Paper No. 1

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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. PGR2025-00003
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

Lead Counsel	Backup Counsel	Backup Counsel
Jeffrey P. Kushan	Leif Peterson	Mark Stewart
Reg. No. 43,401	*Pro Hac Vice* forthcoming	Reg. No. 43,936
Sidley Austin LLP	Sidley Austin LLP	Merck Sharp & Dohme LLC
1501 K Street, N.W.	1 S Dearborn Street	126 E. Lincoln Ave.
Washington, D.C. 20005	Chicago, IL 60603	Rahway, New Jersey 07065
jkushan@sidley.com	leif.peterson@sidley.com	Mark.stewart@merck.com
(202) 736-8914	(312) 853-7190	(732) 594-6302

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

III. Grounds

The grounds advanced in this Petition are:

(a) Claims 1-21 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 "$PH20_{1-n}$" is used to refer 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 ("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

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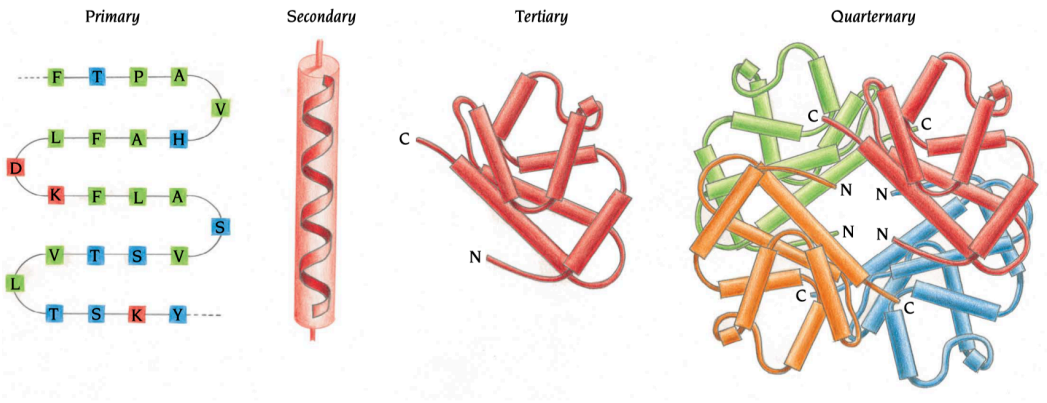
[7] EX1003, ¶ 15.

[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]

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[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.

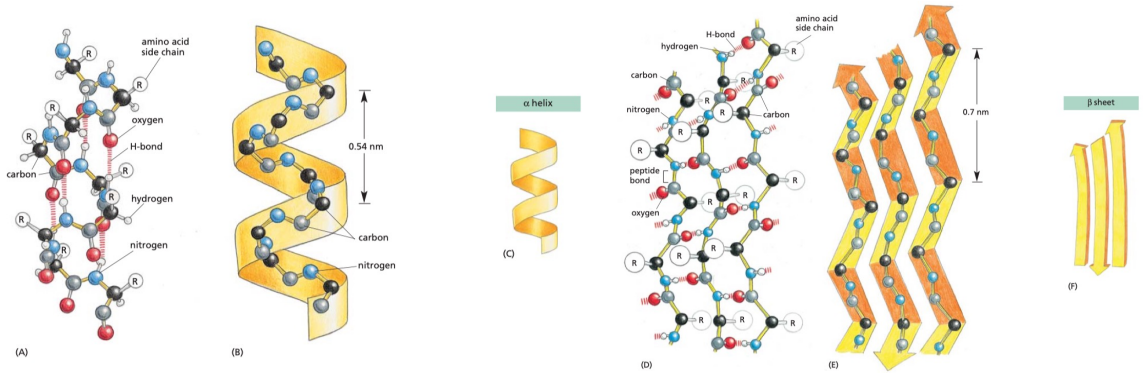

Figure 3–7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N–H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N–H 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,

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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.

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[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 $PH20_{1\text{-}447}$ 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 <u>and</u> 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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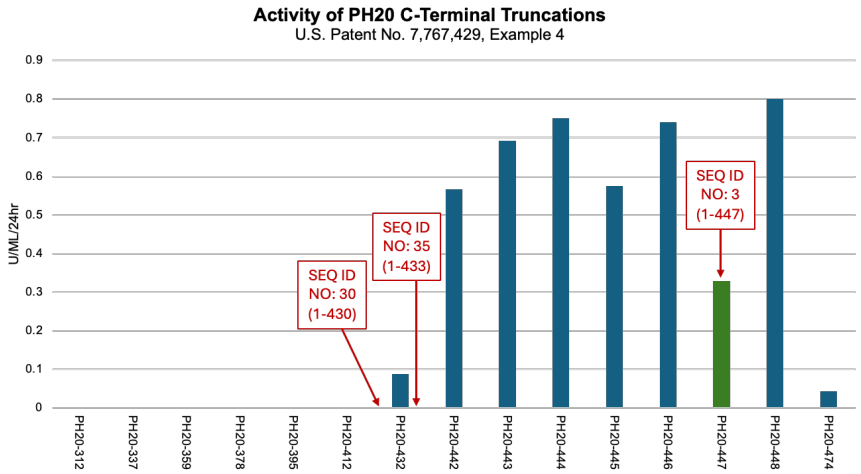
[89] EX1003, ¶¶ 97, 167-169.

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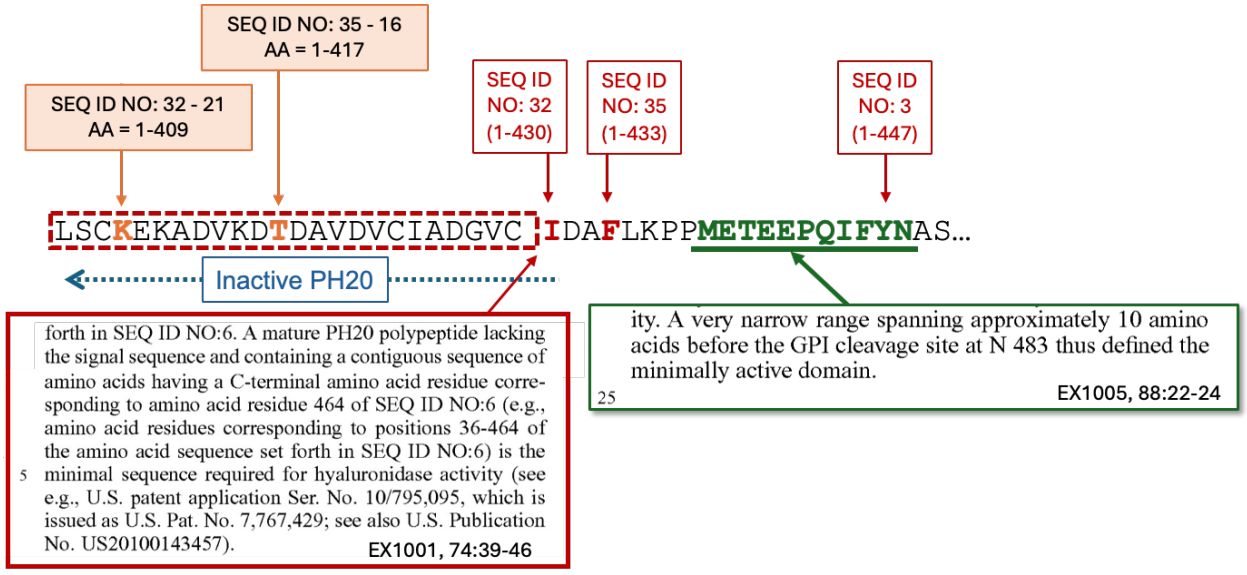
91 EX1005, 6:65-7:7 ("…sHASEGP from amino acids 36 to Cys 464 [429] … comprise the minimally active human sHASEGP hyaluronidase domain").

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.

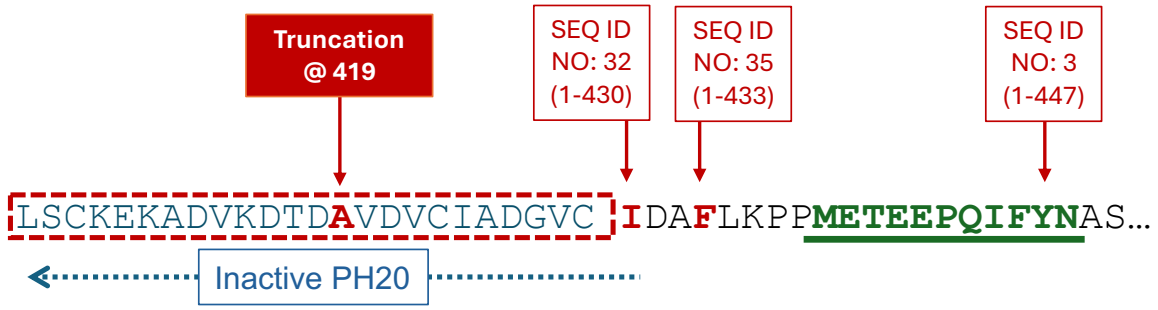


93 EX1006, 6912; EX1003, ¶¶ 84-96, 153.

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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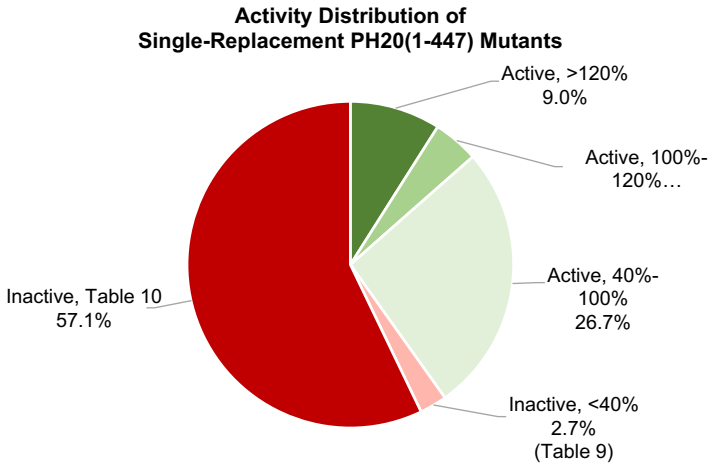
[98] EX1001, 134:48-59, 202:15-17, 201:12-202:1.

[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]

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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.

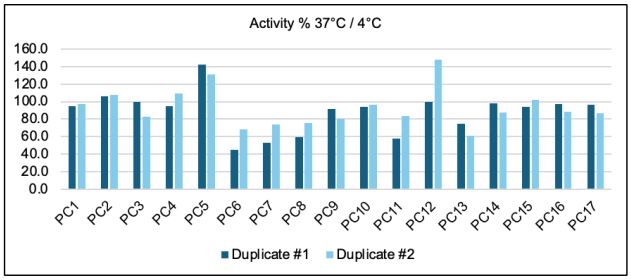
[115] *Id*.

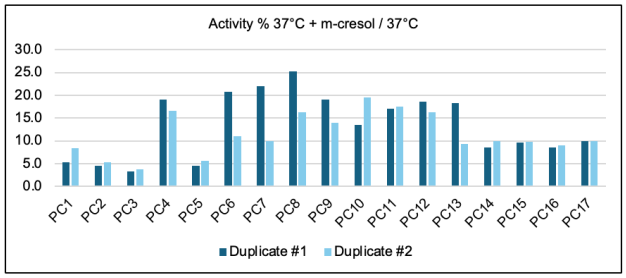
[116] EX1003, ¶ 71; EX1001, 287 (Table 12).

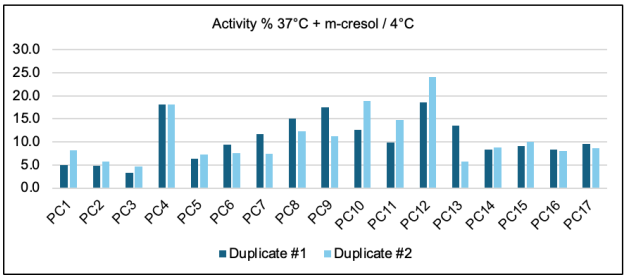
[117] EX1003, ¶ 71, Appx. A-7, A-8.

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 $PH201_{-447}$ 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

[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 $PH20_{1\text{-}447}$ mutants fit into one box of the array below.

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[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																						
39																						
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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 $PH20_{1\text{-}447}$ 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 $PH20_{1\text{-}447}$.

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

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[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

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[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 $PH20_{1\text{-}447}$ 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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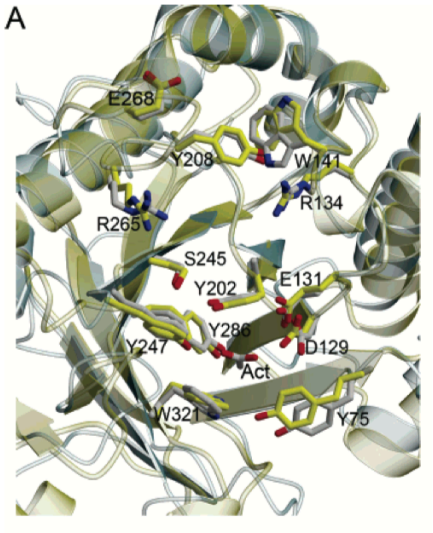
[233] EX1003, ¶ 209-210.

[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.

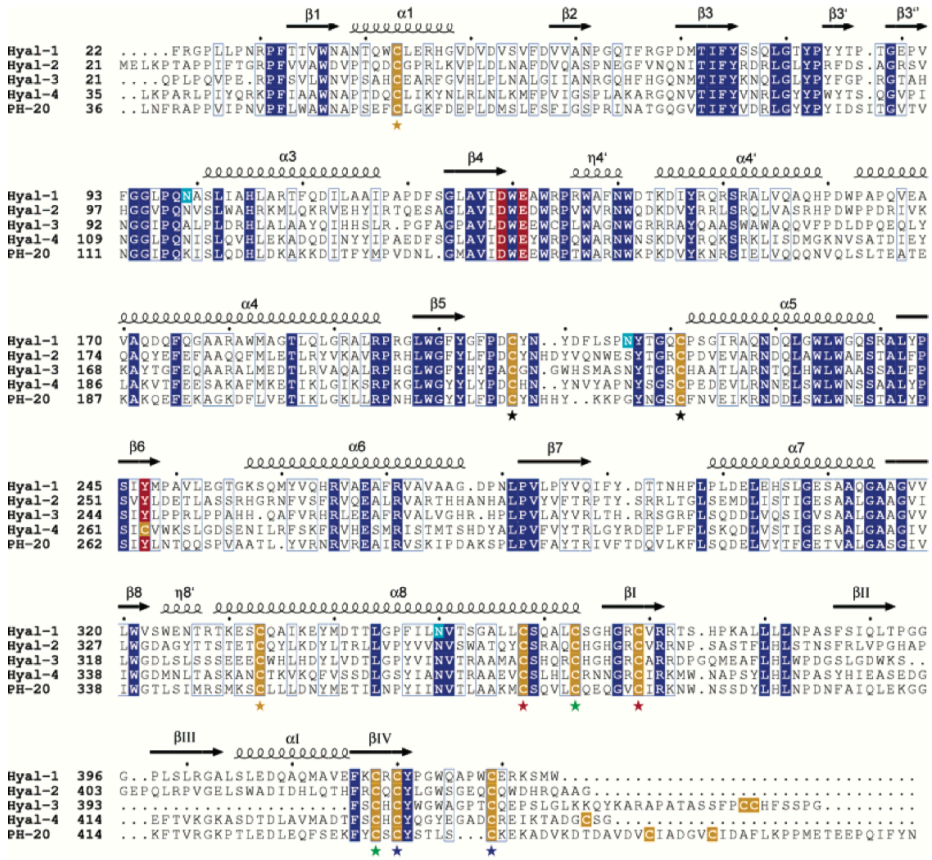

FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative 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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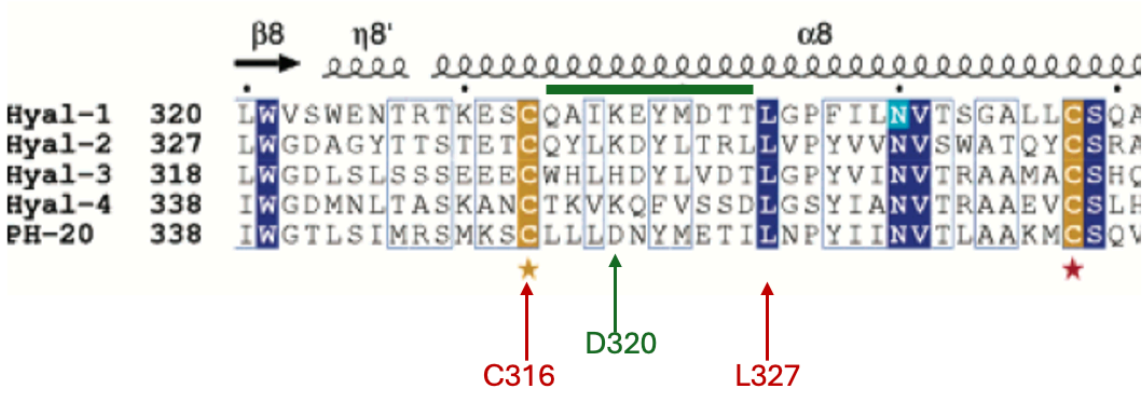
[245] EX1004, ¶¶ 13-17, 22-24.

[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]

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[254] EX1004, ¶¶ 30-32, 41-43, Appendix D-1.

[255] EX1004, ¶¶ 43, 116, Appendix D-1.

[256] EX1003, ¶ 214.

AA at position 355/320 in $PH20_{1-447}$

Most frequent AA at position in set of proteins

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wt 355: D 10.22 K 57.95
res394: K 51 57.95
res394: D 9 10.22
res394: H 9 10.22
res394: R 5 5.68
res394: N 5 5.68
res394: Q 4 4.54
res394: S 2 2.27
res394: G 2 2.27
res394: E 1 1.13
```

% of occurrence of AA in set of proteins

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]

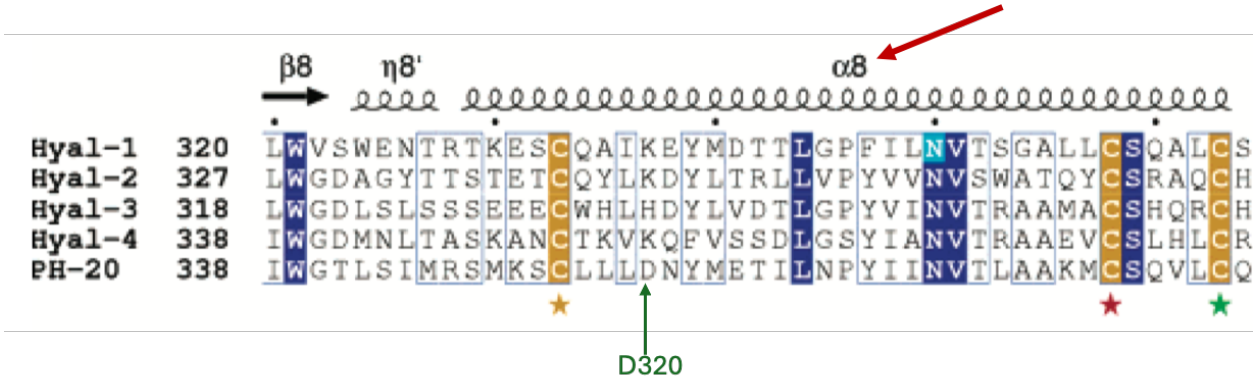
A skilled artisan would also have had several specific reasons to make the single substitution of lysine for aspartic acid at position 320.

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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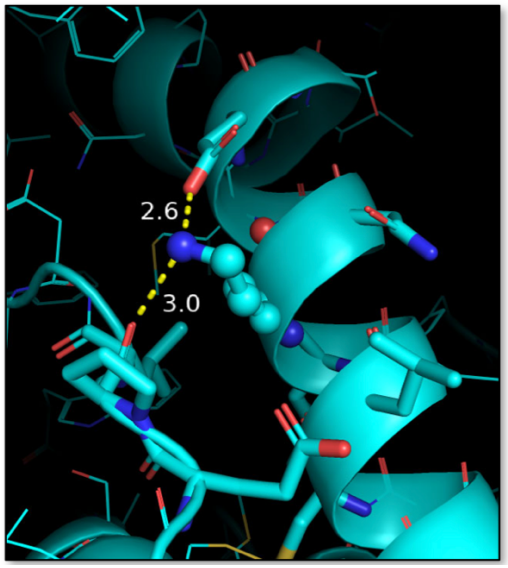
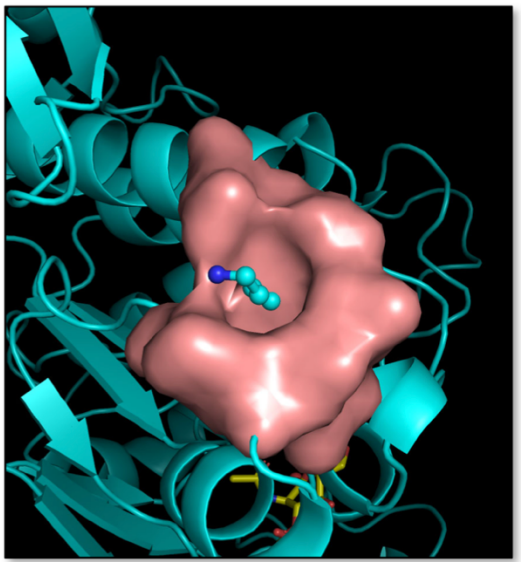
[280] EX1004, ¶ 123, Appendix C.

[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]

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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.

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.

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Respectfully Submitted,

/Jeffrey P. Kushan/
Jeffrey P. Kushan
Reg. No. 43,401
Sidley Austin LLP
1501 K Street, N.W.
Washington, D.C. 20005
jkushan@sidley.com
(202) 736-8914
Attorney for Petitioners

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)
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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)
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1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
1057	Ph20_pre2011.aln-clustal_num
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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

Respectfully Submitted,

/Jeffrey P. Kushan/
Jeffrey P. Kushan
Reg. No. 43,401
Sidley Austin LLP
1501 K Street, N.W.
Washington, D.C. 20005
jkushan@sidley.com
(202) 736-8914
Attorney for Petitioners

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:

Morgan, Lewis & Bockius LLP
2222 Market Street
Philadelphia, PA 19103
United States

Robert Smyth
Morgan, Lewis & Blockius LLP
1111 Pennsylvania Avenue, NW
Washington, DC 20004-2541
United States

Mark Snyder
Senior Vice President, General Counsel, CCO & Secretary
Halozyme Therapeutics
12390 El Camino Real
San Diego, CA 92130
United States

Dated: November 12, 2024

Respectfully Submitted,

/Jeffrey P. Kushan/
Jeffrey P. Kushan
Reg. No. 43,401
Sidley Austin LLP
1501 K Street, N.W.
Washington, D.C. 20005
jkushan@sidley.com
(202) 736-8914
Attorney for Petitioners