; EX1004, ¶¶ 32, 108, 117-118.

proteins like PH20.[261] A skilled artisan would find lysine to be an alternative to methionine pursuant to this guidance in the '429 Patent.[262]

For all of the reasons above, a skilled person would have found it obvious change the methionine (M) at position 313 to lysine (K) in $PH20_{1-447}$.[263]

5. A Skilled Artisan Would Have Reasonably Expected the M313K Substitution in $PH20_{1-447}$ Would Yield an Enzymatically Active PH20 Protein

a) Patent Owner Cannot Contradict Its Past Representations to the PTO

Replacing the methionine (M) at position 313 with lysine (K) yields a $PH20_{1-447}$ with a single amino acid substitution in a non-essential region of the polypeptide.[264] In its '429 Patent, Patentee stated:

> Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.[265]

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261 EX1005, 16:4-32, Table 1, 10:9-13.

262 EX1003, ¶¶202-204.

263 EX1003, ¶¶ 213-216.

264 *See* § VI.B.3; EX1003, ¶¶ 213-14; EX1004, ¶ 32.

265 EX1005, 16:17-20.

Patentee also represented in its '429 Patent that "conservative substitutions, such as those set forth in Table 1 … do not eliminate proteolytic activity" and listed lysine for methionine as one such "conservative substitution."[266]

Patentee then secured claims in the '429 patent to modified $PH20_{1-447}$ proteins with at least one substitution (*e.g.*, claim 1), even though it provided no examples of any PH20 proteins with any substitutions. Patentee, thus, made and relied on its affirmative statements that a skilled artisan would have expected ***any*** single amino acid substitution in ***any*** non-essential position of $PH20_{1-447}$ to not substantially affect the biological activity of the enzyme, and particularly ones listed in Table 1. Patentee should not be permitted to change its position now and contend that a skilled artisan would not have reasonably expected that making the M313K substitution in $PH20_{1-447}$ would yield an enzyme with substantially the same activity as unmodified $PH20_{1-447}$.

b) Skilled Artisans Would Reasonably Expect M313K to be Tolerated in $PH20_{1-447}$

Independently, a skilled artisan would have reasonably expected that the M313K substitution in $PH20_{1-447}$ would not substantially alter the biological activity (hyaluronidase activity) of $PH20_{1-447}$.

[266] EX1005, 16:7-9, 27-32.

Both experts noted that many naturally occurring homologous hyaluronidase proteins contain lysine at the position corresponding to position 313 in PH20.[267] The high frequency of occurrence of lysine at positions equivalent to 313 in naturally-occurring hyaluronidases, including in 2 of 4 human homologs of PH20 (Chao), along with lysine's high helix propensity, would have led a skilled artisan to reasonably expect the M313K substitution would be tolerated in $PH20_{1-447}$.[268]

c) The PH20 Structural Model Confirms that $PH20_{1-447}$ Would Tolerate Lysine at 313

Dr. Park further assessed whether a variety of single amino acid substitutions in $PH20_{1-447}$ would be tolerated, such as the M313K substitution, using a PH20 protein structural model generated by SWISS-MODEL from Chao's HYAL1 structure as the template, as would have been done in 2011 by a skilled artisan.[269]

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[267] EX1003, ¶ 214; EX1004, ¶ 113.

[268] EX1003, ¶¶ 217-218; EX1006, 6916.

[269] EX1004, ¶¶ 39-40, 156; EX1003, ¶ 221, 223; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

Dr. Park explains that the PH20 model he used was reliable in the region of position 313 of PH20 based on QMEAN values,[270] and would be very similar to a PH20 model generated by SWISS-MODEL in 2011 (*e.g.*, because it used 165 conserved positions in the backbone of the two proteins).[271]

Dr. Park also devised a consistent, objective methodology for assessing substitutions using the $PH20_{1-447}$ model.[272] Factors he considered included, *inter alia*, the number of neighboring residues at position 313 (*i.e.*, those within 5 Å), the various types of possible interactions between neighbors (*e.g.*, hydrophobic, charged, van der Walls, steric, etc.), and solvent accessibility.[273] Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*,

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[270] EX1004, ¶¶ 157-59 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

[271] EX1004, ¶¶ 160-161, 165; EX1038, 3382-4; EX1017, 229-230; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

[272] EX1004, ¶¶ 102-103; *see generally id.* at § IV.C (description of Dr. Park's methodology).

[273] EX1004, ¶¶ 44-47, 53-60, 65-85, Appendix D-5; EX1035, 1408, Table 2; EX1043, 2, Table 1.

hydrophobic-hydrophilic, effects on secondary structures, size related issues such as steric clashes or creation/filling of "holes" in the structure).[274]

Dr. Park assessed the environment of position 313 visually by comparing the wild-type with the version incorporating substituted amino acids at position 313 using functionality within the viewer (PyMol) and as a modeled sequence generated from the $PH20_{1-447}$ sequence incorporating the single substitution in SWISS-MODEL.[275] Again, these technologies were available in 2011.[276] He used his methodology to assess numerous substitutions representing diverse interactions, and confirmed that it provided a consistent, objective and unbiased evaluation of substitutions throughout the protein.[277]

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed (below).[278]

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274 EX1004, ¶¶ 62-63, 85.

275 EX1004, ¶¶ 61, 107, 115, 165-66; EX1003, ¶ 22, 49, 221, 223.

276 EX1004, ¶¶ 155, 160, 165-66, 171-172; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4.

277 EX1004, ¶¶ 102-103.

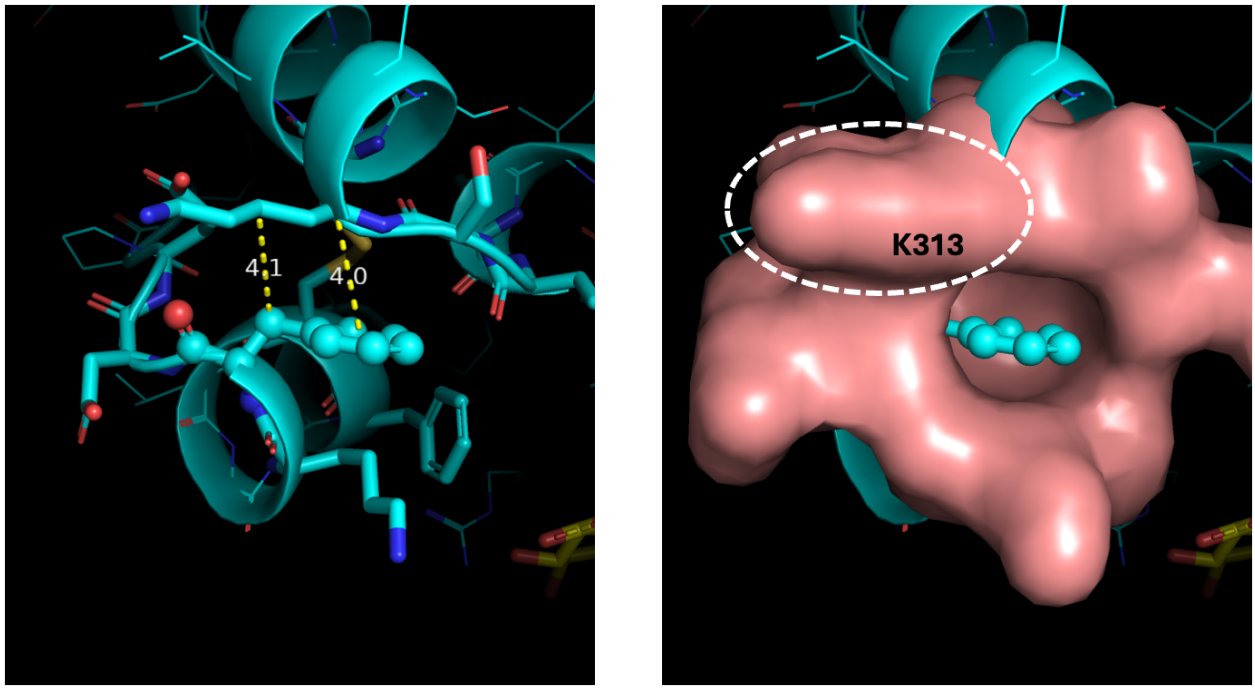
278 EX1004, ¶¶ 85-87.

Score	***Expected Impact***	***Expected Toleration***
1	Significantly Destabilized	Likely Not Tolerated
2	Neutral or Minor Impacts	Tolerated
3	Improved Stability	Tolerated

Dr. Park assigned a score of 3 for the M313K substitution in $PH20_{1\text{-}447}$, indicating that the substitution would be expected to confer improved stability.[279] He observed that in the wild-type environment, position 313 contributes to a hydrophobic pocket around the phenylalanine (F) at position 29, but that position 313 also has a high solvent exposure.[280] He found that while lysine and methionine have chemically different classifications, lysine within the environment of position 313 would be seen as a conservative substitution as it maintains several structural roles of methionine at that position (below).

[279] EX1004, ¶ 118-120, Appendix C.

[280] EX1004, ¶¶ 108-11.



First, due to their similar aliphatic side-chains, when lysine is substituted for methionine at position 313, it maintains the three interactions that occur between the C-α, C-β and C-γ carbons of methionine with phenylalanine at position 29.[281] Also, the C-α through C-γ atoms in lysine (like in methionine) help form a solvent-limited pocket around PH20 through interactions with F29 and H47, which is also comparable to lysine's role at position 330 in HYAL1.[282] Second, the terminus of lysine is hydrophilic, making it more compatible in a solvent environment than the thiol group in methionine, and it may also form a salt-bridge with glutamic acid (E)

[281] EX1004, ¶ 118.

[282] *Id*.

at position 66.[283] Dr. Park thus concluded that because the net effect of the interactions associated with substituting lysine for methionine at position 313 in $PH20_{1-447}$ would be stabilizing, the M313K substitution in $PH20_{1-447}$ would be tolerated and thus expected to retain the hyaluronidase activity of the unmodified $PH20_{1-447}$.[284]

Dr. Park's visualization-based assessment is a technique that was prevalent in 2011.[285] Similarly, his technique of assessing interactions between neighbors and assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications (*e.g.*, Dr. Moult's

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283 EX1004, ¶ 119.

284 EX1004, ¶ 120.

285 EX1017, 228 ("… a structural biologist's intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this."); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 22, 49, 221, 223.

group reported using this technique to assess single substitutions caused by single-nucleotide polymorphisms, and classified the net effects on a 3-point scale).[286]

Dr. Hecht reviewed Dr. Park's analysis and conclusions, and agreed with both.[287] Through his own assessment, he observed that lysine substituted into position 313 would have a stabilizing effect due to (i) the compatibility of the shape of lysine with the solvent-exposed pocket at that location, and (ii) the fact that the M313K substitution would introduce a hydrophilic residue (L) into a solvent-exposed position in the protein, all without disturbing pre-existing interactions with neighboring amino acids.[288]

The common disclosure defines an "active mutant" as a modified PH20 polypeptide with as little as 40% of the activity of unmodified $PH20_{1-447}$.[289] Dr. Hecht and Dr. Park each independently concluded that the M313K substitution would have been tolerated by $PH20_{1-447}$, meaning it would exhibit comparable

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286 EX1004, ¶¶ 48-52; EX1031, 439, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 223.

287 EX1003, ¶¶ 225.

288 EX1003, ¶¶ 226-227.

289 EX1001, 74:11-16; *also id.* at 77:61-65.

hyaluronidase activity to unmodified $PH20_{1-447}$ (*i.e.*, activity well above 40%).[290] A skilled artisan considering the M313K substitution in $PH20_{1-447}$ thus would have reasonably expected the M313K $PH20_{1-447}$ mutant would exhibit comparable activity to unmodified $PH20_{1-447}$ protein.[291]

Based on the '429 Patent, Chao, and information available in 2011, the M313K $PH20_{1-447}$ mutant polypeptide would have been obvious to a skilled artisan in 2011. And because claims 1-4 each encompass the single-replacement modified M313K $PH20_{1-447}$ polypeptide, each claim is unpatentable.

C. Dependent Claims 7-19 and Claims 20-22 Are Obvious

None of the dependent claims or claim 22 define subject matter that is independently patentable from claims 1-4. For the reasons below, each would have been obvious to a skilled artisan.

1. Claims 7-9

Claims 7-9 require the modified PH20 polypeptide to "comprise[] one or more modifications" including glycosylation (claims 7-8) and be a "glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine residues" (9).

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290 EX1003, ¶¶ 225-27, 229; EX1004, ¶¶ 115-120.

291 EX1003, ¶ 229.

The ’429 Patent teaches (i) that human PH20 must be glycosylated to exhibit activity, and (ii) expression of $PH20_{1-447}$ in mammalian (CHO) host cells that yield active forms of $PH20_{1-447}$.[292] It further teaches that “N- and O-linked glycans are attached to polypeptides through asparagine-N-acetyl-D-glucosamine … linkages,” and claims PH20 polypeptides (including $PH20_{1-447}$) having asparagine-linked sugar moieties.[293] Frost reports that the recombinant production of $PH20_{1-447}$ in CHO cells “resulted in a 447 amino acid 61 kDA glycoprotein with a properly processed amino terminus and 6 N-linked glycosylation sites.”[294]

Based on the ’429 Patent and knowledge in the art, a skilled artisan would have found it obvious to produce M313K $PH20_{1-447}$ in a CHO cell, and that doing so causes six N-linked glycosylation sites to be glycosylated.[295]

2. Claims 10-12 and 22

Claims 10-12 broadly specify a nucleic acid encoding any modified PH20 polypeptide of claim 1, an expression vector comprising that nucleic acid, and a host cell comprising that vector. Claim 22 similarly claims methods of

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292 EX1005, 95:13-30; 40:41-51, 89:53-91:67; 88:5-9.

293 EX1005, 3:27-35, claims 1, 6.

294 EX1013, 432.

295 EX1003, ¶¶ 197-98, 200-201.

recombinantly producing a genus that includes M313K $PH20_{1-447}$ by transfecting a plasmid containing a cDNA encoding it into a host cell, culturing the cells, and harvesting the protein from the cell culture.

The '429 Patent teaches the recombinant production of $PH20_{1-447}$ in CHO cells comprising (i) preparing a nucleic acid encoding $PH20_{1-447}$, (ii) inserting it into a plasmid expression vector, and (iii) transfecting CHO cells with the plasmid to produce the $PH20_{1-447}$ protein.[296] It also teaches "nucleic acid molecules that encode a polypeptide … that have at least" 95% sequence identity with a full length PH20 (*i.e.*, up to 22+ substitutions).[297]

From their training and experience, and the guidance in the '429 Patent, a skilled artisan would have found it obvious to prepare and insert into a plasmid a nucleic acid encoding a single-replacement (*e.g.*, M313K) $PH20_{1-447}$, transfect a CHO host cell with it, express and then harvest the protein from the cell culture.[298] For example, Arming and Zhang both reported recombinant production of single-substitution forms of active soluble PH20 polypeptides.[299]

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296 EX1005, 89:54-90:15, 90:19-91:67.

297 EX1005, 11:60-66.

298 EX1003, ¶¶ 198, 200.

299 EX1011, 810-11; EX1010, 9433-35.

3. Claims 13-21

Claims 13-21 specify a pharmaceutical composition comprising any modified PH20 polypeptide in the genus of claim 1, alone (claim 13) or in combination with a therapeutic agent (14), several genera of agents, (15) an antibody (16), and "a small molecule drug" (17). Claims 18 and 19 concern methods of administering the compositions of claim 14 (18) and doing so subcutaneously (19). Claims 20 and 21 concern methods of treating cancer by administering the composition of claim 14 to a patient (claim 20) including a patient being treated with an anticancer drug (21).

The '429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*, $PH20_{1-447}$), alone or in combination with other therapeutic agents including antibodies, small molecule drugs, and agents used in treating cancer.[300] It similarly describes and claims methods of administering them subcutaneously via formulations that combine an enzymatically active hyaluronidase protein with the

[300] EX1005, 8:60-9:4, 54:52-55:35, 56:28-57:21, 55:61-56:9, 56:66-57:21, 73:4-74:29, claims 14, 29, 33.

other therapeutic agent, which together enable "spreading" of the therapeutic agent after injection.[301]

A skilled artisan would have appreciated that a single-replacement $PH20_{1-447}$ polypeptide with comparable hyaluronidase activity to $PH20_{1-447}$ (such as the M313K mutant) would be equivalently useful in the therapeutic compositions, methods of administration, and methods of treatment described in the '429 Patent for $PH20_{1-447}$.[302] Indeed, in the '429 Patent, Patentee secured claims encompassing pharmaceutical compositions containing certain modified PH20 polypeptides and chemotherapeutic agents despite the absence of any exemplification.[303] Claims 13-21 also impose no restrictions on the makeup of the pharmaceutical compositions, and claim only categories of therapeutic agents. A skilled artisan would have found such agents and methods of administration and treatment to have been obvious from the '429 Patent for the above reasons.[304]

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301 EX1005, 8:25-38, 56:28-56, 57:22-36, 58:59-59:12, 63:40-64:4, 76:18-77:37, claim 27.

302 EX1003, ¶¶ 199, 203, 217-18, 229.

303 EX1005, claims 29, 30, 50.

304 EX1003, ¶¶ 199, 203.

D. There Is No Nexus Between the Claims and Any Evidence of Putative Secondary Indicia

Well-established law holds that evidence of secondary indicia cannot support non-obviousness if it does not have nexus to the claims. A key question in a nexus analysis is whether such evidence is commensurate with the scope of the claims. The answer here is a definitive no.

Patentee is likely to dispute that the M313K $PH20_{1-447}$ is obvious because it is reported to have unexpectedly high hyaluronidase activity as a single substitution mutant. Demonstrating that result for one mutant out of the ~10^{49}-10^{66} modified PH20 polypeptides encompassed by the claims, however, utterly fails to establish a nexus between that evidence and the claims. As explained above, the single-substitution M313K $PH20_{1-447}$ is not representative of the numerous, structurally different proteins that are encompassed by the claims, particularly those that would be expected to be inactive. *See* § V.A.2. No evidence or explanation is provided in the common disclosure that resolves this confusion.

Petitioner submits that if Patentee advances evidence or arguments concerning a nexus, consideration of that issue should be deferred until after institution. Petitioner otherwise reserves its right to contest such evidence.

VII. The Board Should Not Exercise Its Discretion Under § 324(a) or § 325(d)

Discretionary denial is assessed using the factors set forth in *Apple Inc. v. Fintiv, Inc.,* IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020). None weigh in favor of denial as there is currently no parallel litigation regarding the '298 Patent.

Also, during examination, no patentability issues relevant to the grounds were considered.[305] Notably, Chao was not cited to the Office, and the Examiner did not have the benefit of Dr. Hecht or Dr. Park's detailed expert testimony. The Examiner also did not consider Petitioner's § 112 arguments regarding the lack of support for the immense genus of claimed modified PH20 polypeptides (or any substantially similar arguments) during prosecution.[306] Rather, the first § 112 rejection concerned whether a dependent claim to a soluble PH20 polypeptide was further limiting, which was mooted when the Applicant cancelled the claim.[307] The second concerned whether an independent pharmaceutical composition claim

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[305] The Examiner's double patenting rejections were mooted by the filing of terminal disclaimers, not on the merits. *Supra* § IV.C.

[306] *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7-11 (P.T.A.B. Feb. 13, 2020).

[307] EX1002, 436-39, 555-57.

and its dependent claims were definite, which was withdrawn after the Applicant amended the independent claim to cover only a single composition.[308]

VIII. CONCLUSION

For the foregoing reasons, the challenged claims are unpatentable.

Dated: November 26, 2024

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[308] EX1002, 440, 531, 555-57.

EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,018,298
1002	File History of U.S. Patent No. 12,018,298
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Brandon & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '298 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," Methods in Enzymology, 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," Protein Eng'g & Design, Ch. 10, 223-237 (2010)
1018	Chica et al., "Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design," Curr. Opin. Biotechnol., (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," Reprod., 127:325-334 (2004)
1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," Am. J. Reprod. Immunol., (3):174-82 (2002)
1021	Baba et al., "Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg," J. Biol. Chem., 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," Biol Reprod., 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 56(5):1133-41 (1997)
1024	Rosengren et al., "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects," BioDrugs, 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	[Reserved]
1028	[Reserved]
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," FEBS Letters, 3:545-548 (1993)

No.	Exhibit Description
1030	Sills, "Retraction," Science, 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," J. Mol. Biol., 353:459-473 (2005)
1032	Wang & Moult, "SNPs, Protein Structure, and Disease," Hum. Mutation, 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," Structure, 8:1025-1035 (2000)
1034	"Negative Results," Nature: Editorials, 453:258 (2008)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," Protein Sci., 12:1406-1417 (2003)
1036	Hayden, "Chemistry: Designer Debacle," Nature, 453:275-278 (2008)
1037	Benkert et al., "Toward the Estimation of the Absolute Quality of Individual Protein Structure Models," Bioinformatics, 27:343-350 (2010)
1038	Schwede et al., "SWISS-MODEL: An Automated Protein Homology-Modeling Server," Nucleic Acids Rsch., 31:3381-3385 (2003)
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007).
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," PNAS, 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," PNAS, 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," Nature Comm., 14 (2023)
1043	Sievers et al., "Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega," Molecular Sys. Biology, 7.1 (2011)
1044	Mihel, "PSAIA – Protein Structure and Interaction Analyzer," BMC Structural Biology, 8:21 (2008)

No.	Exhibit Description
1045	Redline Comparison of the ’731 and ’298 Specifications
1046	Beasley & Hecht, “Protein Design: The Choice of *de Novo* Sequences,” J. Biological Chemistry, 272:2031-2034 (1997)
1047	Xiong et al., “Periodicity of Polar and Nonpolar Amino Acids is the Major Determinant of Secondary Structure in Self-Assembling Oligomeric Peptides,” PNAS, 92: 6349-6353 (1995)
1048	Hayden, “Key Protein-Design Papers Challenged,” Nature, 461:859 (2009)
1049	KEGG, *DRUG: Hyaluronidase (human recombinant)*, available at: https://www.genome.jp/entry/D06604
1050	Pace & Scholtz, “A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins,” Biophysical J. 75:422-427 (1998)
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
1057	Ph20_pre2011.aln-clustal_num
1058	Ph20_pre2011 Alignment html
1059	Leisola & Turunen, “Protein Engineering: Opportunities and Challenges,” Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	Hecht et al., “De Novo Proteins from Designed Combinatorial Libraries,” Protein Sci., 13:1711-1723 (2004)
1061	Rosengren et al., “Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration,” AAPS J., 17:1144-1156 (2015)
1062	[Reserved]
1063	[Reserved]

No.	Exhibit Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with M313K Mutation
1071	Swiss Model Printout of PH20 Model with M313A Mutation
1072	Swiss Model Printout of PH20 Model with M313R Mutation
1073	Swiss Model Printout of PH20 Model with M313Y Mutation
1074	Swiss Model Printout of PH20 Model with M313P Mutation
1075	Swiss Model Printout of PH20 Model with M313L Mutation

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,676 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

Dated: November 26, 2024

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 26th day of November, 2024, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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Paper No. 1

Filed: November 12, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00003
U.S. Patent No. 11,952,600

PETITION FOR POST GRANT REVIEW

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I. Introduction

Petitioner Merck Sharp & Dohme LLC ("Merck") requests post grant review of claims 1-21 of U.S. Patent No. 11,952,600 ("'600 Patent").

The '600 Patent claims are unpatentable for three independent reasons.

The first two are linked to the extreme breadth of the claims, which encompass between 10^{49} and 10^{65} different mutated forms of an enzymatically active human hyaluronidase protein called PH20. That breadth results from the unconstrained language in claims 1 to 4, which each define a genus of PH20 polypeptides that ***requires one*** amino acid substitution at position 320, but then ***permits*** (via sequence identity language) up to 16, 20, 21, or 22 additional substitutions at ***any*** of between 430 and 465 positions of PH20, and to ***any*** of 19 other amino acids. The scale of this genus is unfathomable. A set containing one molecule of each polypeptide in one genus would dwarf the weight of the Earth, and using the iterative methodology the patent describes, would take a skilled artisan many lifetimes to "make-and-test."

These immensely broad claims, measured against the common disclosure of the '600 Patent and its ultimate parent '731 Application[1], utterly fail to satisfy the written description and enablement requirements of § 112(a). That deficiency renders every claim of the '600 Patent unpatentable. It also precludes those clams

[1] 13/694,731 ('731 Application) (EX1026).

from a valid § 120 benefit claim to the ’731 Application, the only non-provisional application filed before March 16, 2013, thus making the ’600 Patent PGR eligible.

First, regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by enzymatically active, multiply-modified PH20 polypeptides within each claimed genus. The disclosed examples also are plainly not representative of that gargantuan and structurally diverse genus: every disclosed mutant has only ***one*** amino acid substitution in ***one*** PH20 sequence (1-447), while the claims encompass myriad structural variants of PH20, resulting from incorporation of innumerable, ***undescribed*** combinations of 5, 10, 15 or 20+ substitutions anywhere in the PH20 sequence. The claims even capture mutated PH20 polypeptides the disclosure says to exclude, such as those which rendered the original PH20 inactive from a single mutation, or truncated forms the disclosure and the prior art describe as inactive. The disclosure is nothing more than a research plan, lacking any blaze marks, while the claims improperly seek to capture any enzymatically active, multiply-mutated PH20 polypeptides that might be discovered now or in the future.

Second, regarding enablement, the common disclosure suffers equally fatal problems. It neither describes nor characterizes ***any*** modified PH20 with 2 or more substitutions. It provides no guidance about which ***combinations*** of substitutions should be made, much less affirmatively guides the selection of those

that do yield enzymatically active proteins. And the only disclosed process for making PH20 mutants with multiple substitutions is a prophetic, "iterative" research plan. That plan explicitly requires the same type of "trial-and-error" experiments in another 2011-era patent that the Supreme Court recently found incapable of enabling a large genus of diverse polypeptides.[2] Indeed, to practice the full scope of the claims using this process would require scientists to repeat this "make-and-test" methodology innumerable times until they had made and tested between 10^{49} and 10^{65} unique proteins. That is far more than undue experimentation—it is impossible.

Finally, claims 1-4 and 7-21 are also independently unpatentable because each captures a ***single*** PH20 mutant with a ***single*** amino acid substitution at position 320 (from aspartic acid (D) to lysine (K)) ("D320K $PH20_{1-447}$"). But Patentee's earlier '429 Patent (EX1005)[3] makes that mutant obvious; it directs artisans to make single amino acid substitutions in non-essential regions of the $PH20_{1-447}$ sequence (and explicitly claimed them). Implementing that guidance in 2011 would have led the skilled artisan to an intervening publication—Chao (EX1006)—that is ignored in Patentee's 2011-era disclosure and was never cited to

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2 *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023).

3 U.S. Patent No. 7,767,429.

the Office during examination. When the collective guidance of the '429 Patent and Chao is considered by a skilled artisan in 2011, it (i) readily identifies position 320 as being in a non-essential region of PH20 and (ii) motivates the skilled artisan to substitute lysine at that position—the most commonly occurring amino acid in that position in known, homologous hyaluronidase enzymes. And the skilled artisan would have reasonably expected this one substitution to retain the enzymatic activity of its parent because that is precisely what the '429 Patent says ("Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity").[4] A skilled artisan, in 2011, would have considered D320K $PH20_{1-447}$ to be ***one*** obvious PH20 mutant within the broad genus claimed..

The evidence demonstrates the '600 Patent claims are unpatentable. The Board should institute post grant review.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the '600 Patent 's issuance. Petitioner also certifies it is not barred or estopped from requesting this

[4] EX1005, 16:17-22.

PGR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '600 Patent.

The '600 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

A patent is PGR eligible if it issued from an application filed after March 16, 2013 "if the patent contains... at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought." *See Inguran, LLC v. Premium Genetics (UK) Ltd.*, Case PGR2015-00017, Paper 8 at 16-17 (P.T.A.B. Dec. 22, 2015); *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17 at 8 (P.T.A.B. Jan. 29, 2016); *Collegium Pharm., Inc. v. Purdue Pharma L.P.*, 2021 WL 6340198, at *14-18 (P.T.A.B. Nov. 19, 2021) (same) *aff'd Purdue Pharma L.P. v. Collegium Pharm., Inc.*, 86 F.4th 1338, 1346 (Fed. Cir. 2023); *Intex Recreation Corp. v. Team Worldwide Corp.*, 2020 WL 2071543, at *26 (P.T.A.B. Apr. 29, 2020) (same).

The '600 Patent claims benefit under 35 U.S.C. § 120 and/or § 121 to seventeen earlier-filed non-provisional applications. Only one—U.S. Application No. 13/694,731 (the '731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to and

incorporates by reference the disclosures of two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011), as well as WO 01/3087 ("WO087"). The '731 application alters several passages of the provisional disclosures, adds new examples and tested mutants and makes other changes.[5]

The disclosure of the '731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '600 Patent (§§ V.A, V.B). The same is true for the '600 Patent, whose disclosure is substantively identical to the '731 Application.[6] The '600 Patent is PGR-eligible as at least one of its claims does not comply with § 112(a) based on the '731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

Merck Sharp & Dohme LLC is the real party-in-interest for this Petition.

2. Related Proceedings

There are no related proceedings to this Petition.

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[5] EX1026, 153:15-163:26, 324-334, 19:25-26, 28; EX1051; EX1052.

[6] References to the "common disclosure" are to the shared disclosure of the '600 Patent and the '731 Application (EX1026). Citations are to the '600 Patent, and EX1015 correlates citations to the '731 Application.

3. Counsel and Service Information

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III. Grounds

The grounds advanced in this Petition are:

(a) Claims 1-21 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.

(b) Claims 1-21 are unpatentable under 35 U.S.C. § 112 as not being enabled.

(c) Claims 1-4 and 7-21 are unpatentable as obvious under 35 U.S.C. § 103 based on the ’429 Patent (EX1005), Chao (EX1006) and knowledge held by a person of ordinary skill in the art.

Petitioner’s grounds are supported by the evidence submitted with this Petition, including testimony from Dr. Michael Hecht (EX1003) and Dr. Sheldon Park (EX1004).

In this Petition, “PH20” refers to the human PH20 hyaluronidase protein. The full-length form of the protein (SEQ ID NO: 6) includes a 35 amino acid

signal sequence, while mature forms of PH20 are numbered from position 1 of the mature sequence (position 36 in sequences containing the signal sequence)(*e.g.*, SEQ ID NO: 6).[7] The annotation "$PH20_{1\text{-}n}$" is used to refer a sequence of 1-n residues in PH20 (e.g., $PH20_{1\text{-}447}$ is SEQ ID NO:3), and "AxxxB" is used to identify the position of a substitution ("D320K").

IV. Background on the '600 Patent

A. Field of the Patent

The '600 Patent concerns the human PH20 hyaluronidase enzyme, and structurally altered forms of that protein that retain enzymatic activity.[8]

1. Protein Structures

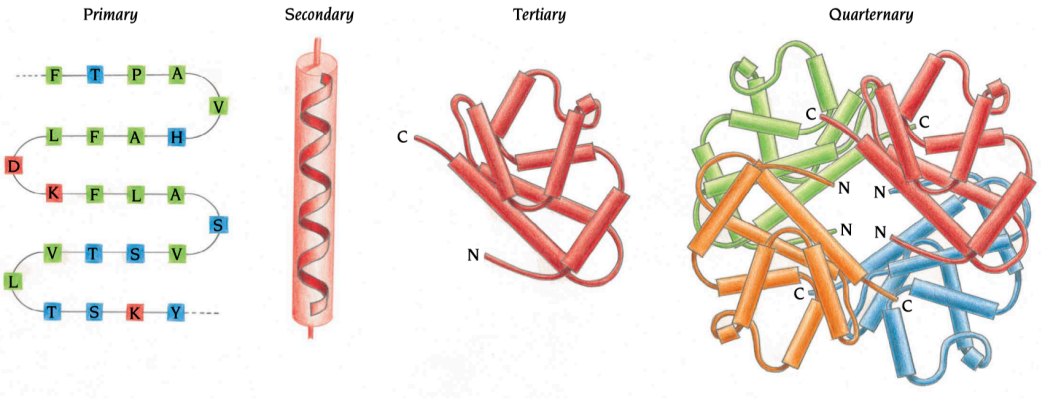
Proteins are comprised of sequences of amino acids. The activity of a protein, however, derives from its unique, three-dimensional shape—its structure.[9] That, in turn, is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary

[7] EX1003, ¶ 15.

[8] EX1001, 4:15-19.

[9] EX1003, ¶ 36.

structures and structural motifs, which are packed into compact domains that define the protein's overall structure (tertiary structure).[10]



For example, secondary structures, such as α-helices or β-strands, are formed and stabilized by different but characteristic patterns of amino acids (below).[11]

[10] EX1014, 3-4, 24-32, Fig. 1.1; EX1039, 136-37 (Fig. 3-11); EX1003, ¶¶ 36-40.

[11] EX1039, 134; EX1014, 14-22, Figures 2.2, 2.5, Table 2.1; EX1047, 2031-2032; EX1003, ¶¶ 40-43.

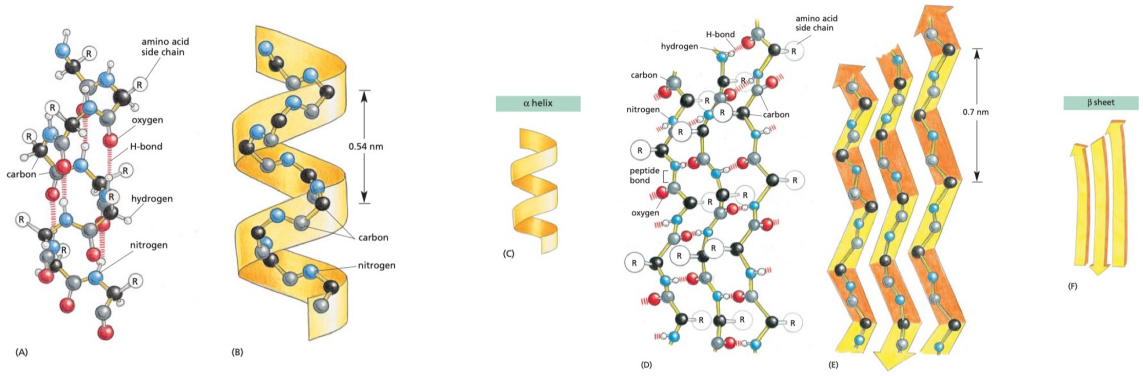


Figure 3–7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT>
(A, B, and C) The α helix. The N–H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N–H groups point up in this diagram and that all of the C=O groups point down (toward the C-terminus); this gives a polarity to the helix, with the C-terminus having a partial negative and the N-terminus a partial positive charge. (D, E, and F) The β sheet. In this example, adjacent peptide chains run in opposite (antiparallel) directions. Hydrogen-bonding between peptide bonds in different strands holds the individual polypeptide chains (strands) together in a β sheet, and the amino acid side chains in each strand alternately project above and below the plane of the sheet. (A) and (D) show all the atoms in the polypeptide backbone, but the amino acid side chains are truncated and denoted by R. In contrast, (B) and (E) show the backbone atoms only, while (C) and (F) display the shorthand symbols that are used to represent the α helix and the β sheet in ribbon drawings of proteins (see Panel 3–2B).

Intervening sequences between those characteristic sequences are important too; they direct and facilitate positioning and arrangement of the various secondary structures into structural motifs and the protein's tertiary structure.[12]

Changes to a protein's amino acid sequence can affect the folding, formation and stability of these various structures that define the protein's overall shape. For example, changing even a single residue known to be critical to the protein's structure or activity can render a protein inactive.[13]

Making many concurrent changes to a protein's sequence was highly unpredictable, as they can cause myriad effects on the protein's structure,

[12] EX1003, ¶¶ 44-46; EX1014, 21-22.

[13] EX1003, ¶¶ 54, 150; EX1004, ¶ 25.

particularly when those changes are in or affect the same region(s) of the protein.[14] For example, introducing numerous changes in a protein's amino acid sequence can disrupt the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of secondary structures, while changes to intervening sequences can disrupt folding and positioning of the secondary structures and structural motifs into the protein's tertiary structure.[15] Multiple changes introduced at different regions of the amino acid sequence also can cause unfavorable spatial interactions that destabilize or impair folding.[16] In 2011, predicting the possible effects of the myriad interactions that may be disrupted by multiple amino acid changes was beyond the capacity of skilled artisans and the computational tools available at that time.[17]

2. Hyaluronidase Enzymes

PH20 is one of five structurally similar hyaluronidase proteins found in humans and is homologous—evolutionarily related to—hyaluronidase proteins in

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14 EX1003, ¶¶ 158.

15 EX1003, ¶¶ 55-56, 142; EX1047, 6349; EX1046, 2034; *also* EX1040, 14412-413; EX1041, 21149-50; EX1042, 1-3.

16 EX1003, ¶¶ 57-59.

17 EX1003, ¶¶ 50, 158, 190, 224; EX1004, ¶¶ 160-162.

many species.[18] It breaks down hyaluronan ("HA") by selectively hydrolyzing glycosidic linkages in it.[19] The human PH20 protein exists naturally as a GPI anchored protein, but a truncation at the C-terminal region of PH20 yields a soluble, neutral active form of the enzyme.[20]

Various groups before 2011 had identified essential residues in PH20. These included several in the catalytic site of the protein, a conserved structure shared by many species.[21] Mutating certain residues in or near the catalytic site can abolish the enzymatic activity of hyaluronidases.[22] Conserved cysteine residues that stabilize the protein structure are another example,[23] as are conserved

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[18] EX1007, 10:18-30; EX1006, 6911, 6916 (Fig.3); EX1003, ¶¶ 33, 77.

[19] EX1003, ¶ 77; EX1008, 819.

[20] EX1005, 2:40-61, 87:52-88:24; EX1013, 430-432, Fig.2; EX1003, ¶¶89, 196; EX1029, 546, Fig.1.

[21] EX1006, 6914-6916, Fig.3; EX1007, 35:28-36:10; EX1011, 810-14; EX1008, 824-25; EX1009, 6912-17.

[22] EX1011, 812-814; EX1010, 9435-39, Table 1.

[23] EX1006, 6914-6916, Fig.3; EX1011, 810-11; EX1005, 88:21-22.

asparagine residues involved in glycosylation, which was known to be important for PH20 activity.[24]

In 2007, Chao reported an experimentally determined structure of the human HYAL1 hyaluronidase, and used an alignment of the known sequences of the five human hyaluronidases to illustrate shared secondary structures and conserved residues in these proteins.[25] Among its findings was that human hyaluronidases contain a unique, previously undisclosed structure—the Hyal-EGF domain.[26] Using its sequence analysis, an earlier structure of bee venom hyaluronidase and a computer model of the protein structures, it analyzed the catalytic site of HYAL1 and identified residues in it that interact with HA.[27]

3. Engineering Proteins in 2011

In 2011, skilled artisans used two general approaches to engineer changes into proteins.[28] "Rational design" employed common computational tools like

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24 EX1005, 7:9-27; EX1007, 36:12-20; EX1010, 9433, 9435-40.

25 EX1006, 6914-6918.

26 EX1006, 6916-18; EX1010, 9439-40; EX1004, ¶ 98.

27 EX1006, 6912-6913, 6916-18, Fig. 2C, 4A; EX1033, 1028-1029, 1035; EX1010, 9434, 9436, Fig. 1.

28 EX1003, ¶ 47.

sequence alignments and protein structure models to study the protein sequence and structure. Then, using known sequence-structure relationships for the protein, they selected where and what changes to introduce into the protein sequence.[29] For example, known sequences homologous (evolutionarily related) to the one being studied (PH20) would be compiled and compared in a "multiple-sequence alignment" ("MSA").[30] The MSA identifies conserved ("essential") positions with no or little amino acid variation as well as positions where different amino acids occur in naturally occurring homologous proteins ("non-essential" residues).[31] A structural model of the protein made with its amino acid sequence but based on a suitable template structure from a homologous protein was then used to visualize locations within the protein's structure to identify and assess interactions of the amino acids at that position.[32] In 2011, while skilled artisans could assess, with varying amounts of effort, the effects of changing one or a few amino acids,

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[29] EX1016, 181-182; EX1017, 223, 236; EX1003, ¶¶ 48-50.

[30] EX1017, 224-227; EX1016, 181-186 (Fig. 1); EX1003, ¶¶ 48-50.

[31] EX1004, ¶¶ 21, 25, 30-31-32; EX1016, 181-184; EX1017, 224-225; EX1014, 351.

[32] EX1017, 228-230; EX1031, 461, 463, 469-71; EX1014, 351-352; EX1004, ¶ 33, 39-40; EX1032, 265-266.

predicting the effects of many changes was not possible, given the escalating complexity of predicting numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.[33]

"Directed evolution" techniques arose due to the limits of rational design.[34] It uses "trial-and-error" experiments to find mutants with randomly distributed changes that exhibit desired properties, but requires creation and screening of large libraries of mutants, each with one amino acid randomly changed at one position in its sequence.[35] Importantly, until a desired mutant is made, tested and found, whether it exists and its sequence are unknown.[36] Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale of experimentation this technique requires.[37] The '600 Patent embodies this approach.[38]

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33 EX1003, ¶¶ 50, 158; EX1004, ¶¶ 160-162.

34 EX1003, ¶¶ 51; EX1059, 1225-1226; EX1018, 378.

35 *Id*.

36 EX1003, ¶¶ 184.

37 EX1003, ¶¶ 52-53.

38 EX1003, ¶¶ 138, 173, 186.

B. Person of Ordinary Skill in the Art

The ’600 Patent claims priority to two provisional applications filed in 2011. § II.A. Its claims, however, are not entitled to those dates or the filing date of the ’731 Application (December 28, 2012), as they are not supported as § 112(a) requires by those earlier-filed applications. *See* § V.A, V.B. The prior art of the grounds, however, was published by December 2011, and the obviousness grounds thus use that date to assess the knowledge and perspectives of the skilled artisan.

In 2011, a person of ordinary skill in the art would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).[39]

C. Prosecution History

Only one office action issued during examination of the ’600 Patent.

[39] EX1003, ¶ 13.

First, the Examiner rejected claims directed to methods of treating cancer for lack of enablement and written description, arguing the specification failed to support treatment of all types and stages of cancer, and lacked working examples of treating cancer.[40] Patentee mooted the rejection by cancelling the claims.[41]

Second, the claims were rejected for non-statutory double patenting over U.S. Patent 10,865,400 and Application No. 18/064,886 either alone or in view of WO2010/077297.[42] Patentee overcame those rejections with terminal disclaimers.[43]

The claims were allowed without further rejections.[44]

D. The Challenged Claims

The terms used in the claims are either expressly defined in the specification of the common disclosure or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition. A clear understanding of the ***breadth*** of the claims, however, is

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40 EX1002, 421-426.

41 EX1002, 677-681.

42 EX1002, 426-440.

43 EX1002, 681-82.

44 EX1002, 683-90.

important to assess the grounds. Specifically, each claim captures a massive genus of structurally distinct mutant PH20 polypeptides that is neither adequately described in nor enabled by the common disclosure of the '731 Application and the '600 Patent.

1. The Claims Encompass a Staggering Number of Modified PH20 Polypeptides

Claim 1 defines an incredibly broad and diverse genus of "modified PH20 polypeptides," which are defined as "a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement … in its sequence of amino acids compared to a reference unmodified PH20 polypeptide."[45]

Claim 1 specifies the modified PH20 polypeptides in its genus:

- ***must*** contain ***one*** amino acid replacement at position 320 (*i.e.*, from D to any of H, K, R or S); and
- ***may*** contain ***additional*** modifications, provided each polypeptide retains ***at least 95% sequence identity*** to one of the 35 unmodified sequences (SEQ ID NOs: 3 or 32-66), ranging in length from 430 (SEQ ID NO:32) to 465 residues (SEQ ID NO:35).

[45] EX1001, 48:38-43.

Claim 2 requires position 320 to be to K. Claims 3 and 4 restrict claim 1's genus by specifying each polypeptide has: (i) 96% sequence identity to SEQ ID NO: 35 ($PH20_{1-433}$), or (ii) 95% sequence identity to SEQ ID NO:32 ($PH20_{1-430}$).

The specification explains that "sequence identity can be determined by standard alignment programs…"[46] It then provides an example, explaining a polypeptide that is "'at least 90% identical' refers to percent identities from 90 to 100% relative to the reference polypeptide" where "no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides."[47] Per claim 1, "terminal gaps" are "treated as non-identical" residues.

The specification explains that "differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence" and that "[d]ifferences are defined as [] amino acid substitutions, insertions or deletions."[48] Also, "amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids" (*e.g.*, 10-18

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46 EX1001, 60:14-16.

47 EX1001, 60:49-58.

48 EX1001, 60:59-67; *also id.* at 5:1-2; 47:43-47, 56-58.

of the 19 alternative amino acids).[49] Consistent with these passages, there is no language used in the claims that restricts where substitutions can occur within the amino acid sequence of the modified PH20 polypeptides, or which of 19 other amino acids can be substituted into that position.

The parameters in claims 1-4 cause them to encompass an immense number of distinct polypeptides, each with a unique amino acid sequence.[50] In particular, the sequence identity language permits the modified PH20 polypeptides with between 17 and 23 total changes, with only one being restricted in nature (*i.e.*, the substitution at 320 must be to 1 (claim 2) or 4 alternatives (claims 1, 3, 4)). Based on Dr. Park's calculations, each claim's parameters capture an immense number of distinct polypeptides (below).[51]

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[49] EX1001, 137:29-36; *also id.* at 142:49-51.

[50] EX1003, ¶¶ 120, 122.

[51] EX1004, ¶¶ 168-171, Appx. F.

Claim	SEQ ID/ % Identity	PH20 length	# Changes	Pos. 320 Choices	Add'l Changes	# Distinct Polypeptides
1	**3** /95%	447	22	4	21	1.50×10^{63}
	66 /95%	465	23	4	22	1.35×10^{66}
2	**3** /95%	447	22	1	21	3.76×10^{62}
3	**35** / 96%	433	17	4	16	6.14×10^{49}
4	**32** / 95%	430	21	4	20	1.76×10^{60}

2. The Claims Encompass One Particular PH20 Mutant: D320K PH20$_{1\text{-}447}$

The structural parameters used in claims 1-4 (the only ones with such parameters) also cause them to capture a ***single*** modified PH20 polypeptide with ***one*** replacement. That is the PH20$_{1\text{-}447}$ protein (SEQ ID NO:3), in which the aspartic acid (D) at position 320 is changed to lysine (K) ("D320K PH20$_{1\text{-}447}$"). This single-replacement PH20 mutant has the D320K substitution and is, relative to the parameters of claims 1, 3, and 4: (i) 99.8% identical to SEQ ID NO: 3 (1 change / 447 residues), (ii) 96.5% identical to SEQ ID NO: 35 (15 changes/433 residues) and 95.8% identical to SEQ ID NO: 32 (18 changes / 430 residues).[52]

[52] EX1003, ¶ 136.

3. The Claims Are Restricted to One of Two Alternative Embodiments in the Patents: "Active Mutants"

When a specification discloses alternative embodiments, the language used in the claims may cause them to be limited to only one.[53] That is the case here: the specification describes two mutually exclusive categories of "modified PH20 polypeptides" (*i.e.*, "active mutants" vs. "inactive mutants") but the claims are limited to one of them: "active mutants."

According to the specification:

- "***Active mutants***" are modified PH20 polypeptides that "exhibit at least 40% of the hyaluronidase activity of the corresponding PH20 polypeptide not containing the amino acid modification (e.g., amino acid replacement)."[54]
- "***Inactive mutants***" are modified PH20 polypeptides that "generally exhibit less than 20% ... of the hyaluronidase activity of a wildtype or

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[53] *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008).

[54] EX1001, 75:47-52; *also* 79:29-33 ("active mutants" "can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide…").

> reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7."[55]

It then classifies mutants into tables of "active" and "inactive" mutants using the >40% threshold (Table 3 and 9) or <20% threshold (Tables 5 and 10).[56]

The common disclosure reports no examples of a modified PH20 with two replacements.[57] More directly, it reports no examples of a $PH20_{1447}$ that was made and tested and which incorporated: (i) a mutation listed in Tables 3 and 9 ("active mutants") and (ii) a mutation listed in Tables 5 and 10 that yielded an "inactive mutant (Tables 5 and 10).

The specification also portrays "active" and "inactive" mutants as having distinct utilities requiring mutually exclusive properties.

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55 EX1001, 119:12-21. *See also id*. at 257:23-27 (mutants exhibiting <20% hyaluronidase activity "were rescreened to confirm that the dead mutants are inactive" in Table 10).

56 EX1001, 80:60-82:10 (Table 3 "Active Mutants"); 234:27-29 (Table 9 "Active Mutants"); 120:28-51 (Table 5 "Inactive Mutants"), 258:34-38 ("The identified reconfirmed inactive mutants are set forth in Table 10."); EX1003 ¶¶ 98, 104-105, 107, 126-128.

57 *E.g.*, EX1003, ¶¶ 141, 172.

- "Active mutants" are portrayed as being therapeutically useful ***because they possess hyaluronidase activity***. For example, the specification explains that ***due to*** having hyaluronidase activity, "the modified PH20 polypeptides can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents." [58]
- "Inactive mutants" are portrayed as being therapeutically useful ***because they lack hyaluronidase activity***. Their only identified utility is "as antigens in contraception vaccines," which is implausible (*see* § V.C) but ostensibly requires them to lack activity.[59]

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[58] EX1001, 181:27-33; *see also id*. at 4:33-36 ("By catalyzing HA degradation…(e.g., hyaluronidases) can be used to treat diseases or disorders …"), 73:33-47 ("By catalyzing the hydrolysis of hyaluronic acid, PH20 hyaluronidase lowers the viscosity of hyaluronic acid, thereby increasing tissue permeability."), 181:27-194:54.

[59] EX1001, 72:60-62; *also* 194:55-56, 75:56-58, 194:54-195:6 (for "contraception" "the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.")

Notably, the specification does not portray "active mutants" as having such contraceptive utility even though they may differ by only one amino acid. Instead, it proposes using "active mutants" ***in combination*** with contraceptive agents.[60]

The claim language reinforces that they are limited to the "active mutant" embodiment.

First, every claim requires each modified PH20 polypeptide in its scope to have one of four replacements at position 320 that yielded an "active mutant" as a single-replacement $PH20_{1-447}$ polypeptide (*i.e.*, D320H, D320K, D320R, or D320S). These mutants are listed in Table 3 and reported as having >40% activity in Table 9.[61]

Second, claims 5 and 6 restrict the genus of active mutants in claim 1 (*i.e.* those with at least 40% activity) to active mutant modified PH20 polypeptides that have at least 100% or 120% of the activity of unmodified PH20, respectively.

Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one modification," but can also "have up to 150

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[60] EX1001, 157:50-63 ("co-formulations containing a modified PH20 polypeptide and a therapeutic agent that is … a contraceptive agent…"); EX1003, ¶¶ 121, 124-125; EX1060, 1711.

[61] EX1001, 87 (Table 3), 237 (Table 9).

changes, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity.***"[62] This aligns with the specification's prophetic methodology for discovering PH20 polypeptides with multiple changes, which starts with one substitution that yields an "active mutant," randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity.[63] This tracks the claims, which require one substitution and permit others.

Patentee may contend the claims should be read as encompassing both alternative embodiments (*i.e.*, "active" and "inactive" mutants). Reading the claims in that manner is incorrect. It also exacerbates the § 112 problems, as every claim still necessarily includes (and thus must describe and enable) the full sub-genus of "active mutants" defined by claims 5 and 6.[64]

V. All Challenged Claims Are Unpatentable Under § 112 and None Are Entitled to Benefit to Any Pre-March 13, 2013 Application

Claims 1-21 are unpatentable because each lacks written description in and is not enabled by the common disclosure of the '600 Patent and the '731 Application.

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62 EX1001, 48:38-53; *also id*. at 47:61-65, 76:5-8, 76:67-77:7.

63 EX1001, 142:15-26; *also id*. at 42:48-55.

64 EX1003, ¶ 135.

As explained in § IV.D.1, the claim language defines enormous genera: between 10^{49} and 10^{65} distinct polypeptides. To illustrate the real-world absurdity of those claims, consider what practicing their full scope requires. Excluding single-replacement $PH20_{1-447}$ mutants, and only focusing on mutants with multiple substitutions in $PH20_{1-447}$, a skilled artisan would need to make-and-test ~ 10^{63} mutants having between 2 and 22 substitutions. Producing only one molecule of each—each has to be made and tested to see if it is active or inactive—would require consuming an aggregate mass (~5.5 x 10^{27} kg,) that exceeds the mass of the Earth (~6 x 10^{24} kg).[65] Testing every polypeptide within the claims' scope in search of "active mutants" is impossible—literally.

In support of that broad scope, the '600 Patent and the '731 Application provide only a meager disclosure: ***singly***-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones. The patent provides ***nothing*** that demonstrates possession of the vast remainder of multiply-modified polypeptides in the claims' scope or which enables a skilled artisan to practice that full-range of structurally diverse mutant polypeptides without undue experimentation.

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[65] EX1003, ¶¶ 123, 189; *also, e.g.*, EX1039, 136-137 (cell theoretically can make 10^{390} forms of a polypeptide with 300 amino acids).

A. Claims 1 to 4 Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.[66] "To fulfill the written description requirement, a patent owner 'must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent."[67] If the claims define a genus, the written description must "show that one has truly invented a genus…" "[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus."[68]

"[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the

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66 *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

67 *Idenix Pharm., LLC v. Gilead Scis., Inc.,* 941 F.3d 1149, 1163 (Fed. Cir. 2019).

68 *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1300 (Fed. Cir. 2014).

members of the genus."[69] "One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent… [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus."[70]

A disclosure that fails to "provide sufficient blaze marks to direct a POSA to the specific subset" of a genus with the claimed function or characteristic does not satisfy §112(a).[71] And "merely drawing a fence around the outer limits of a purported genus" is insufficient.[72] Instead, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."[73]

Three cases applying these principles are particularly relevant here. First, in *AbbVie.*, the Federal Circuit affirmed a finding that the disclosure of 300 examples

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69 *Idenix*, 941 F.3d at 1164.

70 *AbbVie*, 759 F.3d at 1299-1300.

71 *Idenix*, 941 F.3d at 1164.

72 *Ariad*, 598 F.3d at 1350-54.

73 *Ariad*, 598 F.3d at 1349.

of IL-12 antibodies was not representative of functionally defined genus of antibodies, explaining:

> Although the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.[74]

The court also criticized the character of the patent's disclosure presented to support the non-exemplified portion of the claim scope, portraying that as "only a research plan, leaving it to others to explore the unknown contours of the claimed genus" and being a "trial and error approach." That criticism is particularly relevant to the present disclosure, which exemplifies only single-substitution PH20 mutants, but claims multiply-modified PH20 mutants with 2 to 22 additional substitutions.

Second, in *Idenix,* the court considered claims defining broad genera of compounds defined by formulas analogous to the challenged claims here: "eighteen position-by-position formulas describing 'principal embodiments' of compounds that may treat HCV," each with "more than a dozen options" at each position (totaling "more than 7,000 unique configurations."[75] The court criticized

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[74] *AbbVie*, 59 F.3d, 1300-01.

[75] *Idenix*, 941 F.3d at 1158-1164.

the specification's failure to indicate which of the thousands of compounds would be effective, and found that "providing lists or examples of supposedly effective nucleosides," without "explain[ing] what makes them effective, or why" deprives a skilled artisan "of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result" because they "fail to provide sufficient blaze marks to direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV." Again, that logic resonates strongly with the deficiencies of this disclosure.

Finally, the Board's decision in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found.*, PGR2020-00076, Paper 42, 6 (PTAB Jan. 31, 2022) provides another direct analogy. There the claims used "90% sequence homology" language to capture "a broad genus of amino acid sequence homologues" but (like here) imposed no restrictions on where particular amino acids replacements could be made, thus causing the claim "to cover, at minimum, thousands of amino acid sequences."[76] Again, the specific shortcoming was the specifications' failure to "explain what, if any, structural features exist (e.g., remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification" and concluded that the

[76] *Boehringer*, at 16.

homology limitation "serves to merely draw a fence around the outer limits of a purported genus [which] is not an adequate substitute for describing a variety of materials constituting the genus…" for purposes of section 112(a).[77]

The deficiencies of claims 1 to 4 dwarf those identified in these three cases. The present claims define much larger, much less predictable and much more diverse genera of modified PH20 polypeptides, and the common disclosure is far more limited. As explained below, it neither discloses a representative number of species within each immense claimed genus, nor identifies sufficient structural features common to the members of each claimed genus. The common disclosure thus falls woefully short of demonstrating possession of the genera of modified PH20 polypeptides defined by claims 1 to 4 of the '600 Patent.

1. The Claims Define a Massive and Diverse Genus of Enzymatically Active PH20 Polypeptides

The incredible breadth of the genus defined by claims 1 to 4 has been described above. *See* § IV.D.1 The genera of each claim are also incredibly diverse in their structures and functions.

Most significantly, the use of a *maximum* sequence identity boundary with no condition or restrictions other than one required substitution means the claims capture mutants with 2 substitutions, 3 substitutions and so on up to a number set

[77] *Id.* at 35-36.

by the boundary (*i.e.*, 17 for claim 3, 21 for claim 4, and 23 for claim 1). The substitutions can be anywhere in the protein sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, regardless of the physicochemical profile of those residues, and arranged in any manner. They capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with 22 substitutions mixing polar, charged, aliphatic and aromatic residues in another, and in any manner.[78]

There is more. Each claim -also encompasses substitutions being made in PH20 sequences that vary in length. Claim 1 does this explicitly, specifying 35 alternative sequences ranging from 430 to 465 residues. Claims 1, 3 and 4 also encompass varying lengths for the reference sequence, as the claims permit both "additions" and "deletions." In other words, if one makes the D320K substitution and makes 5 more substitutions to SEQ ID 32, claim 4's parameters would capture that mutant as well as one that also deletes 14 residues from the C terminus. As explained below (§V.A.2.c)), that yields an unmodified PH20 sequence that is inactive , but apparently by adding 5 substitutions anywhere in its sequence may

[78] EX1003, ¶¶ 119-120.

not be? The common disclosure contains no explanation or data indicating this is even possible, yet Patentee purports to claim all such polypeptides.[79]

2. The Claims Capture Modified PH20 Polypeptides the Common Disclosure Says to Avoid or Not Make

The unconstrained sequence identity language in the claims causes them to capture three categories of PH20 mutants a skilled artisan would understand the disclosure to be saying to avoid or not make.

Because each category of mutants raises unique questions relative to the remainder of the genus, they are "sub-genera" of PH20 mutants that are not representative of other "sub-genera" within the genera being claimed. But instead of providing guidance that navigates this confusing landscape, the patent simply instructs the skilled artisan to "… to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein."[80] In other words, it directs the skilled artisan to blindly make-and-test all such candidate mutants using trial-and-error experimentation.[81]

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79 EX1003, ¶¶ 164-167.

80 EX1001, 78:33-38.

81 EX1003, ¶ 193.

a) Multiply-Modified PH20 Mutants to Not Make

The common disclosure affirmatively addresses only six, specific modified PH20 polypeptides with more than one identified (*i.e.*, position and amino acid) substitution, but that guidance is to ***not make those polypeptides***:

> [W]here the modified PH20 polypeptide contains only two amino acid replacements, the amino acid replacements are ***not*** P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A or N333A/N358A. In a further example, where the modified PH20 polypeptide contains only three amino acid replacements, the amino acid replacements are ***not*** N47A/N131A/N219A.[82]

Notably, the common disclosure provides ***no explanation*** why these particular combinations of replacements should not be made, and provides no data testing their activity or other characteristics.[83] Further, none (P13A, N47A, N131A, N219A, N333A, N358A, L464W) are included in Tables 5 and 10, which are single-replacements that rendered $PH20_{1-447}$ an "inactive mutant." Indeed, one (N219A) yielded a $PH20_{1-447}$ with increased activity (129%) as a single replacement.[84] Again, the disclosures do not explain ***why*** the these combinations are singled out as ones to avoid in multiple-substitution mutants, and the skilled

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82 EX1001, 77:45-57 (emphases added).

83 EX1003, ¶¶ 146-147.

84 EX1001, 247 (Table 9).

artisan is left to discover this information themself. And nothing in the claim language excludes these combinations.

b) Substitutions to Avoid in Active Mutants

The common disclosure indicates that active mutant modified PH20 polypeptides should not incorporate specific amino acid substitutions that rendered $PH20_{1-447}$ inactive, stating:

> ***To retain hyaluronidase activity***, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.[85]

It identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10 that are made at other positions.[86]

Notably, the common disclosure does not condition this observation on single-replacement $PH20_{1-447}$ mutants, and as such, it clearly conveys to a skilled artisan that modified PH20 polypeptides with "hyaluronidase activity" do not include, and should not be modified to contain, the amino acid replacements listed

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85 EX1001, 80:13-15 (emphases added).

86 EX1001, 80:15-55 ("For example, generally modifications are not made at a position corresponding to position …").

in Tables 5 and 10, and that is true regardless of the length or the number of additional amino acid substitutions in the PH20 polypeptide.[87]

The skilled artisan also would find no description of, much less guidance concerning, ***which*** of these identified substitutions that did render $PH20_{1-447}$ inactive should be incorporated into enzymatically active multiply-modified PH20 polypeptides (and what other substitutions should be combined with them).[88] Instead, by stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that the ***claimed*** enzymatically active multiply-modified PH20 polypeptides do not contain them. And again, nothing in the claim language operates to exclude such combinations.

c) PH20 with Significant C-terminal Truncations Can Lose Activity

The common disclosure describes no multiply-modified "active mutant" PH20 polypeptides having fewer than 447 residues (or even an unmodified PH20 with such lengths) and provides no guidance about making enzymatically active

[87] EX1003, ¶¶ 148-151.

[88] EX1003, ¶¶ 151, 161-162, 169.

mutants based on PH20 sequences ending before position 447 and containing 2 or more substitutions.[89]

This omission creates significant uncertainty, because both the common disclosure and the prior art report that PH20 polypeptides with fewer than 442 residues significantly ***reduce or eliminate*** hyaluronidase activity in unmodified PH20 polypeptides. For example, Patentee's prior art '429 Patent reported that PH20 with fewer than 432 residues lacked hyaluronidase activity, while those with between 432 and 448 residues had widely varying activities (below):[90]

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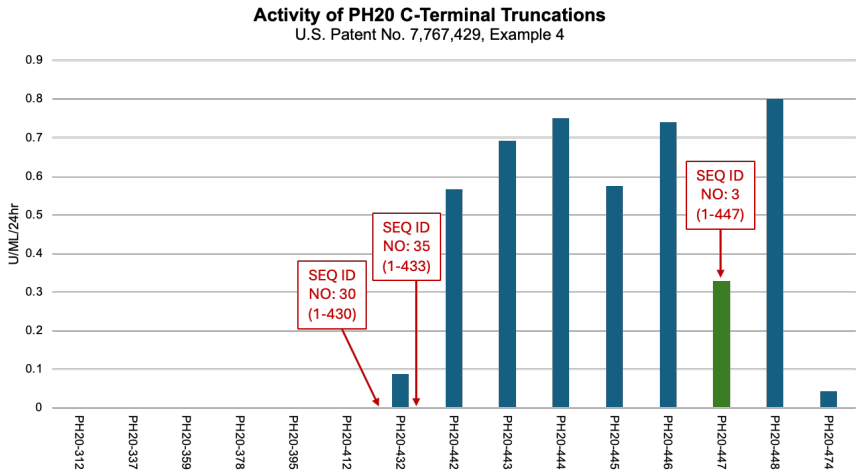
89 EX1003, ¶¶ 97, 167-169.

90 EX1005, 87:52-88:24 (activity of $PH20_{1-442}$ "decreased to approximately 10% of that found" in the $PH20_{1-447}$ polypeptides); EX1013, Fig. 2, 430-432 ("soluble hyaluronidase activity could be recovered in the conditioned medium from deletion mutants terminating after amino acids 477 – 483 [442-448]" but "[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA").



Position (w/leader)	Mutant	U/ML/24hr	Normalized to PH20(1-447)
347	PH20-312	0	0.00
372	PH20-337	0	0.00
394	PH20-359	0	0.00
413	PH20-378	0	0.00
430	PH20-395	0	0.00
447	PH20-412	0	0.00
467	**PH20-432**	**0.089**	**27.05**
477	PH20-442	0.567	172.34
478	PH20-443	0.692	210.33
479	PH20-444	0.75	227.96
480	PH20-445	0.575	174.77
481	PH20-446	0.74	224.92
482	**PH20-447**	**0.329**	**100.00**
483	PH20-448	0.8	243.16
509	PH20-474	0.044	13.37

The '429 Patent also reported that "a very narrow range spanning … [437-447] ... defined the minimally active domain" of human PH20, and elsewhere observed this "minimally active" human PH20 domain contains at least residues 1-429.[91] The common disclosure concurs, stating that PH20 polypeptides must contain extend to at least position 429 to exhibit hyaluronidase activity:

> A mature PH20 polypeptide … containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue ***464*** of SEQ ID NO:6 [position ***429*** without signal] … ***is the minimal sequence required for hyaluronidase activity***.[92]

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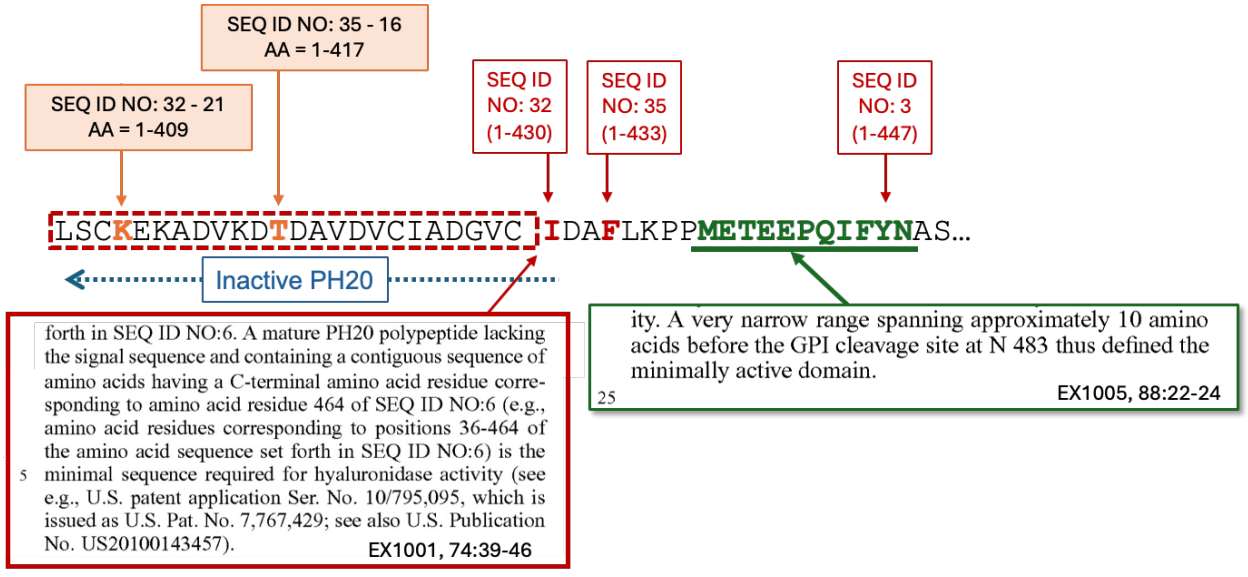
91 EX1005, 6:65-7:7 ("…sHASEGP from amino acids 36 to Cys 464 [429] … comprise the minimally active human sHASEGP hyaluronidase domain").

92 EX1001, 69:66-70:8 (emphasis added).

Before 2011, the C-terminal region of PH20 also was known to contain a unique domain linked to a characteristic pattern of sequences first reported in 2007 by Chao ("Hyal-EGF").[93] In PH20, the Hyal-EGF domain is found at positions 337-409, and it was shown in 2009 to be essential to hyaluronidase activity.[94]

The C terminus of PH20 is illustrated below, showing the location where SEQ ID NOS:**3** (447), **32** (430) and **35** (433) terminate (arrows). It also shows the "minimally active domain" at 437-447 in green and residues below position 429 shaded in a red dashed box.[95] Positions that truncate 21 and 16 residues from SEQ ID NOS: 32 and 35 are also shown ending before position 429.

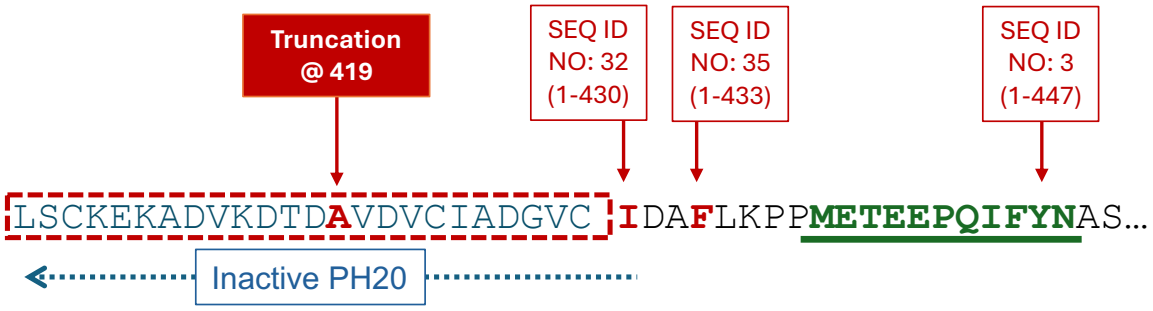


93 EX1006, 6912; EX1003, ¶¶ 84-96, 153.

94 EX1004, ¶ 98; EX1010, 9438; EX1003, ¶¶ 95-97.

95 EX1003, ¶ 153.

From the prior art and the common disclosure, a skilled artisan in 2011 would believe that C-terminal deletions yielding PH20 polypeptides that terminate before position 430 would be inactive.[96]



But the common disclosure provides no examples of (and provides zero guidance concerning producing) enzymatically active PH20 mutants that terminate below position 447, thus ignoring the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433.[97] And, again, the mathematical boundaries of the claims explicitly encompass modified PH20 polypeptides with these types of truncations.

3. Empirical Results from Testing Single-Replacement Modified PH20 Does Not Identify Multiply-Modified Enzymatically Active PH20 Polypeptides

The empirical results reported in the common disclosure provide no predictive guidance to a skilled artisan about the structural features of the vast

[96] EX1003, ¶¶ 160-165.

[97] EX1003, ¶¶ 143, 159, 167-169.

genus of amino acid changes that can be combined to form multiply-modified PH20 polypeptides.

a) Data Showing Most Single-Replacements Were Inactive or Less Active Is Not Probative of Multiple-Replacement Mutants

The common disclosure reports results from testing a portion of a randomly generated library of ~6,743 single-replacement $PH20_{1-447}$ polypeptides.[98] It explains the mutants were generated with a mutagenesis process which substituted one of ~15 amino acids into random positions in $PH20_{1-447}$ "such that each member contained a single amino acid change." [99] Approximately 5,917 were tested, while ~846 were uncharacterized.[100] More than half (~57%) of these mutants were classified as "inactive mutants," while ~30% (1335) were reported to have less

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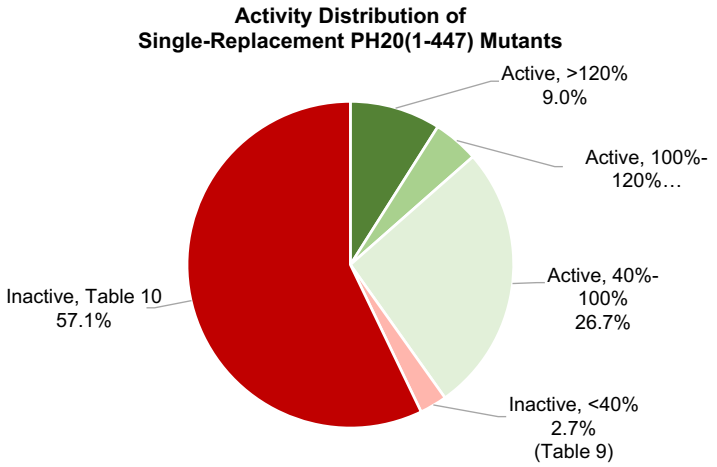
98 EX1001, 134:48-59, 202:15-17, 201:12-202:1.

99 EX1001, 201:12-202:4.

100 EX1003, ¶¶ 103-104. The common disclosure reports inconsistent numbers of tested mutants and classifications of mutants. Table 3 lists 2,516 single-replacement $PH20_{1-447}$ mutants as "active mutants," but Table 9 identifies only 2,376 mutants that exhibit >40% hyaluronidase activity. Likewise, Tables 5 and 10 list 3,368 and 3,380 $PH20_{1-447}$ "inactive mutants," respectively. The discrepancies are not explained.

activity than unmodified PH20$_{1-447}$ (20%-100%)[101] In other words, ~87% of the single-replacement PH20$_{1-447}$ polypeptides had ***less*** activity than unmodified PH20$_{1-447}$.

Activity vs. Unmodified PH20	**Number**	**% of Tested (5916)**
Active Mutants (Table 9)		
>120%	532	9.0%
100%-120%	267	4.5%
40%-100%	1577	26.7%
Inactive Mutants (Table 9)		
<40%	160	2.7%
Inactive Mutants (Table 10)		
Table 10 'inactive mutants"	3,380	57.1%



The measured activity of single-replacement PH20$_{1-447}$ mutants shows no trends or correlations even for single-replacement PH20$_{1-447}$ polypeptides.[102]

101 EX1003, ¶ 105.

102 EX1003, ¶¶ 106, 142-143.

Moreover, there are numerous examples in the dataset where the effects of introducing different amino acids into a single position in $PH20_{1-447}$ resulted in (i) increased activity, (ii) decreased activity or (iii) inactive mutants (below).[103]

Position	Inactive	Decreased Activity	Increased Activity
008	P	L, M	I
067	R	L, Y	V
092	H	M, T	C, L, V
165	C	A, R, Y	D, F, N, S, V, W
426	K, S	E, G, N, Q, Y	P

The data on activities of tested single-replacement $PH20_{1-447}$ mutants is not analyzed or explained in the common disclosure—it is simply presented. There is no attempt to extrapolate its results to particular combinations of substitutions in PH20 polypeptides, or to even assess the impact the single substitution had on the protein's structure.[104] The quality of the data is also questionable: no control values are reported or statistical assessments.[105] The only realistic takeaway from the data is that most of the tested, random single-substitution mutants impaired PH20's activity.[106] Unlike single substitutions, multiple concurrent mutations can

[103] Data from Tables 3, 5, 9, 10.

[104] EX1003, ¶ 139.

[105] EX1003, ¶ 106.

[106] EX1003, ¶ 138.

cause complex and unpredictable effects on a protein's structure and resulting function.[107] The patent's empirical set of test results provides no insights of value to a skilled artisan attempting to identify which of the many possible mutants with different sets of 2-22 substitutions will be enzymatically active modified PH20 polypeptides.[108]

b) Purported Stability Data is Not Reliable or Probative

The common disclosure reports results in Tables 11 and 12 from two runs of supposed "stability" testing of ~409 single-replacement $PH20_{1-447}$ polypeptides. Table 11 reports the hyaluronidase activity of single-replacement $PH20_{1-447}$ mutants tested at 4° and 37 °C, and in the presence of a preservative (m-cresol),[109] while Table 12 compares relative activities under pairs of these conditions.[110]

The data in Tables 11 and 12 provides no meaningful insights.[111] For example, it is unsurprising that single-replacement $PH20_{1-447}$ polypeptides showed higher activity at 37°C than at 4°C, given that PH20 exists at that temperature in

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107 EX1003, ¶¶ 139, 142

108 EX1003, ¶¶ 140, 143.

109 EX1001, 271:7-276:67 (Table 11).

110 EX1001, 277:1-287:67 (Table 12).

111 EX1003, ¶ 76.

humans.[112] Testing with a phenolic preservative, on the other hand, showed that only a few mutants were able to resist its effects.[113]

More generally, the examples fail to demonstrate that measured activity data was attributable to improved stability in the PH20 structure, and do not identify to the skilled artisan which multiple substitutions may improve stability.[114] They provide no probative insight regarding multiply-modified PH20 polypeptides.[115]

The values are also largely meaningless, as many of them fall within the huge variability measured for the positive control.[116] The chart below shows coloring reflecting relative percentage values from 0 to 120% for the positive controls from Table 11/12 and plots those values below.[117]

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112 EX1003, ¶ 73.

113 EX1003, ¶ 69.

114 EX1003, ¶¶ 75-76.

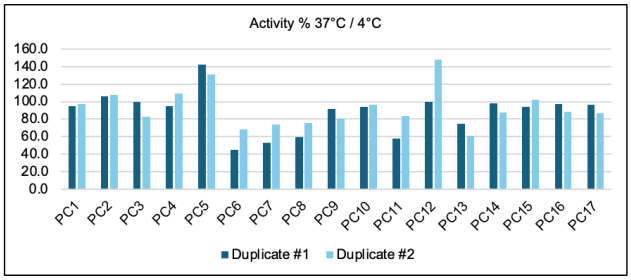
115 *Id*.

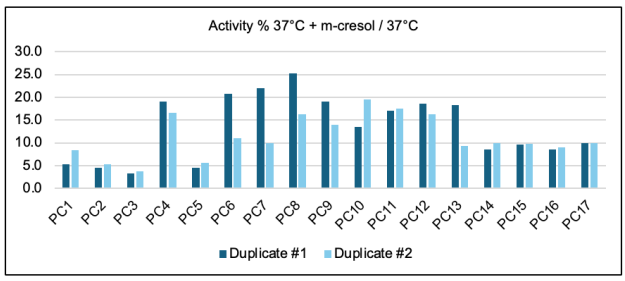
116 EX1003, ¶ 71; EX1001, 287 (Table 12).

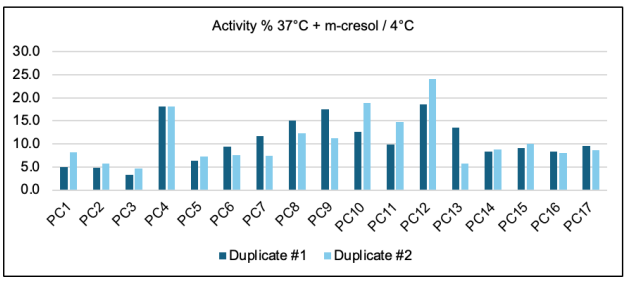
117 EX1003, ¶ 71, Appx. A-7, A-8.

Positive Control ("PC") (OHO)	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol / 37°C	% Activity at 37°C+mcr/4°C
PC1	94.998	5.230	4.970	96.871	8.456	8.190
PC2	105.798	4.480	4.740	108.066	5.246	5.670
PC3	100.000	3.330	3.330	82.778	3.759	4.590
PC4	94.762	19.070	18.070	109.539	16.529	18.110
PC5	142.024	4.480	6.360	130.947	5.595	7.330
PC6	45.115	20.770	9.370	68.017	11.035	7.510
PC7	53.324	21.950	11.710	74.253	9.960	7.400
PC8	59.581	25.240	15.040	75.872	16.231	12.310
PC9	91.844	19.050	17.500	80.371	13.977	11.230
PC10	93.828	13.470	12.630	96.630	19.454	18.800
PC11	57.773	17.040	9.850	83.536	17.573	14.680
PC12	100.000	18.560	18.560	148.226	16.239	24.070
PC13	74.325	18.290	13.600	61.119	9.286	5.680
PC14	98.132	8.480	8.320	87.677	10.006	8.770
PC15	93.817	9.620	9.020	102.223	9.745	9.960
PC16	96.922	8.560	8.300	87.993	9.064	7.980
PC17	96.648	9.910	9.580	86.891	9.938	8.630

KEY
Coloration of Percent (%) Activity Values
n/a
>120
between 100 and 120
between 80 and 100
between 40 and 80
between 20 and 40
between 10 and 20
between 0 and < 10







	Duplicate #1			Duplicate #2		
	% Activity at 37°C/4°C	% Activity at 37°C + m-cresol	% Activity at 37°C + mcr/4°C	% Activity at 37°C/4°C	% Activity at 37°C+m-cresol	% Activity at 37°C+mcr/ 4°C
High	142.02	25.24	18.56	148.23	19.45	24.07
Low	45.12	3.33	3.33	61.12	3.76	4.59
Range	96.91	21.91	15.23	87.11	15.70	19.48
Average	88.17	13.38	10.64	93.00	11.30	10.64
Mean	94.76	13.47	9.58	87.68	9.96	8.63

The table and graphs above show the extensive variability observed for the positive control in the assay being used, with the range in values of almost 100%. As Dr. Hecht observes, the "significant variation raises serious doubts about how probative or instructive the values of individual tested mutants that fall within the range of variability observed for the control can possibly be," meaning the data not only is uninformative, it is unreliable.[118]

4. The Common Disclosure's Research Plan Does Not Identify Multiply-Mutated Enzymatically Active PH20 Polypeptides

Instead of describing any multiply-modified PH20 polypeptides that are "active mutants," the common disclosure provides only a prophetic research plan based on iterative rounds of "make-and-test" experiments that were never

[118] EX1003, ¶ 70-72.

performed. This prophetic method provides absolutely no insights into which multiply-modified PH20 polypeptides are active mutants.[119]

The common disclosure merely outlines ***the idea*** of multiply-modified PH20 polypeptides. It declares that "[a] modified PH20 polypeptide can have up to 150 amino acid replacements," "[t]ypically" contains between 1 and 50 amino acid replacements and "can include any one or more other modifications**,** in addition to at least one amino acid replacement as described herein."[120] In addition to PH20 polypeptides with single amino acid replacements, it contends that a modified PH20 polypeptide "having a sequence of amino acids that exhibits" between 68% and 99% sequence identity with any of unmodified Sequence ID Nos. 74-855 "***can*** exhibit altered, such as improved or increased properties or activities compared to the corresponding PH20 polypeptide not containing the amino acid modification (e.g., amino acid replacement)."[121]

None of these statements identify ***any*** actual multiply-modified PH20 polypeptides—it does not identify ***any*** sets of specific amino acid substitutions.

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[119] EX1003, ¶¶ 173, 184-185, 190.

[120] EX1001, 48:43-50.

[121] EX1001, 100:23-100:37 (emphasis added).

They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides.

The common disclosure then outlines an "iterative" make-and-test research plan for discovering modified PH20 polypeptides with multiple substitutions that might exhibit hyaluronidase activity. It too is prophetic, and states:

> The method provided herein [] is ***iterative***. In one example, after the method is performed, any modified hyaluronan-degrading enzymes identified as exhibiting stability… ***can be modified or further modified*** to increase or optimize the stability. A secondary library ***can be*** created by introducing additional modifications in a first identified modified hyaluronan-degrading enzyme. … The secondary library ***can be*** tested using the assays and methods described herein.[122]

The guidance in this research plan is effectively meaningless. It says to make mutants, test them to find activity, and keep repeating the process until you find something via screening. It does not indicate that any useful multiply-modified PH20 polypeptides will be found, much less what their specific characteristics or activities are.[123]

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[122] EX1001, 142:14-26 (emphases added); *also id.* 42:48-55.

[123] EX1003, ¶¶ 187-190.

The specification also incorrectly portrays the experimental readout—hyaluronidase activity—as a measure of "stability."[124] As Dr. Hecht explains, to assess a protein's stability directly one performs experiments that measure the energy associated with the protein's transition between its folded and unfolded states.[125] Activity may or may not be influenced by stability but is not itself a measure of stability.[126]

An alternative focus is then proposed: mutations can be "targeted near" "critical residues" which supposedly "can be identified because, when mutated, a normal activity of the protein is ablated or reduced."[127] But the Tables 5 and 10 show that at least one substitution at each of 405 positions between positions 1 and 444 of $PH20_{1-447}$ resulted in an inactive mutant.[128] In other words, the guidance is to target locations "near" ~90% of the amino acids in $PH20_{1-447}$, which is no

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124 EX1003, ¶¶ 67, 69, 179.

125 EX1003, ¶¶ 63-66.

126 EX1003, ¶ 67.

127 EX1001, 142:27-53.

128 EX1003, ¶ 180, Appendix A-3.

different than targeting every residue in the protein.[129] It is, like the first proposed "iterative" process, meaningless.

These prophetic research plans, based entirely on unfocused, iterative "make-and-test" experiments, provide no direction to the skilled artisan about which of the trillions and trillions of possible multiply-modified PH20 polypeptides are "active mutant" PH20 polypeptides. Instead, it requires the skilled artisan to repeat the cycle of mutagenesis iteratively, screening and selection until 10^{49} to 10^{65} modified PH20 polypeptides are produced and screened for activity.[130] That in no way demonstrates possession of the claimed genus.

5. The Common Disclosure Does Not Identify a Structure-Function Relationship for Multiply-Modified, Enzymatically Active PH20 Polypeptides

The common disclosure does not identify the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are

[129] EX1003, ¶ 180.

[130] EX1003, ¶¶ 175-177, 181, 187-188.

responsible for the measured change in hyaluronidase activity.[131] Instead, it simply lists single replacements made across effectively the entire protein sequence that incorporate randomly selected amino acids being classified as "active mutants" in a hyaluronidase assay, without further explanation, and nothing is said about the effects (if any) of substitutions on the protein's structure.[132]

The common disclosure also does not identify any ***sets*** of specific amino acid replacements that correlate to structural domains or motifs that positively or negatively influence hyaluronidase activity, much less ***predictably*** increase activity to defined thresholds.[133] Again, it simply reported activity data from testing randomly generated ***single***-replacement $PH20_{1-447}$ mutants.

The common disclosure's empirically identified examples of "active mutant" single-replacement $PH20_{1-447}$ mutants also do not ***by themselves*** identify any "structure-function" relationship between "active mutants" and the set of single-replacement modified $PH20_{1-447}$ polypeptides.[134] And they plainly do not do so for the much larger genus of modified PH20 polypeptides having varying

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131 EX1003, ¶¶ 139-140, 151.

132 EX1001, 234:27-56.; EX1003, ¶¶ 139-140, 142.

133 EX1003, ¶¶ 55, 142-143.

134 EX1003, ¶¶ 61, 143, 157, 159.

lengths and between 2 and 22 substitutions, with or without additions or deletions.[135]

Critically, the common disclosure also ***does not even contend*** that a particular amino acid replacement at a particular position that makes a $PH20_{1-447}$ an "active mutant" will make any other modified PH20 polypeptide with that same amino acid replacement (plus between 2 to 22 additional replacements or truncations) an "active mutant."[136] Such an assertion would have no scientific credibility—the activity of a protein such as PH20 is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.[137] Thus, even the inventors did not view their compilation of test results as identifying a structure-function correlation for multiply-modified PH20 polypeptides.

The common disclosure, thus, does not identify to a skilled artisan ***any*** structural features shared by the many, diverse "active mutant" modified PH20 polypeptides within the scope of the claims.[138] As such, it cannot satisfy the

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135 EX1003, ¶¶ 157.

136 EX1003, ¶¶ 168, 192-193.

137 EX1003, ¶¶ 56-57.

138 EX1003, ¶ 157.

written description requirement of § 112(a) as being a disclosure that links a functional property shared by members of the genus to a particular structure ***shared*** by the members of the genus.

6. The Common Disclosure Does Not Describe a Representative Number of Multiply-Modified Enzymatically Active PH20 Polypeptides

The ~2,500 single-replacement $PH20_{1-447}$ polypeptides that are "active mutants" are not examples representative of the claimed genera of claims 1 to 4, much less its various sub-genera.[139]

First, the single-replacement $PH20_{1-447}$ examples are not representative of the trillions and trillions of $PH20_{1-447}$ polypeptides with between ***2 and 22 substitutions*** at any of hundreds of positions within the protein.[140] The latter group of proteins is structurally distinct from single replacement PH20 polypeptides, both as to their sequence and due to the various structures within the folded protein that, when incorporating different amino acid substitutions, may alter their structures and their interactions with neighboring residues.[141] The effects of those numerous substitutions on a protein's various secondary structures and structural motifs

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[139] EX1003, ¶¶ 61, 143, 155, 159.

[140] See § V.A.2.b; EX1003, ¶¶ 61, 143, 159.

[141] EX1003, ¶¶ 54-56, 58, 120, 156, 159.

within the protein is not described in the common disclosure, and at the magnitude of concurrent substitutions encompassed by the claims was unknowable in 2011.[142] The overall activity of a protein with multiple substitutions also will not be due to one amino acid, but to the unique structure of each protein that reflects ***the totality*** of effects of those many substitutions.[143]

More specifically, introducing a first amino acid substitution often affects the neighbors of that original/replaced amino acid by, for example, (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, (iii) introducing a conflicting interaction (e.g., adverse charge or hydrophobicity interactions).[144] Introducing a second substitution in that region may reverse those interactions (or not) with each neighboring residue, and a third substitution may do the same, up to 22 rounds each potentially impacting each interaction.[145] The data associated with a single amino acid substitution thus cannot be representative of the properties of any of these downstream, multiply-substituted mutants, which will have an

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142 EX1003, ¶ 224.

143 EX1003, ¶¶ 36, 61, 140, 143, 151.

144 EX1003, ¶¶ 56-58.

145 EX1003, ¶¶ 58-60, 142.

unknowable combination of substitutions that each uniquely impact the properties of the mutated protein.[146]

Single-replacement $PH20_{1-447}$ polypeptides are also not representative of multiply-modified PH20 polypeptides that incorporate structural modifications that rendered the wild-type protein inactive, including polypeptides (i) with truncations terminating below position 429, and (ii) which incorporated a single substitution at a position that rendered $PH20_{1-447}$ inactive.[147] Single-replacement $PH20_{1-447}$ polypeptides are not representative of those sub-genera of mutants because they do not have the additional structural features that are distinct from those in the wild-type sequence and that impart detrimental effects. For example, a single-replacement, active $PH20_{1-447}$ PH20 polypeptides would not be considered representative of a PH20 with multiple substitutions and a sequence with 409 to 433 residues (which would still be in the claims' scope). [148] A skilled artisan could not have predicted—based on the disclosed data, all of which are in a $PH20_{1-447}$ sequence—whether a severely truncated mutant could be further modified to

[146] EX1003, ¶¶ 61, 142-143, 159, 169.

[147] EX1003, ¶¶ 161-164.

[148] EX1003, ¶¶ 167-169

restore hyaluronidase activity, much less what additional substitutions would restore activity.[149]

The Patents thus provide a very narrow set of working examples relative to the diversity of modified PH20 polypeptides being claimed.[150] The examples are restricted to ***one type of change*** (a single amino acid replacement) in ***one type of PH20 polypeptide*** (SEQ ID NO:3).[151] By contrast, the claims encompass changes in 35 different unmodified PH20 sequences, and include, in addition to one identified replacement, anywhere from 1 to 21 (claim 1), 1-16 (claim 3) or 1-20 (claim 4) additional changes.[152] A simple illustration demonstrates how ***non-representative*** the examples are: all of the Patents' examples of single-replacement $PH20_{1-447}$ mutants fit into one box of the array below.

[149] EX1003, ¶ 168.

[150] EX1003, ¶ 155.

[151] EX1003, ¶¶ 97, 99, 103.

[152] EX1003, ¶¶ 115-120.

	Number of Changes																				
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
3																						
32																						
33																						
34																						
35																						
36																						
37																						
38																						
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Consequently, the skilled artisan would not have viewed the Patents' examples of individual single amino acid replacements in $PH20_{1-447}$ as

representative of the diversity of modified PH20 polypeptides encompassed by the claims.[153]

7. The Claims Capture Multiply-Modified PH20 Polypeptides the Disclosure Excludes from the Class of Enzymatically Active PH20 Proteins

Patentee's position on the breadth of the claims is unknown. However, by their literal language, the claims capture several sub-genera of "active mutant" modified PH20 polypeptides the common disclosure says caused single-replacement $PH20_{1-447}$ mutants to be rendered inactive (*i.e.*, those with replacements in Tables 5/10 or in PH20 sequences truncated below position 429) . Likewise, the claim language captures modified PH20 polypeptides with the six combinations of replacements the common disclosure explicitly says to not make: P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, N333A/N358A and N47A/N131A/N219A.[154] The claims thus improperly capture subject matter the common disclosure affirmatively excluded from the genus of enzymatically active modified PH20 polypeptides having multiple substitutions and other changes.

The common disclosure provides no exemplification of multiply-modified species of PH20 polypeptides that violate these prohibitions in the common

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153 EX1003, ¶ 143.

154 *See* § V.A.2.a; EX1001, 77:45-57.

disclosure.[155] There is no explanation of the types of substitutions that might be made to restore activity that, under the logic of the common disclosure, will result in enzymatically inactive PH20 polypeptides or which the specification teaches ***not*** to make.[156] Yet the claims encompass such proteins,. The claims therefore independently violate the written description requirement for the reasons articulated by the Federal Circuit in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed Cir. 1998)—if a disclosure "unambiguously limited" the invention, but the claims circumvent that limitation, those claims are "broader than the supporting disclosure" and are unpatentable.

8. The Dependent Claims Lack Written Description

a) Claims 5 and 6 Lack Written Description

Claims 5 and 6 add a purely functional requirement to the genus defined by claim 1: that the modified PH20 polypeptides exhibit increased (>100% (claim 5) or >120% (claim 6)) hyaluronidase activity relative to unmodified $PH20_{1-447}$.

The reasons provided in §§ V.A.1-V.A.7 explaining why claims 1-4 lack written description apply with full force to claims 5 and 6. Stated simply, the common disclosure's recitation of a ***desired*** level of hyaluronidase activity in

[155] EX1003, ¶ 161.

[156] EX1003, ¶ 168.

claims 5 and 6 does not identify ***which*** of the many trillions of PH20 polypeptides having 95% sequence identity with SEQ ID NOS: 3 or 32-66 and one of four replacements at position 320 will exhibit those functional requirements.[157]

First, the identification of three $PH20_{1-447}$ mutations at position 320 that exhibit 120% or higher activity (H, K, R, S) of unmodified $PH20_{1-447}$ is not representative of each claim's genus of PH20 polypeptides with 2 to 22 additional substitutions and/or truncations.[158] There is no description of multiply-modified PH20 polypeptides with the claimed substitutions at 320, much less one that identifies the 2 to 22 more substitutions and would retain this elevated enzymatic activity.[159] Indeed, the common specification does not identify even one multiply-modified PH20 polypeptide with any level of hyaluronidase activity.[160]

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides and exhibiting the recited >100% or >120% activity.[161] Certainly, the mere presence of a D320K replacement in a

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157 EX1003, ¶¶ 185, 191-192.

158 EX1001, 237 (Table 9); EX1003, ¶¶ 191-192.

159 EX1003, ¶¶ 140, 190-193.

160 EX1003, ¶¶ 130, 172.

161 EX1003, ¶¶ 157, 190.

multiply-modified PH20 does not dictate such a result, and the common disclosure makes no claim that it does.[162]

Claims 5 and 6 lack written description in the common disclosure.

b) Claim 7 Lacks Written Description

Claim 7 requires the modified PH20 polypeptide of claim 1 to be "soluble." Because the specification fails to support the genus of modified PH20 polypeptides of claim 1, it lacks written description support for the same reasons.

Additionally, while the common disclosure provides varying observations on what the word "soluble" means, it also acknowledges that "soluble" forms of PH20 are those lacking the C-terminal GPI attachment sequence.[163] The GPI anchor sequence was known to be hydrophobic, consistent with its role in anchoring the PH20 protein in the cell membrane.[164] The common disclosure thus explains that PH20 polypeptides that retain the GPI sequence "are insoluble in solution.[165] It

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[162] EX1003, ¶¶ 143, 168, 192.

[163] EX1001, 46:28-30, 72:8-9.

[164] EX1005, 86:18-22.

[165] EX1005, 2:56-61 ("Attempts to make human PH20 DNA constructs that would not introduce a lipid anchor into the polypeptide resulted in either a catalytically inactive enzyme, or an insoluble enzyme") (citing EX1011).

also teaches that PH20 is rendered soluble by deleting sequences above position 448.[166]

Because claim 7 is based on claim 1, it encompasses PH20 polypeptides based on SEQ ID NOS:59-66, which terminate between positions at 457 to 464 respectively (*i.e.*, beyond position 456). The claims do not restrict where in the PH20 polypeptide changes are made, other than the replacement at position 320.

Consequently, the claims as written capture modified PH20 polypeptides that, per the common disclosure, ***are not*** "soluble modified PH20 polypeptides" because each contains "all or a portion of" the GPI attachment sequence.[167]

Patentee may contend that some unidentified number of modified PH20 polypeptides based on SEQ ID NOS:59-66 ***may*** be soluble, suggesting that between 1-10 residues within the GPI anchor "can be retained, provided the polypeptide is soluble."[168] But, again, the common disclosure provides no examples of modified PH20 polypeptides that contain the GPI anchor sequence that ***are*** soluble. It also provides no reason to expect that many modified PH20 polypeptides within the claim's scope would be soluble, much less provide

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166 EX1001, 75:16-18; EX1005, 3:57-62.

167 EX1001, 46:55-61.

168 EX1001, 74:19-25.

guidance to identify ***which*** PH20 polypeptides extending beyond position 456 are soluble.

Thus, claim 7 is unpatentable for lack of written description for this additional, independent reason.

c) Claims 8-10 Lack Written Description

Claims 8-10 employ claim 1's definition of the genus of modified PH20 polypeptides, and do not add requirements that limit the numbers of polypeptides in that genus. Claims 8-10 lack written description for the same reasons as claim 1.

d) Claims 11 to 20 Lack Written Description

Claims 11-20 employ claim 1's definition of the genus of modified PH20 polypeptides to define nucleotides, host cells, pharmaceutical compositions and methods of administering such compositions, but do not limit the genus that claim 1 defines. Claims 11-20 lack written description for the same reasons as claim 1.

e) Claim 21 Lack Written Description

Claim 21 defines a method of producing a genus of PH20 polypeptides that employs the same genus definition as claim 1, and thus lacks written description for the same reasons.

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

"If a patent claims an entire class of … compositions of matter, the patent's specification must enable a person skilled in the art to make and use the ***entire*** class," *i.e.* "the ***full scope*** of the invention."[169] So, the "more one claims, the more one must enable."[170] "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."[171] "Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation."[172]

Although not required, enablement may be assessed using the *Wands* factors, which consider: "(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the

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169 *Amgen*, 598 U.S. at 610 (emphasis added).

170 *Id.*

171 *Idenix*, 941 F.3d at 1159.

172 *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention."[173]

Where the scope of the claims is large, there are few working examples disclosed in the patent, and the only guidance to practice "the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims' functional limitations—the asserted claims are not enabled."[174]

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the 10^{49}+ PH20 polypeptides having multiple amino acid replacements and/or truncations are "active mutant" PH20 polypeptides within the scope of the claims.[175]

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[173] *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

[174] *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, T., sitting by designation) *aff'd* 81 F.4th 1362 (Fed. Cir. 2023).

[175] EX1003, ¶¶ 170-171, 190.

1. Claims 1 to 4 Are Not Enabled

The facts of this case are a textbook example of claims that are not enabled under the reasoning articulated by the Supreme Court in *Amgen*. An analysis of the common disclosure under the Federal Circuit's framework for assessing undue experimentation using the factors in *In re Wands*, 858 F. 2d 731 (Fed. Cir. 1988) also compels the same conclusion.

a) Extreme Scope of the Claims

As explained in § IV.D.1, each of claims 1 to 4 define an immense and structurally diverse genus of between 10^{49} and 10^{65} modified PH20 polypeptides, which introduces substantial scientific questions that are left unanswered by the common disclosure.

The claims encompass many modified PH20 polypeptides that terminate below position 429.[176] The common disclosure and the prior art, however, report that unmodified human PH20 must include residues through position 429 to have hyaluronidase activity.[177] Several of the claims (1-2, 5-21) also encompass modified PH20 polypeptides that, per the common disclosure's guidance, would be expected to be insoluble because they include all or some of the GPI anchor

[176] EX1003, ¶¶ 154, 164.

[177] EX1001, 69:66-70:8; EX1003, ¶¶ 93, 152-153.

sequence.[178] And, to the extent patentee contends the claims should be read as covering any polypeptide that falls within the mathematical "sequence identity" boundaries set by the claim language, they would capture modified PH20 polypeptides with 2-22 amino acid replacements the common disclosure instructs "are less tolerant to change or required for hyaluronidase activity"[179] or which the common disclosure affirmatively says to not make.[180]

In other words, the claims capture a massive genus of modified PH20 polypeptides, most of which would have unknowable properties absent individual production and testing.[181]

Claims that capture a massive and diverse genus of proteins have routinely been found non-enabled. For example, the claims in *Amgen* covered "millions" of different, untested antibodies,[182] while in *Idenix*, a skilled artisan would "understand that 'billions and billions' of compounds literally meet the structural

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178 EX1001, 46:28-30, 72:8-9, 74:19-25, 75:16-18; EX1005, 2:56-61, 3:57-62.

179 EX1001, 80:13-15.

180 EX1001, 77:45-57.

181 EX1003, ¶ 158.

182 598 U.S. at 603.

limitations of the claim."[183] In both cases, the enormous claim scope was found non-enabled after being contrasted to the limited working examples in the patent, the existence of unpredictability, and the quantity of experimentation needed to practice the full scope of the claims (*Wands* Factors 1, 3, 4, and 7). And, as the *Idenix* court observed, one cannot rely on the knowledge and efforts of a skilled artisan to try to "fill the gaps in the specification" regarding which of the "many, many thousands" of possible compounds should be selected for screening, and which in this case is impossible.[184]

b) Limited Working Examples and Only a Research Plan for Discovering Active Mutant PH20 Polypeptides

The common disclosure provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement $PH20_{1-447}$ polypeptides, of which ~2500 were "active mutants."[185] Those examples are a tiny fraction of the 10^{49} to 10^{66} modified PH20 polypeptides covered by the claims, and provide no guidance that would help a skilled artisan navigate the "trial-and-error" methodology the common disclosure describes using to make modified PH20

183 941 F.3d at 1157.

184 *Id.* at 1159.

185 EX1003, ¶ 103.

polypeptides; indeed, none incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.[186]

The common disclosure provides no credible guidance on the full scope of the genus comprising multiple combinations of changes to PH20 polypeptides.[187] Instead, it describes an explicitly prophetic and "iterative" process for ***discovering*** active mutant PH20 polypeptides. See § V.A.4.

The purely-prospective research plan in the common disclosure demands that a skilled artisan engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of ***randomized*** mutations (up to 21 rounds per starting molecule under the broadest claims) to ***discover*** which of the 10^{49}+ possible modified PH20 polypeptides having 2 to 21 replacements to any of 19 other amino acids in any of 35 starting PH20 sequences might possess hyaluronidase activity.[188]

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186 EX1003, ¶¶ 155, 159, 167.

187 EX1003, ¶ 131, 139.

188 EX1003, ¶¶ 188-190; *see also* EX1018, 382 (noting that "combinatorial randomization of only five residues generates a library of 205 possibilities (3.2 x 106 mutants), too large a number for manual screening"). Chica also credited a supposed "ground-breaking" advancement in predictive molecular

Second, it provides no meaningful guidance in producing "active mutant" modified PH20 polypeptides:

(i) it does not identify ***any*** specific combination of two or more replacements within any PH20 polypeptide that yield "active mutants";

(ii) it provides no data from testing ***any*** PH20 polypeptide with two or more substitutions;

(iii) it does not identify any regions or residues that are "associated with the activity and/or stability of the molecule" or "'critical residues involved in structural folding or other activities' of the molecule" when two or more concurrent replacements have been made.[189]

A skilled artisan could not predict whether a particular multiply-modified PH20 polypeptide will be enzymatically active without making and testing each one.

Regardless of whether individual rounds of "iterative" production and testing might be considered "routine," the process described in the common

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modeling techniques. EX1018, 384, 382. That supposed advancement, however, was later shown to be false. EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859..

[189] EX1003, ¶¶ 144, 158, 172, 184-185.

disclosure is indistinguishable from the "***iterative, trial-and-error process[es]***" that have consistently been found to not enable broad genus claims to modified proteins.[190] Simply put, the common disclosure's prophetic, iterative and labor-intensive process requires making and screening an immense number of modified PH20 polypeptides, before which the skilled artisan will not know which multiply-modified PH20 polypeptides are within the claims' scope.[191]

c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable

Like any protein, the activity of PH20 can be unpredictably influenced by changes to its amino acid sequence.[192] Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary structures or structural motifs within the protein that are important to its biological activity (e.g., catalysis, ligand binding, *etc*.).[193]

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190 *Idenix*, 941 F.3d at 1161-63 (emphasis added); *see also Amgen,* 598 U.S. at 612-15; *Wyeth*, 720 F.3d at 1384-86; *Baxalta*, 597 F. Supp. 3d at 616-619; *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 n.2 (Fed. Cir. 2020).

191 EX1003, ¶¶ 172, 184-185, 189.

192 EX1003, ¶ 161.

193 *Id.*

As explained in § VI, below, by 2011, skilled artisans could have assessed whether certain ***single*** amino acid substitutions at certain positions would be tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.[194] That person, using a rational design approach, would have performed such an assessment by, *inter alia*, analyzing evolutionarily non-conserved positions and evaluating specific changed residues using a PH20 protein structure model using experimental evidence available before 2011 that is not disclosed in or referenced by the common disclosure.[195]

By contrast, the skilled artisan could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011-2012.[196] Introducing ***multiple*** concurrent changes into a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity, and can even introduce new ones into the protein.[197] Replacing multiple amino acids

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194 EX1003, ¶ 194.

195 EX1003, ¶¶ 20-22, 49, 211-212, 216.

196 EX1003, ¶ 224.

197 EX1003, ¶¶ 59-60.

thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.[198]

The cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure.[199] The further away the modeled amino acid is from the original model's structure, the less reliable that model becomes.[200] In addition, depending on the structural template used to produce the model, regions of the protein not supported by a corresponding structure cannot be reliably used to assess particular changes.[201] And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.[202]

Consequently, a skilled artisan could not have used conventional rational design techniques to identify, much less predict the outcome of attempts to make, the enormous number of PH20 polypeptide sequences that incorporate the myriad

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198 EX1003, ¶ 58.

199 EX1003, ¶¶ 158, 224.

200 EX1003, ¶¶ 159, 224; EX1004, ¶ 161.

201 EX1003, ¶¶ 158, 224; EX1004, ¶¶ 152-153; EX1012, 4, 8.

202 EX1003, ¶¶ 51; EX1059, 1225-1226; EX1018, 378.

possible combinations of between 5 and 22 substitutions the claims encompass.[203] Stated another way, practicing the full scope of the claims would have been well beyond the ability of the skilled artisan's ability to reasonably predict which multiply-modified PH20 polypeptides would be enzymatically active, and, even if possible, doing so would have taken an extreme amount of time and effort even for a small handful of the vast universe of multiply-modified polypeptides within the claims.[204]

d) Other Wands Factors and Conclusion

The remaining *Wands* factors either support the conclusion that practicing the full scope of the claims would require undue experimentation or are neutral.

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of multiply-changed PH20 polypeptides.[205] Likewise, while there was significant knowledge in the public art about hyaluronidases, there was no solved structure of the PH20 protein, experimental reports generally reported on ***loss of activity*** from mutations, and did not predictably teach how to introduce changes

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203 EX1003, ¶¶ 61, 158, 224.

204 EX1003, ¶¶ 158, 190.

205 EX1003, ¶¶, 158, 224.

that ***enhanced*** stability or activity. Indeed, the patent disclosure at issue in *Amgen* dates to the 2011-timeframe as the common disclosure.

Practicing the full scope of claims 1-4 thus would have required a skilled artisan to engage in undue experimentation, which renders those claims non-enabled.

2. The Dependent Claims Are Not Enabled

a) Claims 5 and 6 Are Not Enabled

Claims 5 and 6 require the modified PH20 polypeptides to have specific levels of increased activity (*i.e.*, >100% or >120% of unmodified PH20).

The reasons why claims 1-4 are not enabled (see § V.B.1) establish why Claims 5 and 6 are also not enabled. Specifically, a skilled artisan could not have predicted which of the trillions of PH20 polypeptides having up to 21 changes in addition to a required change at position 320 would exhibit greater than 100% or 120% of the hyaluronidase activity of an unmodified PH20.[206] Instead, a skilled artisan would need to make-and-test each of those molecules in order to practice the "full scope" of the claims.[207]

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[206] EX1003, ¶ 185, 190.

[207] *Id.*

b) Claim 7 is Not Enabled

Because claim 7 encompasses a substantial portion of the genus defined by claim 1, it is not enabled for the same reasons that claims 1-4 are not enabled.

Additionally, as explained in §§ V.A.8.b), a skilled artisan would have not predicted that PH20 polypeptides (modified or unmodified) that extend past position 456 would be "soluble." Instead, based on the published literature, a skilled artisan would have believed the presence of the highly hydrophobic GPI sequence would lead to a much greater propensity for the PH20 protein to misfold, to aggregate, and/or to not be successfully expressed from a host cell.[208] The common disclosure reinforces that these problems can occur, but provides no guidance as to how solve them and no examples of modified PH20 polypeptides extending past position 456 that are soluble. Claim 7 is thus not enabled.

c) Claims 8-10 Are Not Enabled

Claims 8-10 employ the genus definition used in claim 1, and do not add requirements that limit the numbers of polypeptides in the claim 1 genus. Claims 8-10 are therefore not enabled for the same reasons as claim 1.

d) Claims 11-20 Are Not Enabled

Claims 11-20 employ the definition of the genus of modified PH20 polypeptides used in claim 1 to define nucleotides, host cells, and PH20-based

[208] EX1003, ¶ 196.

pharmaceutical compositions and methods of administering them. None of claims 11-20 limit the number of polypeptides in the claim 1 genus. Claims 11-20 are therefore not enabled for the same reasons as claim 1.

e) Claim 21 Is Not Enabled

Claim 21 defines a method of producing a genus of PH20 polypeptides that employs the same genus definition in claim 1. Claim 21 is not enabled for the same reasons as claim 1.

C. Inactive PH20 Polypeptides Are Not Useful and Do Not Remedy the § 112(a) Deficiencies of the Claims

Patentee may contend the claims do not require the modified PH20 polypeptides to be "active mutants." Such a contention, even if accepted, does not solve the written description and enablement problems of the claims.

First, it ignores that at least a portion of the claimed genus ***does*** require the modified PH20 polypeptides to be an "active mutant." See §IV.D.3. Because dependent claims 5 and 6 require the modified PH20 polypeptides to exhibit increased hyaluronidase activity levels (>100% or 120% of unmodified PH20), parent claim 1 necessarily encompasses a sub-genus comprised of "active mutant" modified PH20 polypeptides. A failure to enable or describe a subgenus within the scope of the claims demonstrates that the claim ***as a whole*** is unpatentable for lack of written description and non-enablement.

Second, the common disclosure fails to provide any correlation between changes to PH20 polypeptides and ***either*** active or inactive mutants.[209] Rather, it leaves to the skilled artisan the burdensome task of making and testing, through trial-and-error iteration, each of the 10^{49}+ candidate polypeptides within the claims' scope to determine which exhibit hyaluronidase activity and which are inactive mutants.[210]

Third, the only putative utility identified for "inactive" polypeptides is as "antigens in contraception vaccines."[211] This assertion is not scientifically credible, but regardless, the common disclosure provides no guidance about which epitopes on the PH20 protein must be preserved in an "inactive mutant" (if any) to induce contraceptive antibody production in a human subject.[212] Notably, while the specification cites two studies in guinea pigs,[213] it ignores numerous publications before 2011 that showed that immunizing mammals with PH20 did

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209 EX1003, ¶ 143.

210 EX1003, ¶ 173-174, 182-184.

211 EX1001, 75:56-58, 194:54-195:6.

212 EX1003, ¶ 113.

213 EX1001, 194:54-195:6; EX1022 1142-43; EX1023, 1133-34.

not cause contraception.[214] Moreover, Patentee's own clinical studies of the unmodified $PH20_{1-447}$ protein reported in 2018 that, despite producing anti-PH20 antibodies, those anti-PH20 antibodies ***did not affect fertility*** in humans:

> Although some antisperm antibodies are associated with decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex.[215]

Notably, Patentee reported this clinical result almost seven years before filing the application that issued as the '600 Patent.

Even if one considers the unlikely possibility than some epitope on human PH20 might induce contraceptive effects in a human, a skilled artisan could not have reasonably predicted from the common disclosure whether any "inactive mutant" modified PH20 polypeptides would preserve that epitope or induce antibody production that would confer (contrary to Patentee's clinical evidence)

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[214] *See* EX1019, 325, 331-33 ("recombinant mPH20 is not a useful antigen for inclusion in immunocontraceptive vaccines that target mice"); EX1020, 179-81 ("immunization [of rabbits] with reproductive antigens …are unlikely to result in reduced fertility…"); EX1021, 30310, 30314 ("PH-20 is not essential for fertilization, at least in the mouse…").

[215] EX1024, 87-88; *also* EX1061, 1154; EX1003, ¶¶ 110-111.

contraceptive effects in humans.[216] Indeed, a skilled artisan would have expected the vast majority of "inactive mutant" PH20 polypeptides would have no utility at all.[217] Consequently, a skilled artisan would not have accepted the common disclosure's assertion that "inactive mutants" are useful as contraceptive vaccines, particularly in humans.[218]

Finally, and most significantly, the common disclosure does not identify a single inactive PH20 mutant (with any number of substitutions) that was shown to have contraceptive effect.[219] Therefore, at most, the common disclosure presents

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216 EX1003, ¶ 112-113.

217 *Id.*; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharmaceutical Resources, Inc. v. Roxane Labs., Inc.*, 253 F. App'x. 26, 30 (Fed. Cir. 2007).

218 EX1003, ¶ 112-113; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005) (implausible scientific statements not entitled to weight).

219 EX1003, ¶ 113.

only a "research proposal" to discover such "inactive mutants."[220] It does not demonstrate possession of or enable the immense and diverse genus of PH20 polypeptides claimed, regardless of whether the claims are appropriately limited to "active mutants" or, instead, include "inactive mutants."

D. The Original Claims of the '731 Application Do Not Cure the Written Description and Enablement Deficiencies

The specifications of the pre-AIA '731 Application and AIA '600 Patent are substantially identical, and the challenged claims are not supported as § 112(a) requires by either. The claims are both PGR-eligible and unpatentable under § 112(a).

The originally-filed claims of the '731 Application employed different claim formats but encompassed an equivalently large genus of multiply-substituted polypeptides. For example, original claim 1 required a "modified PH20 polypeptide" with an "amino acid replacement [that] confers… increased stability" and having "85% sequence identity to SEQ ID NO: 3" (claim 3) or between "1 [and] 75 or more amino acid replacements" (claim 4). Dependent claims list positions (claim 12) or replacements (claims 13-16) in those polypeptides. And,

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[220] *See Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("[t]he utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research").

while certain claims contemplated 2-3 particular combinations of amino acid replacements (from dozens of locations), the claims also encompassed other unspecified substitutions at unspecified locations.[221]

The original claims provide no additional guidance or insight that would demonstrate written description of or would enable the claimed sets of modified PH20 polypeptides. As such, the original claims do not provide §112 support for the challenged claims.[222]

VI. Challenged Claims 1-4 and 7-21 Are Unpatentable Under § 103

As explained in § IV.D.2 above, claims 1-4 each define a genus that includes ***one*** specific modified PH20 polypeptide: D320K $PH20_{1-447}$. Because that particular modified PH20 polypeptide would have been obvious from the '429 Patent in view of Chao and the knowledge of a skilled artisan before 2011, each of claims 1-4 is unpatentable. Each of claims 7-21 also would have been obvious, as

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[221] EX1026, at 335.

[222] *See, e.g.*, *Ariad Pharms.*, 598 F.3d at 1349 ("original claim language" does not "necessarily disclose[] the subject matter that it claims"); *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993) (original claim amounted to no more than a "wish" or "plan" for obtaining the claimed DNA and "attempt[ed] to preempt the future before it has arrived").

each specifies attributes that are met by the D320K modified $PH20_{1-447}$ polypeptide, or involve issues taught or suggested by the ’429 Patent alone or with other prior art.

A. The Prior Art

The ’429 Patent (EX1005) is owned by Patentee, was originally filed in 2003, and issued on Aug 3, 2010.

Chao (EX1006) is an article published in the scientific journal “Biochemistry” in 2007. Chao is not discussed in the common disclosure of the ’600 Patent and ’731 Application, and was not cited or considered during examination of either.

Knowledge of the skilled artisan relevant to obviousness is described in the testimony of Drs. Hecht (EX1003) and Park (EX1004), and is also documented in the prior art, including Patentee’s earlier-published application, WO297 (EX1007).

B. Because D320K $PH20_{1-447}$ Would Have Been Obvious, Claims 1-4 Are Unpatentable

As explained below, Patentee’s ’429 Patent would have motivated a skilled artisan to produce modified $PH20_{1-447}$ polypeptides having a single amino acid substitution in a non-essential region of the protein. That person, guided by her familiarity with conventional rational protein design principles and the teachings of the ’429 Patent and Chao, would have readily identified single amino acid substitutions in non-essential regions of PH20 that would be tolerated by the PH20

protein, such that the PH20 with the substitution would be expected to substantially retain its enzymatic activity. This process would have led the skilled artisan to identify D320K as one such single-amino acid substitution in $PH20_{1-447}$ that would be expected to retain hyaluronidase activity. Because claims 1-4 each encompass this obvious variant of $PH20_{1-447}$, each is unpatentable.

1. Patentee's '429 Patent Motivates a Skilled Artisan to Make Single Amino Acid Substitutions in Non-Essential Regions of $PH20_{1-447}$

Patentee's '429 Patent, filed in 2003, describes as its invention soluble hyaluronidase glycoproteins ("sHASEGPs") based on PH20 that are enzymatically active at neutral pH.[223] It exemplifies and claims one such "sHASEGP" produced by truncating the human PH20 sequence at position 447 (positions 36-482 of SEQ ID NO:1).[224]

The '429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, when combined with other therapeutic agents into

[223] EX1005, 6:4-10, 10:30-59.

[224] EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

formulations for subcutaneous injection.[225] A $PH20_{1-447}$ was approved by the FDA as Hylenex® in 2005.[226]

The '429 Patent's teachings combined with the status of $PH20_{1-447}$ as an approved human therapeutic before 2012 would have induced a skilled artisan to focus on this particular length PH20 polypeptide.[227]

Patentee's '429 Patent defines sHASEGPs as not only being the wild-type $PH20_{1-447}$ sequence, but as also including "equivalent" proteins "with amino acid substitutions that do not substantially alter activity" of the protein.[228] It then expands on this guidance, explaining:

> Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity …[229]

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225 EX1005, 8:25-9:4.

226 EX1049, 1.

227 EX1003, ¶ 195.

228 EX1005, 9:65-10:13; *also id.* 18:64-19:6 ("equivalent" proteins)

229 EX1005, 16:14-22.

The ’429 Patent explains that single amino acid substitutions can include “conservative” substitutions in Table 1, but that “[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions.”[230]

The ’429 Patent thus teaches making a *particular* type of modification (a single amino acid substitution) at a *particular* location (non-essential regions of PH20) in a *particular* PH20 sequence ($PH20_{1\text{-}447}$) to yield equivalents of $PH20_{1\text{-}447}$ (*i.e.*, those that do not substantially alter the activity or function of $PH20_{1\text{-}447}$).[231]

The ’429 Patent motivates skilled artisans to undertake this effort to design and produce such single-amino acid substituted $PH20_{1\text{-}447}$ proteins because it assures them their efforts will be successful.[232] As it states, skilled artisans recognized that such “single amino acid substitutions in non-essential regions” of PH201-447 “do not substantially alter biological activity” of $PH201_{1\text{-}447}$.

2. Chao Provides Information Useful for Engineering the Changes to $PH20_{1\text{-}447}$ that the ’429 Patent Suggests

In 2011, a skilled artisan looking to implement the ’429 Patent’s suggestion to make a single-amino acid modification in a non-essential region of $PH20_{1\text{-}447}$

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230 EX1050, 16:24-36.

231 EX1004. ¶¶ ; EX1003, ¶ 202-204.

232 EX1003, ¶ 203-204.

would have recognized this type of change could best be accomplished using conventional rational design techniques, as it involves determining (i) which regions are non-essential in PH20, and (ii) which single amino acids to substitute into positions in those non-essential regions.[233]

The ’429 Patent was written eight years before 2011. Given that, a skilled artisan would have looked for additional published insights into the structure of human hyaluronidase enzymes like PH20.[234] That would have led the person directly to Chao (EX1006), which reported an experimentally determined structure for human HYAL1, and provided new insights into the shared characteristics of human hyaluronidase enzymes.[235]

First, by superimposing the HYAL1 and bee venom hyaluronidase structures, Chao showed that human and non-human hyaluronidases share a highly conserved catalytic active site structure and identified residues within this catalytic site that interact with the HA substrate.[236]

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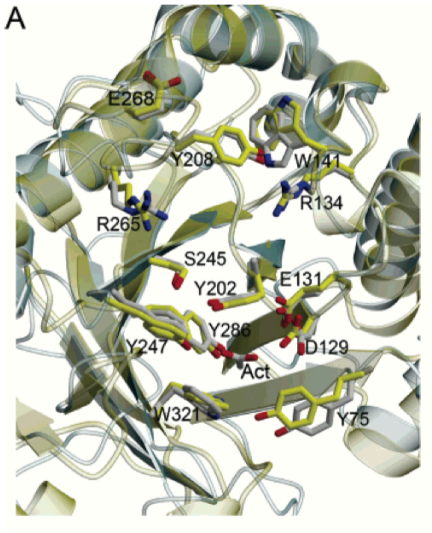
233 EX1003, ¶ 209-210.

234 EX1004, ¶ 88; EX1003, ¶¶ 86-88.

235 EX1004, ¶¶ 89-93; EX1006, 6912-6917; EX1003, ¶¶ 81-85, 205-207.

236 EX1006, 6917 (Fig. 4A); *also id.* 6914-6916, Figure 2C; EX1004, ¶¶ 89-91.



The ’429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20.[237] It also taught that hyaluronidase domains share similarity among and between species, including certain residues in conserved motifs necessary for enzymatic activity.[238]

Second, using an alignment of five human hyaluronidases, Chao identifies predicted secondary structures in the proteins (*e.g.*, β-sheets, α-helices) (Figure 3, below), as well as, invariant conserved positions (blue), residues involved in catalysis (red), conserved cysteines that form disulfide bonds (gold) and (iv) conserved asparagine residues that are glycosylated (turquoise).[239]

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[237] EX1005, 4:12-22, 86:49-53, 88:14-24.

[238] EX1005, 2:6-67, 4:11-22.

[239] EX1006, 6916.

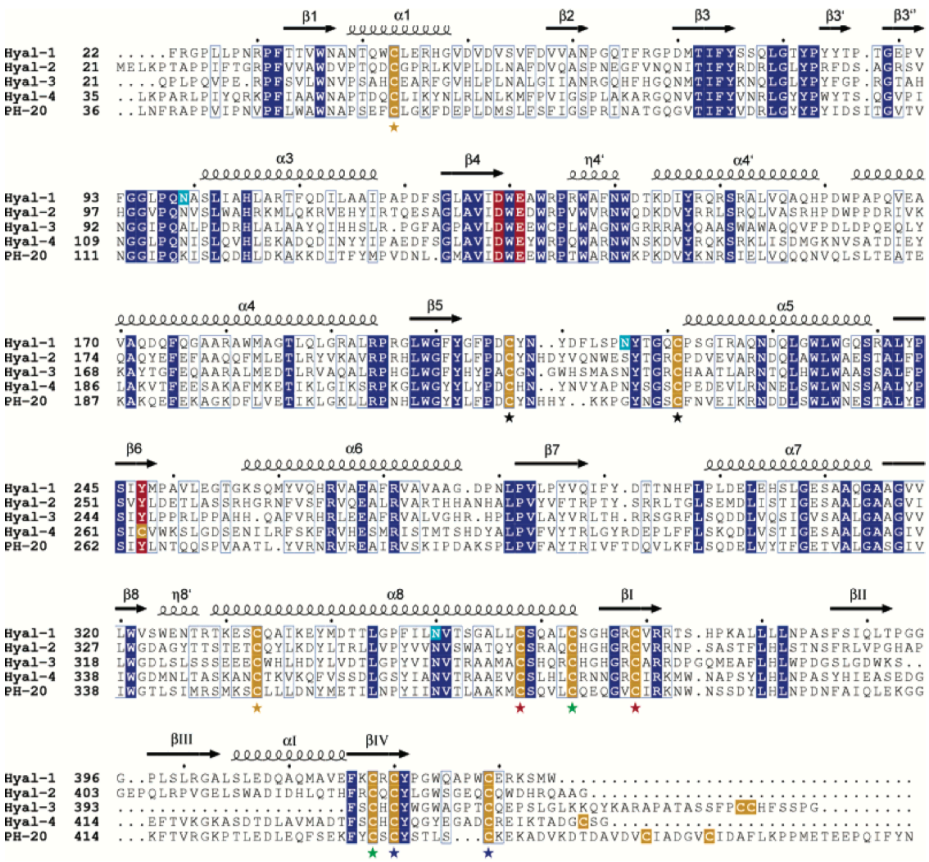

FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative replacements are blocked in blue. Pairs of cysteine residues that form disulfide bonds are indicated by stars with matching colors. Secondary structure units are labeled as in Figure 2B.

Third, Chao reported the presence of a "a novel, EGF-like domain" in the C-terminal region of human hyaluronidases that was "closely associated" with the catalytic domain (discussed above, § V.A.2.c)). Of note here, Chao identifies a characteristic pattern for the Hyal-EGF domain in PH20 (at 337-409).[240]

240 EX1006, 6912; EX1004, ¶¶ 97-98.

3. A Skilled Artisan Would Have Identified D320K as Being in a Non-Essential Region of $PH20_{1-447}$ in 2011

To implement the '429 Patent's suggestion to produce modified $PH20_{1-447}$ polypeptides with single amino acid substitutions in non-essential regions that retain hyaluronidase activity, the skilled artisan would first identify the non-essential regions of $PH20_{1-447}$.[241] The person would have done that with conventional sequence alignment tools using the guidance and information provided in the '429 Patent and Chao, and information publicly known in 2011.[242]

The skilled artisan would use a multiple sequence alignment to identify the essential residues in PH20 using proteins homologous to PH20 that were known as of December 2011.[243] The alignment also identifies the non-essential regions in PH20—they are the sequences between the essential residues at which variations above 5% occur (illustrated in Chao for five homologous sequences below).[244]

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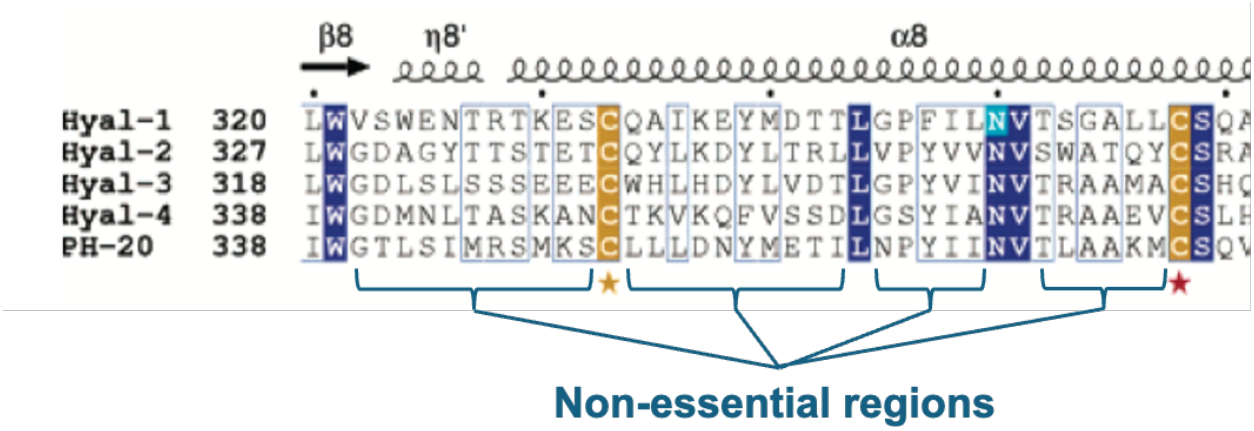
241 EX1003, ¶¶ 208-209.

242 EX1003, ¶¶ 20-21, 211-212; EX1004 ¶¶ 22-32; EX1017, 224-26.

243 EX1003, ¶¶ 209-210; EX1004, ¶¶ 22-30.

244 EX1004, ¶¶ 20, 31-32, Appendix D-2; EX1003, ¶ 211.



Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps on a set of homologous hyaluronidase protein sequences published by December 29, 2011.[245] He first identified 88 non-redundant homologous sequences known before the end of 2011.[246] Dr. Park then prepared a multiple-sequence alignment of these 88 homologous proteins, similar to what Chao did with the five human hyaluronidases, and from that alignment identified essential (Appendix D-3) and non-essential (Appendix D-2) residues.[247]

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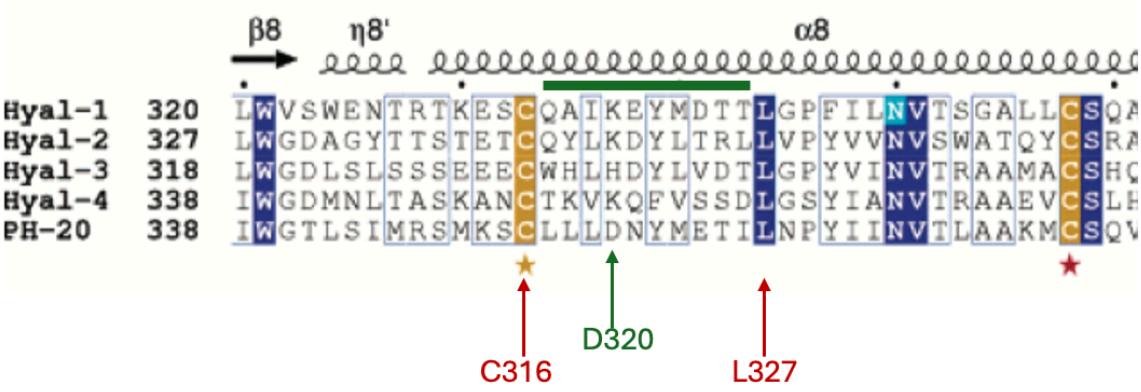
245 EX1004, ¶¶ 13-17, 22-24.

246 EX1004, ¶¶ 27, 143-146; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

247 EX1004, ¶¶ 28-32, 147-148, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

Position 320 is within a non-essential region of $PH20_{1-447}$.[248] This is shown not only by Dr. Park's analysis, but also by Chao's Figure 3, which both report the same bounding essential residues (*i.e.*, C316 and L327) (below).[249]



Thus, following the guidance and information in the '429 Patent and Chao, and using information and techniques publicly available in December 2011, a skilled artisan would have identified position 320 as a position in a non-essential region $PH20_{1-447}$.[250]

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[248] EX1004, ¶¶ 32, 31, Appendix D-2; EX1003, ¶ 213.

[249] EX1003, ¶¶ 213.

[250] EX1003, ¶ 216; EX1004, ¶¶ 31-32, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6912-6217.

4. A Skilled Artisan Would Have Found Lysine to Be Suggested as an Obvious Single Amino Acid Substitution at Position 320 of $PH20_{1-447}$

The multiple-sequence alignment reveals a second powerful insight: it identifies ***which*** amino acids have been tolerated at specific positions in the amino acid sequence of homologous, stable and active naturally occurring hyaluronidase enzymes.[251] This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms those variations in the sequences of a protein that do not yield stable and active forms of the protein.[252] Thus, a skilled artisan can readily compile a list of the specific amino acids that have been tolerated at positions within non-essential regions of PH20 using a multiple-sequence alignment of homologous hyaluronidase enzymes.[253]

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[251] EX1003, ¶¶ 214-216; EX1004, ¶ 21.

[252] EX1004, ¶¶ 21, 31, 41-42; EX1003, ¶ 214; EX1017, 224 ("Evolution provides a tremendously useful model for protein design. … By considering the common features of the sequences of these proteins, it is possible to deduce the key elements that determine protein structure and function—even in absence of any explicit structural information."); EX1014, 351.

[253] EX1003, ¶¶ 214, 216.

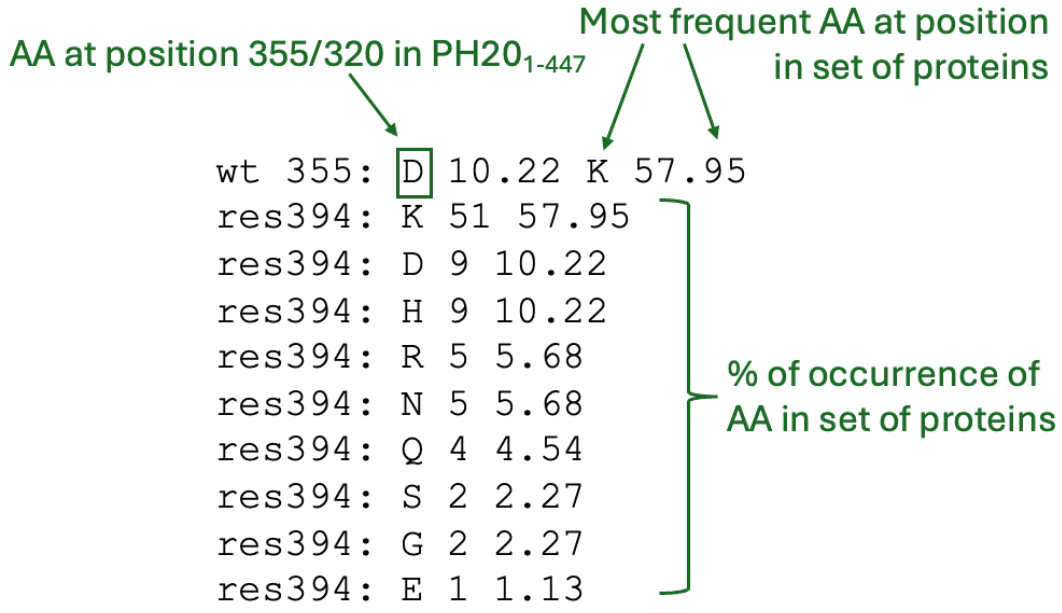
Dr. Park did this; he used the alignment he produced of the 88 hyaluronidase proteins known by December 2011 to identify and calculate the frequency of occurrence of each different amino acid that occurs at positions corresponding to each position in the non-essential regions of $PH20_{1-447}$.[254]

The amino acids appearing at position 320 of PH20 in the corresponding positions of the 88 naturally occurring hyaluronidase enzymes known by 2011 are shown below.[255] The wild-type residue at position 320 in PH20 is aspartic acid (D), which occurs in ~10% of the proteins (including PH20). The most prevalent amino acid found at position 320 in this set of homologous sequences is lysine (K) (57.95%), which is present in 51 different hyaluronidase proteins.[256]

[254] EX1004, ¶¶ 30-32, 41-43, Appendix D-1.

[255] EX1004, ¶¶ 43, 116, Appendix D-1.

[256] EX1003, ¶ 214.



Several amino acids other than aspartic acid occur with significant frequency at a position corresponding to 320 in PH20 in known, stable, and homologous hyaluronidase enzymes. A skilled artisan would have found those amino acids to be the obvious choices to assess as single amino acid substitution at that position 320 PH20$_{1-447}$.[257]

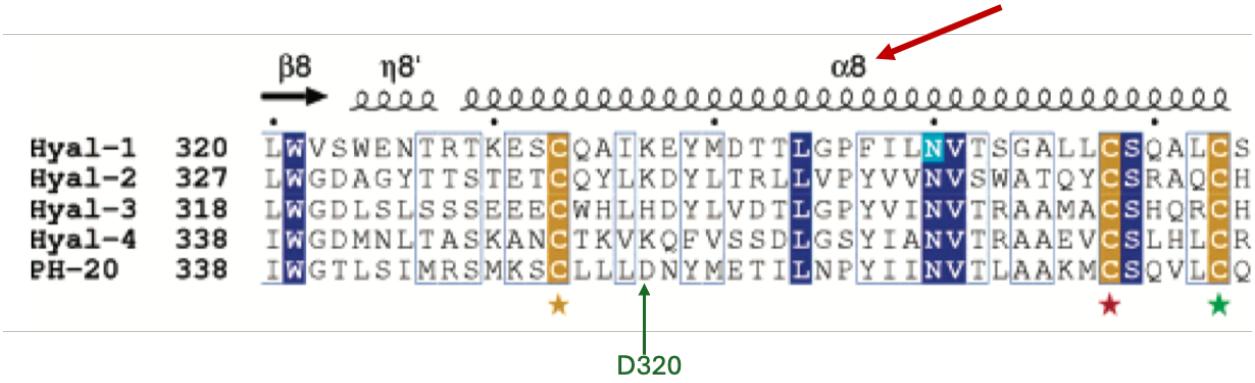
A skilled artisan would also have had several specific reasons to make the single substitution of lysine for aspartic acid at position 320.

First, lysine is the most prevalent amino acid at this position in the set of homologous hyaluronidase enzymes—it occurs in nearly 60% of those proteins (51 different hyaluronidase enzymes) and in 3 of the 5 human hyaluronidases. The

[257] EX1003, ¶¶ 216-217; EX1004, ¶¶ 41-42.

high frequency with which lysine occurs in this position makes it an obvious candidate for being incorporated into position 320 of PH20.[258]

Second, lysine has a high helix propensity, meaning it is more likely to be favored in sequences that form α-helix secondary structures.[259] Position 320 of PH20 is within the middle of a long α-helix sequence designated "α8" (below):[260]



The high propensity of lysine to favor (*i.e.*, support) α-helix structures would have made lysine a logical option to incorporate as a substitution for aspartic acid at position 320 in the α8 helix region of in $PH20_{1-447}$.[261]

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[258] EX1004, ¶ 116; EX1003, ¶¶ 216-217.

[259] EX1050, 422 (abstract), 423-424, Table 2; EX1004, ¶¶ 69-70, Appendix C; EX1003, ¶ 215.

[260] EX1006, Figure 3; EX1004, ¶ 108.

[261] EX1004, Appendix C; EX1003, ¶ 215.

Thus, a skilled person would have found it obvious to create a single-substitution mutant of $PH20_{1-447}$ by changing aspartic acid (D) at position 320 to lysine (K).[262]

5. A Skilled Artisan Would Have Reasonably Expected the D320K Substitution in $PH20_{1-447}$ Would Yield an Enzymatically Active PH20 Protein

a) Patent Owner Cannot Contradict Its Past Representations to the PTO

Substituting a lysine (K) for the aspartic acid (D) at position 320K is a single amino acid substitution in a non-essential region of $PH20_{1-447}$.[263]

In its '429 Patent, Patentee stated:

> Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.[264]

Patentee also secured claims in that patent to single amino acid substitutions in the wild-type sequence of $PH20_{1-447}$, even though it provided no examples of any PH20 proteins with any substitutions (*e.g.*, claim 1). Patentee, thus, made and relied on an affirmative statement that a skilled artisan would have expected ***any***

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262 EX1003, ¶ 217.

263 See § VI.B.3; EX1003, ¶¶ 213-214; EX1004, ¶ 32.

264 EX1005, 16:17-20.

single amino acid substitution in ***any*** non-essential position of $PH20_{1-447}$ to not substantially affect the biological activity of the enzyme. Patentee should not be permitted now to dispute that a skilled artisan would have reasonably expected that making the D320K substitution in $PH20_{1-447}$ would yield an enzyme with substantially the same activity as unmodified $PH20_{1-447}$.

b) Skilled Artisans Would Reasonably Expect D320K to be Tolerated in $PH20_{1-447}$

Independently, a skilled artisan would have reasonably expected that the D320K substitution in $PH20_{1-447}$ would not substantially alter the biological activity (hyaluronidase activity) of $PH20_{1-447}$.[265]

Initially, the common disclosure sets the level of enzymatic activity that a modified $PH20_{1-447}$ must retain to be an "active mutant" at only 40% of the activity of the unmodified form of $PH20_{1-447}$.[266]

Dr. Hecht and Dr. Park each independently evaluated the D320K substitution in $PH20_{1-447}$, and each concluded that a skilled artisan would have expected the substitution to have been tolerated by $PH20_{1-447}$, which would satisfy

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[265] EX1003, ¶¶ 216-218.

[266] EX1001, 75:47-52; *also id.* 79:29-33 ("active mutants" "can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide…").

the activity requirement.[267] Both experts noted the high frequency with which lysine is found in homologous hyaluronidase proteins.[268] The high frequency of occurrence of lysine at position 320 in homologous hyaluronidases suggests that lysine is generally tolerated at that position, including in 3 of 4 human homologs of PH20 reported by Chao.[269]

c) Dr. Park Confirmed that $PH20_{1-447}$ Would Tolerate Lysine at 320 Using a Structural Model

To assess whether single amino acid substitutions in $PH20_{1-447}$ would be tolerated, such as the D320K substitution, Dr. Park also assessed the substitutions using a PH20 protein structural model generated by SWISS-MODEL using the human HYAL1 structure in Chao as the template.[270]

Dr. Park describes the preparation of the PH20 structural model in his declaration, and explains why it was reliable in the region of position 320 of PH_{201-}

[267] EX1003, ¶¶ 225-226; EX1004, ¶¶ 116-123.

[268] EX1003, ¶¶ 217; EX1004, ¶¶ 106, 116.

[269] EX1003, ¶ 217; EX1006, 6916.

[270] EX1004, ¶¶ 39-40, 149-159; EX1006, 6915, Fig. 2; EX1012, 4, 2.

$_{447}$.[271] He explained that the model would be very similar to what would have been generated by SWISS-MODEL in 2011 (*e.g.*, 165 positions are conserved in the backbone of the two proteins).[272]

Dr. Park devised a consistent, objective methodology for assessing substitutions using his $PH20_{1-447}$ model.[273] Factors considered included the number of neighboring residues at position 320 (*i.e.*, those within 5 Å), the various types of possible interactions between neighbors (*e.g.*, hydrophobic, charged, van der Walls, steric, etc.), and solvent accessibility.[274] Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*, hydrophobic-hydrophilic, effects on

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[271] EX1004, ¶¶ 36, 150-153 (satisfactory local and global QMEAN values), ¶ 160; EX1069, 3; EX1070, 3; EX1037, 346-347; EX1017, 229; EX1012, 1; EX1014, 348; EX1003, ¶ 227.

[272] EX1004, ¶¶154-155, 159, 37-38; EX1038, 3382; EX1017, 229; EX1012, 1-2; EX1014, 348, 370; EX1066, 3.

[273] EX1004, ¶¶ 102-103. Dr. Park's methodology is described in §IV.C of his declaration.

[274] EX1004, ¶¶ 44-47, 53-60, 65-85, Appendix D-5; EX1035, 1408, Table 2; EX1043, 2, Table 1.

secondary structures, size related issues such as steric clashes or creation/filling of "holes" in the structure).[275]

Dr. Park also assessed the environment visually by comparing the wild-type with the version incorporating the substituted amino acid at position 320 using functionality within the viewer (PyMol) and as a modeled sequence generated from the $PH20_{1-447}$ sequence incorporating the single substitution in SWISS-MODEL.[276] Again, these technologies were available as of 2011.[277] He used his methodology to assess numerous substitutions representing diverse interactions, and confirmed that it provided a consistent, objective and unbiased evaluation of substitutions throughout the protein.[278]

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed.[279] His classification is shown below.

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275 EX1004, ¶¶ 63, 85.

276 EX1004, ¶ 61, 107, 165-166, 115.

277 EX1004, ¶¶ 142, 149-151, 154-155, 163, 165-167; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1010, 2, 4.

278 EX1004, ¶¶ 102-103.

279 EX1004, ¶¶ 85-87.

Score	***Expected Impact***	***Expected Toleration***
1	Significantly Destabilized	Likely Not Tolerated
2	Neutral or Minor Impacts	Tolerated
3	Improved Stability	Tolerated

Dr. Park assigned a score of 3 for the D320K substitution in $PH20_{1-447}$, indicating that the substitution would be expected to confer improved stability.[280] He observed that in the wild-type environment, there is a deep hydrophobic pocket around position 320 that limits solvent accessibility to the side chains, but that it is exposed to solvent at the top.[281] He also observed that there is a negative surface charge at 320 that creates electrostatic repulsion with the charged carboxyl group of D320.[282] When the lysine was substituted in position 320, Dr. Park observed that: (i) it introduces a stabilizing salt-bridge with E324 (left image), and a hydrogen bond to the main carbonyl group of P32, and (ii) the long aliphatic chain of lysine participates in hydrophobic interactions with P32 and L317 residues (right image).[283]

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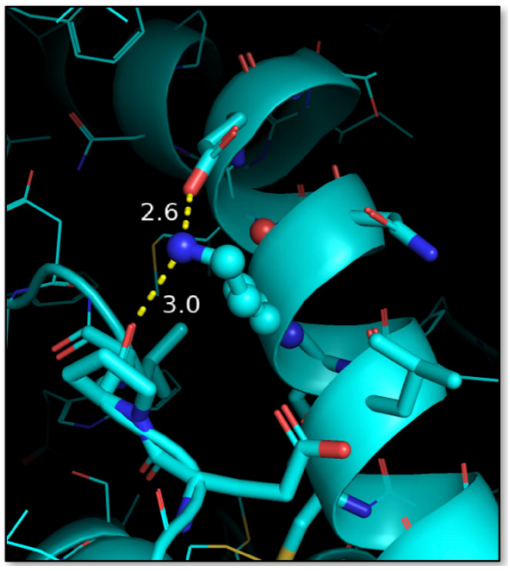
280 EX1004, ¶ 123, Appendix C.

281 EX1004, ¶¶ 109-110

282 EX1004, ¶¶ 111-112; *also id.* ¶¶ 113-114.

283 EX1004, ¶¶ 119-121, 123.



Considering all these factors, Dr. Park concluded that the change would be stabilizing, meaning that D320K $PH20_{1-447}$ would be expected to retain the hyaluronidase activity of the unmodified $PH20_{1-447}$.[284]

Dr. Park's visualization-based assessment is a technique that was prevalent in 2011.[285] Similarly, his technique of assessing interactions between neighbors and assigning an overall score reflecting the aggregate effects of those interactions

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[284] EX1004, ¶ 123.

[285] EX1017, 228 ("…a structural biologist's intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this."); EX1004, ¶¶ 33-34.

is consistent with methods reported in peer review publications. For example, publications by Dr. Moult's group used this technique to assess single substitutions caused by single-nucleotide polymorphisms, and similarly classified the net effects on a 3-point scale.[286]

Dr. Hecht reviewed Dr. Park's analysis and conclusions, and agreed with both.[287] Through his own assessment, he also observed that lysine substituted into position 320 would have a stabilizing effect due to (i) the compatibility of the shape of lysine with the solvent-exposed pocket at that location, and (ii) the formation of a salt bridge with E324.[288]

A skilled artisan considering the D320K substitution in $PH20_{1-447}$ would thus have reasonably expected that it would be tolerated by the protein, such that the D320K $PH20_{1-447}$ protein would exhibit at least a comparable level of activity as the unmodified $PH20_{1-447}$ protein.[289]

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[286] EX1004, ¶¶ 35, 48-52; EX1031, 439, 462-464, 469-471, Table 3; EX1032, 265-266.

[287] EX1003, ¶¶ 219-225.

[288] EX1003, ¶ 226.

[289] EX1003, ¶ 228.

Therefore, based on the '429 Patent, Chao, and information available in 2011, the D320K $PH20_{1-447}$ mutant polypeptide would have been obvious to a skilled artisan in 2011. And because claims 1-4 each encompass the single-replacement modified D320K $PH20_{1-447}$ polypeptide, each claim is unpatentable.

C. Dependent Claims 7-20 and Claim 21 Are Obvious

None of the dependent claims or claim 21 define subject matter that is independently patentable from claims 1-4. For the reasons below, each would have been obvious to a skilled artisan.

1. Claim 7

Claim 7 requires the modified PH20 polypeptide to be "a soluble PH20 polypeptide."

The '429 Patent identifies that $PH20_{1-447}$ exists as a soluble form of the PH20 protein because it omits the C-terminal residues above position 448 (483) containing the GPI anchor sequence.[290] A skilled artisan would believe that changing D to K at position 320 would not change the solubility of the $PH20_{1-447}$ as it would not meaningfully alter the structure of the protein.[291]

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[290] EX1005, 3:57-62; 87:52-88:24.

[291] EX1003, ¶ 196, 218.

2. Claims 8-10

Claims 8-10 require the modified PH20 polypeptide to "comprise[] one or more modification" including glycosylation (claims 8-9) and be a "glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine residues" (10).

The '429 Patent teaches (i) that human PH20 must be glycosylated to exhibit activity, and (ii) expression of $PH20_{1-447}$ in mammalian (CHO) host cells that yield active forms of $PH20_{1-447}$.[292] It further teaches that "N- and O-linked glycans are attached to polypeptides through asparagine-N-acetyl-D-glucosamine … linkages," and claims PH20 polypeptides (including $PH20_{1-447}$) having asparagine-linked sugar moieties.[293] Frost reports that the recombinant production of PH201-447 in CHO cells "resulted in a 447 amino acid 61 kDA glycoprotein with a properly processed amino terminus and 6 N-linked glycosylation sites."[294]

[292] EX1005, 95:13-30; 40:41-51, 89:53-91:67; 88:5-9.

[293] EX1005, 3:27-35, claims 1, 6.

[294] EX1013, 432.

Based on the '429 Patent and knowledge in the art, a skilled artisan would have found it obvious to produce D320K $PH20_{1-447}$ in a CHO cell, and that doing so causes six N-linked glycosylation sites to be glycosylated.[295]

3. Claims 11-13 and 21

Claims 11-13 broadly specify a nucleic acid encoding any modified PH20 polypeptide of claim 1, an expression vector comprising that nucleic acid, and a host cell comprising that vector. Claim 21 similarly claims methods of recombinantly producing a genus that includes D320K $PH20_{1-447}$ by preparing a plasmid containing a cDNA encoding it, transfecting the plasmid into a host cell, culturing the cells and harvesting the protein from the cell culture.

The '429 Patent teaches the recombinant production of $PH20_{1-447}$ in CHO cells comprising (i) preparing a nucleic acid encoding $PH20_{1-447}$, (ii) inserting it into a plasmid expression vector, and (iii) transfecting CHO cells with the plasmid to produce the $PH20_{1-447}$ protein.[296] It also teaches "nucleic acid molecules that encode a polypeptide …that have at least" 95% sequence identity with a full length PH20 (*i.e.*, up to 22+ substitutions).[297]

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295 EX1003, ¶¶ 197-198, 200-201.

296 EX1005, 89:54-90:15, 90:19-91:67.

297 EX1005, 11:60-66.

From their training and experience, and the guidance in the '429 Patent, a skilled artisan would have found it obvious to prepare and insert into a plasmid a nucleic acid encoding a single-replacement (*e.g.*, D320K) $PH20_{1-447}$, transfect a CHO host cell with it, express and then harvest the protein from the cell culture.[298] For example, Arming and Zhang both reported recombinant production of single-substitution forms of active soluble PH20 polypeptides.[299]

4. Claims 14-20

Claims 14-18 specify a pharmaceutical composition comprising any modified PH20 polypeptide in the genus of claim 1, alone (claim 14) or in combination with a therapeutic agent (15), several genera of agents, (16) an antibody (18), and "a small molecule drug" (18). Claims 19 and 20 concern methods of administering the compositions of claim 15 (19) and doing so subcutaneously (20).

The '429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*, $PH20_{1-477}$), alone or in combination with other therapeutic agents including

[298] EX1003, ¶¶ 198, 200.

[299] EX1011, 810-811; EX1010, 9433-35.

antibodies and small molecule drugs.[300] It similarly describes and claims methods of administering them subcutaneously.[301]

A skilled artisan would appreciate that a single-replacement $PH20_{1-447}$ polypeptide with similar expected activity to $PH20_{1-447}$ (such as the D320K mutant) would be equivalently useful in the therapeutic compositions and methods described in the '429 Patent for $PH20_{1-477}$.[302] Claims 14-20 also impose no restrictions on the makeup of the pharmaceutical compositions, and claim only categories of therapeutic agents to be used in combinations. A skilled artisan, thus, would have found such agents and methods of administration to have been obvious.[303]

D. There Is No Nexus Between the Claims and Any Evidence of Putative Secondary Indicia

Well-established law holds that evidence of secondary indicia cannot support non-obviousness if it does not have nexus to the claims. A key question in

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300 EX1005, 8:60-9:4, 54:52-55:35, 56:28-57:21, 55:61-56:9, 73:4-20, claims 14, 29, 33.

301 EX1005, 8:25-38, 56:28-56, 57:22-36, 58:59-59:12, 63:40-64:4, 76:18-77:37, claim 27.

302 EX1003, ¶¶ 199, 217, 228.

303 EX1003, ¶ 199.

a nexus analysis is whether such evidence is commensurate with the scope of the claims. The answer here is a definitive no.

Patentee is likely to dispute that the D320K $PH20_{1-477}$ is obvious because it is reported to have unexpectedly high hyaluronidase activity as a single substitution mutant. Demonstrating that result for one mutant out of the $\sim 10^{49}$-10^{65} modified PH20 polypeptides encompassed by the claims, however, utterly fails to establish a nexus between the claims and that evidence. As explained above, the single-substitution D320K $PH20_{1-447}$ is not representative of the numerous, structurally different proteins that are encompassed by the claims, particularly those that would be expected to be inactive. See §V.A.2. No evidence or explanation is provided that resolves this confusion.

Petitioner submits that if Patentee advances evidence or arguments concerning a nexus, consideration of that issue should be deferred until after institution. Petitioner otherwise reserves its right to contest such evidence.

VII. The Board Should Not Exercise Its Discretion Under § 324(a) or § 325(d)

Discretionary denial is assessed using the factors set forth in *Apple Inc. v. Fintiv, Inc.,* IPR2020-00019, Paper 11, 5-6 (PTAB Mar. 20, 2020). None weigh in favor of denial as there is currently no parallel litigation regarding the ’600 Patent.

Also, during examination, none of the issues in the grounds were considered.[304] Further, Chao and other references discussed herein were not cited to the Office, and the Examiner did not have the benefit of Dr. Park or Dr. Hecht's detailed expert testimony. Finally, the Examiner did not consider Petitioner's § 112 arguments regarding the lack of support for the immense genus of claimed modified PH20 polypeptides (or any substantially similar arguments) during prosecution.[305] Rather, the only § 112 rejection concerned whether two dependent claims to treatment of cancers were supported, which was mooted when the Applicant cancelled those claims.[306]

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304 The Examiner's double patenting rejections were mooted by the filing of terminal disclaimers, not on the merits. *Supra* IV.C.

305 *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7-11 (P.T.A.B. Feb. 13, 2020).

306 EX1002, 687-88.

VIII. CONCLUSION

For the foregoing reasons, the challenged claims are unpatentable.

Dated: November 12, 2024

Respectfully Submitted,

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 11,952,600
1002	File History of U.S. Patent No. 11,952,600
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Brandon & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '600 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," Methods in Enzymology, 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," Protein Eng'g & Design, Ch. 10, 223-237 (2010)
1018	Chica et al., "Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design," Curr. Opin. Biotechnol., (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," Reprod., 127:325-334 (2004)
1020	Pomering et al., "Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20," Am. J. Reprod. Immunol., (3):174-82 (2002)
1021	Baba et al., "Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg," J. Biol. Chem., 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," Biol Reprod., 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," Biol. Reprod., 56(5):1133-41 (1997)
1024	Rosengren et al., "Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects," BioDrugs, 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	[Reserved]
1028	[Reserved]
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," FEBS Letters, 3:545-548 (1993)

No.	Exhibit Description
1030	Sills, "Retraction," Science, 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," J. Mol. Biol., 353:459-473 (2005)
1032	Wang & Moult, "SNPs, Protein Structure, and Disease," Hum. Mutation, 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," Structure, 8:1025-1035 (2000)
1034	"Negative Results," Nature: Editorials, 453:258 (2008)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," Protein Sci., 12:1406-1417 (2003)
1036	Hayden, "Chemistry: Designer Debacle," Nature, 453:275-278 (2008)
1037	Benkert et al., "Toward the Estimation of the Absolute Quality of Individual Protein Structure Models," Bioinformatics, 27:343-350 (2010)
1038	Schwede et al., "SWISS-MODEL: An Automated Protein Homology-Modeling Server," Nucleic Acids Rsch., 31:3381-3385 (2003)
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007).
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," PNAS, 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," PNAS, 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," Nature Comm., 14 (2023)
1043	Sievers et al., "Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega," Molecular Sys. Biology, 7.1 (2011)
1044	Mihel, "PSAIA – Protein Structure and Interaction Analyzer," BMC Structural Biology, 8:21 (2008)

No.	Exhibit Description
1045	Redline Comparison of the ’731 and ’600 Specifications
1046	Beasley & Hecht, “Protein Design: The Choice of *de Novo* Sequences,” J. Biological Chemistry, 272:2031-2034 (1997)
1047	Xiong et al., “Periodicity of Polar and Nonpolar Amino Acids is the Major Determinant of Secondary Structure in Self-Assembling Oligomeric Peptides,” PNAS, 92: 6349-6353 (1995)
1048	Hayden, “Key Protein-Design Papers Challenged,” Nature, 461:859 (2009)
1049	KEGG, *DRUG: Hyaluronidase (human recombinant)*, available at: https://www.genome.jp/entry/D06604
1050	Pace & Scholtz, “A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins,” Biophysical J. 75:422-427 (1998)
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
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1057	Ph20_pre2011.aln-clustal_num
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1059	Leisola & Turunen, “Protein Engineering: Opportunities and Challenges,” Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	Hecht et al., “De Novo Proteins from Designed Combinatorial Libraries,” Protein Sci., 13:1711-1723 (2004)
1061	Rosengren et al., “Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration,” AAPS J., 17:1144-1156 (2015)
1062	[Reserved]
1063	[Reserved]

No.	Exhibit Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with D320K Mutation
1071	Swiss Model Printout of PH20 Model with D320H Mutation
1072	Swiss Model Printout of PH20 Model with D320R Mutation
1073	Swiss Model Printout of PH20 Model with D320S Mutation

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,629 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

Dated: November 12, 2024

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 12th day of November, 2024, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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