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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. PGR2025-00039
U.S. Patent No. 12,104,185

PETITION FOR POST GRANT REVIEW

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I. Introduction

Petitioner Merck Sharp & Dohme LLC ("Merck") requests post grant review of U.S. Patent No. 12,104,185 ("'185 Patent").

Claims 1-11 of the '185 Patent define methods of increasing delivery of another therapeutic agent by administering it in a pharmaceutical composition containing a modified PH20 polypeptide. The PH20 used in this process must be enzymatically active—it increases diffusion ("spreading") of the other agent by modifying the permeability of connective tissue "…***through hydrolysis of hyaluronic acid***."[1]

Claims 1-11 are unpatentable for three independent reasons. The first two are linked to their extreme breadth. Each claim specifies use of modified PH20 polypeptide that (i) ***must have*** one amino acid substitution at position 320, and (ii) ***may have*** between 16 and 22 additional substitutions at ***any*** of 430+ positions, and to ***any*** of 19 other amino acids—genera ranging between 10^{49} and 10^{66} distinct polypeptides. The scale of these genera is unfathomable. A collection of one molecule of each polypeptide in the smallest genus exceeds the weight of the Earth, and practicing the full scope of even the narrowest genus would require many lifetimes of "making and testing" using the patent's methodology.

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1 EX1001, 175:24-26 (emphases added).

But which of the trillions and trillions of modified PH20 polypeptides possess the properties necessary for the claimed methods is never revealed. These immensely broad claims, measured against the common disclosure of the '185 Patent and its ultimate parent '731 Application,[2] thus utterly fail the written description and enablement requirements of § 112(a). That renders every claim of the '185 Patent unpatentable. It also precludes the claims from a valid § 120 benefit claim to the '731 Application, the only non-provisional application filed before March 16, 2013, thus making the '185 Patent PGR eligible.

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by the multiply-modified PH20 polypeptides in each claimed genus that enables them to increase delivery of another therapeutic agent. The disclosed examples also are not representative: each example has only ***one*** amino acid substitution in ***one*** PH20 sequence (1-447), but the claims encompass PH20 proteins with myriad ***undescribed*** combinations of 5, 10, 15, or 20+ substitutions anywhere within PH20 sequences of varying length. The claims even capture mutated PH20 polypeptides the disclosure says to avoid (*e.g.*, $PH20_{1-447}$ mutants rendered inactive by a single

[2] 13/694,731 ('731 Application) (EX1026).

substitution and inactive truncated forms). The disclosure is nothing more than a research plan, lacking any blaze marks, and does not describe the claimed genera.

Regarding enablement, equally fatal problems exist: the disclosure identifies ***no*** enzymatically active modified PH20 with ***2 or more*** substitutions that increases delivery of another therapeutic agent, much less affirmatively guides the selection of ***which*** combinations of substitutions yield such enzymes. The only process it discloses for making enzymatically active multiply-substituted PH20 mutants is prophetic, and requires the "trial-and-error discovery" methodology the Supreme Court found incapable of enabling a much smaller genus of polypeptides.[3] Scientists would need to repeat this "make-and-test" methodology innumerable times until they had made and tested the 10^{49} to 10^{66} unique proteins for activity that the claims specify using. But even that is not enough—each of the enzymatically active PH20 polypeptides must be tested in a second, *in vivo* assay to identify which mutants increase delivery of another therapeutic agents. That is far more than undue experimentation—it is impossible.

Finally, claims 1-11 are unpatentable because each captures methods that use at least one obvious $PH20_{1\text{-}447}$ mutant having a single substitution at position 320. Importantly, Patentee's '429 Patent (EX1005) taught the precise method

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

claimed here—increasing delivery of a therapeutic agent by administering it with an enzymatically active PH20 polypeptide (including mutants). It also directed artisans to make and use modified PH20 polypeptides having single amino acid substitutions in non-essential regions of $PH20_{1-447}$ (and expressly claimed them). Skilled artisans implementing that guidance in 2011 would have found Chao (EX1006)—a 2007 paper ignored in the common disclosure and never cited. Using their knowledge and the collective teachings of Chao and the '429 Patent, they would have (i) readily identified position 320 as being in a non-essential region of PH20, (ii) found it obvious to change aspartic acid at position 320 to lysine, and (iii) reasonably expected this mutant to retain enzymatic activity because that is what Patentee said in its '429 Patent ("Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity").[4] Because the claims use this obvious mutant in the same method that the '429 Patent teaches, they are unpatentable.

The Board should institute trial.

[4] EX1005, 16:17-22.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the ’185 Patent’s issuance. Petitioner certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the ’185 Patent.

The ’185 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).

Only one of the applications to which the ’185 Patent claims benefit under 35 U.S.C. § 120 and/or § 121—U.S. Application No. 13/694,731 (the ’731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011) and WO 01/3087 (“WO087”). The ’731 Application, however, alters several passages of the provisional disclosures, adds new examples and tested mutants and makes other changes.[5]

The ’731 Application (including subject matter (*e.g.*, the provisional applications) incorporated by reference) does not provide written description support for and does not enable any claim of the ’185 Patent (§§ V.A, V.B). The same is also true for the ’185 Patent, whose disclosure relative to the claims is generally the same as the ’731 Application.[6] The ’185 Patent is PGR eligible as at

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

[6] The “common disclosure” refers to the shared disclosure of the ’185 Patent and the ’731 Application (EX1026). Citations are to the ’185 Patent; EX1015 correlates citations to the ’731 Application. The disclosures are highly similar but not identical. *See* EX1068, ¶ 6.

least one of its claims does not comply with § 112(a) based on the ’731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

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

2. Related Proceedings

PGR2025-00003, PGR2025-00004, PGR2025-00006, PGR2025-00009, PGR2025-00017, PGR2025-00024, PGR2025-00030, and PGR2025-00033 are related proceedings.

3. Counsel and Service Information

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

III. Grounds

The grounds advanced in this Petition are:

(a) Claims 1-11 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.

(b) Claims 1-11 are unpatentable under 35 U.S.C. § 112 as not being enabled.

(c) Claims 1-11 are unpatentable as obvious under 35 U.S.C. § 103 based on the ’429 Patent (EX1005), Chao (EX1006), and knowledge held by a person of ordinary skill in the art.

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

In this Petition, “PH20” refers to the human PH20 hyaluronidase protein. The full-length PH20 protein (SEQ ID NO: 6) includes a 35 amino acid signal sequence, yielding position numbers in mature forms of PH20 that differ from SEQ ID NO: 6 by 35 residues.[7] The annotation “$PH20_{1\text{-}n}$” refers to a sequence of 1-n residues in PH20 (*e.g.*, $PH20_{1\text{-}447}$ is SEQ ID NO: 3), and “AxxxB” is used to identify the position of a substitution (*e.g.*, “D320K”).

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7 EX1003, ¶ 15.

IV. Background on the ’185 Patent

A. Field of the Patent

The ’185 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. A protein’s activity, however, derives from its unique, three-dimensional shape—its structure.[9] That is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary structures and structural motifs, which are packed into compact domains that define the protein’s overall structure (tertiary structure).[10]

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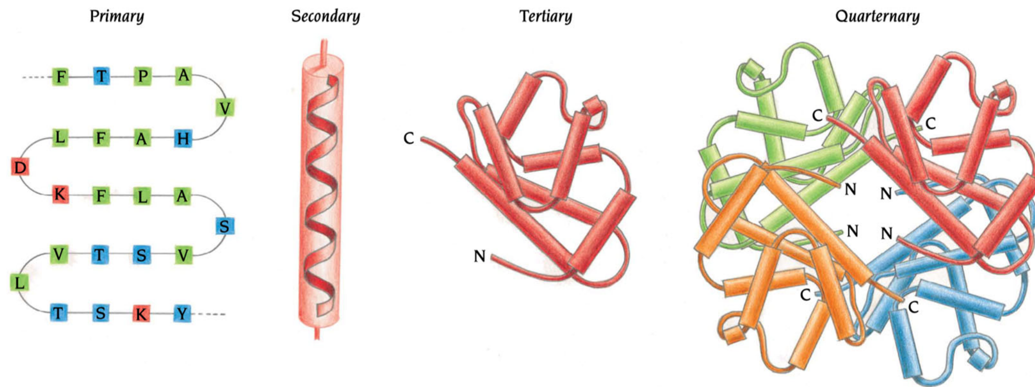
[8] EX1001, 4:16-19.

[9] EX1003, ¶ 36.

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



Secondary structures, such as α-helices or β-strands, are formed and stabilized by different but characteristic patterns of amino acids (below).[11]

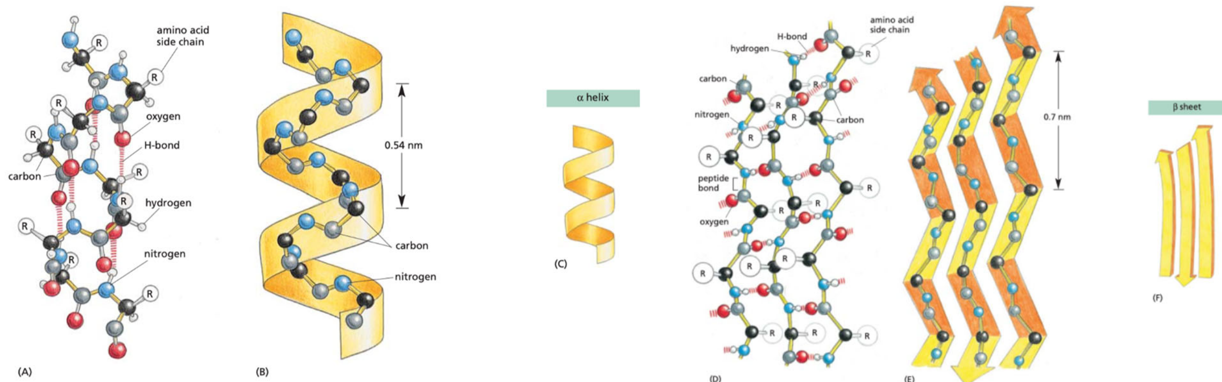


Figure 3–7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N–H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N–H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

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

Intervening sequences between those characteristic sequences are important too; they direct and facilitate positioning and arrangement of the various secondary structures into structural motifs and the protein's tertiary structure.[12]

Changes to a protein's amino acid sequence can affect the folding, formation and stability of these various structures that define the protein's overall shape. For example, changing even a single residue known to be critical to the protein's structure or activity can render a protein inactive.[13]

Making many concurrent changes to a protein's sequence can cause myriad effects on the protein's structure, especially when they are in or affect the same region(s) of the protein.[14] For example, it can disrupt the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of secondary structures, and disrupt folding and positioning of the secondary structures and structural motifs into the protein's tertiary structure.[15] Multiple changes in different regions of the amino acid sequence also cause unfavorable

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[12] EX1003, ¶¶ 44-46; EX1014, 21-22.

[13] EX1003, ¶¶ 54, 157; EX1004, ¶¶ 20, 25.

[14] EX1003, ¶ 165.

[15] EX1003, ¶¶ 55-56, 149; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

spatial interactions that destabilize or impair folding.[16] Consequently, in 2011, predicting the effects of the myriad interactions that may be disrupted by multiple concurrent substitutions was beyond the capacity of skilled artisans and available computational tools.[17]

2. Hyaluronidase Enzymes

PH20 is one of five structurally similar human hyaluronidases and is homologous—evolutionarily related to—hyaluronidases in many species.[18] PH20 breaks down hyaluronan ("HA") by selectively hydrolyzing glycosidic linkages.[19] PH20 exists naturally as a GPI anchored protein; deletion of its GPI-anchoring sequence yields a soluble, neutral active enzyme.[20]

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16 EX1003, ¶¶ 57-59.

17 EX1003, ¶¶ 50, 165, 203, 242; EX1004, ¶¶ 160-162.

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

19 EX1003, ¶ 77; EX1008, 819.

20 EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 92, 209; EX1029, 546, Figure 1.

Before 2011, many essential residues in PH20 were known. Several are in the shared catalytic site of the protein;[21] mutating certain residues in or near that site can abolish enzymatic activity.[22] Conserved cysteine residues that stabilize the protein structure are also essential,[23] as are certain conserved asparagine residues involved in glycosylation.[24]

In 2007, Chao reported an experimentally determined structure of the human HYAL1 hyaluronidase, and used an alignment of the five human hyaluronidases to illustrate shared secondary structures and conserved residues in these proteins.[25] Among its findings was that human hyaluronidases contain a unique structure—the Hyal-EGF domain.[26] Using its sequence analysis, an earlier structure of bee

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

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

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

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

[25] EX1006, 6914-18.

[26] EX1006, 6916-18; EX1010, 9439-40; EX1003, ¶¶ 84-88; EX1004, ¶¶ 97-99.

venom hyaluronidase and a computer model of the protein structures, Chao identified residues in the catalytic site that interact with HA.[27]

3. Protein Engineering

In 2011, skilled artisans used two general approaches to engineer changes into proteins.[28] In "rational design," skilled artisans employed computational tools—sequence alignments and protein structure models—to study the protein and then select where and what changes to introduce.[29] For example, a "multiple-sequence alignment" ("MSA")[30] produced by aligning known sequences of homologous, naturally occurring proteins identifies positions with no or little amino acid variation ("conserved" / "essential" residues) and positions where different amino acids occur ("non-conserved" / "non-essential" residues).[31] A

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

[28] EX1003, ¶ 47.

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

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

[31] EX1003, ¶¶ 226-27; EX1004, ¶¶ 21-22, 25, 30-31; EX1016, 181-84; EX1017, 224-25; EX1014, 351.

structural model using the protein's sequence but based on a known structure of a homologous protein enabled assessment of interactions between amino acids at a particular positions.[32] In 2011, using rational design techniques, a skilled artisan could assess, with varying effort, effects of changing one or a few amino acids, but could not use those techniques to predict the effects of many concurrent changes, given the escalating complexity of numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.[33]

"Directed evolution" techniques arose due to the limits of rational design.[34] They use "trial-and-error" experiments to find mutants with randomly distributed changes that exhibit desired properties, but require creation and screening of large libraries of mutants, each with one amino acid randomly changed at one position in its sequence.[35] Importantly, until a desired mutant is made, found, and tested,

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[32] EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶ 37; *also id.* 33-36; EX1003, ¶¶ 237, 239.

[33] EX1003, ¶¶ 50, 165; EX1004, ¶¶ 160-162.

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

[35] EX1003, ¶ 51; EX1059, 1225-26; EX1018, 378.

whether it exists and its sequence are unknown.[36] Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale of experimentation this approach requires.[37] The ’185 Patent embodies this approach.[38]

B. Person of Ordinary Skill in the Art

While the ’185 Patent claims priority to provisional applications dating to December 30, 2011 and benefit to the ’731 Application (filed December 28, 2012), they are not supported as § 112(a) requires by those earlier-filed applications. *See* §§ II.A, V.A, V.B. Regardless, the obviousness grounds rely on prior art published before and knowledge/perspectives of a skilled artisan before December 2011.

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

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[36] EX1003, ¶ 196.

[37] EX1003, ¶¶ 52-53.

[38] EX1003, ¶¶ 145, 185, 195, 199.

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

No issues relevant to the present grounds were raised during examination of the ’185 Patent. In the three Office actions that issued, indefiniteness rejections were imposed (*e.g.*, unclear references to open instead of closed groups and a lack of antecedent basis for the term “therapeutically active agent”),[40] which Patentee overcame with claim amendments.[41] The Examiner also 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,[42] which Patentee mooted by cancelling all rejected claims.[43] Non-statutory double patenting rejections over

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39 EX1003, ¶ 13.

40 EX1002, 650-51.

41 EX1002, 704-06, 753-55.

42 EX1002, 651-55.

43 EX1002, 704-06, 753-55.

U.S. Patent 11,952,600, alone and in view of US 7,767,429 and other references were overcome with terminal disclaimers.[44]

D. The Challenged Claims

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

The claims define methods of increasing delivery of a therapeutic agent by administering it with a "modified PH20 polypeptide." The claim language then defines massive genera of structurally distinct mutant PH20 polypeptides to be used in that method. But only some of the modified PH20 polypeptides within each genus possess the characteristics necessary for them to be used in the claimed methods. That creates fatal deficiencies for the claims under § 112, as the common disclosure of the '731 Application and the '185 Patent does not identify—much less adequately describe and enable—the subset of modified PH20 polypeptides with the properties necessary for used in the claimed methods.

[44] EX1002, 655-70, 731, 779.

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

The claims define methods that involve administering a "modified PH20 polypeptide," which the common disclosure defines as "a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement … in its sequence of amino acids compared to a reference unmodified PH20 polypeptide."[45] The claims then define certain shared attributes of these modified PH20 polypeptides, stating each:

- ***must*** contain ***one*** amino acid replacement at position 320 (*i.e.*, from D to any of H, K, R, and S); and
- ***may*** contain ***additional*** modifications, provided each polypeptide retains ***at least 95% sequence identity*** to one of 36 unmodified sequences (SEQ ID NOs: 3 or 32-66), ranging in length from 430 (SEQ ID NO: 32) to 465 residues (SEQ ID NO: 66).

The claim language, thus, defines an immense set (genus) of modified PH20 polypeptides that can vary significantly in their structures.

Certain dependent claims restrict these parameters:

(i) claim 2 requires the position 320 substitution to be K,

[45] EX1001, 48:38-43.

(ii) claims 3 and 4 require each polypeptide to have, respectively, 96% sequence identity to SEQ ID NO: 35 ($PH20_{1-433}$), or 95% sequence identity to SEQ ID NO: 32 ($PH20_{1-430}$), and

(iii) claims 5 and 6 require increased hyaluronidase activity (>100% and >120%, respectively) relative to an unmodified PH20.

Claims 7-11 depend from claim 1 but do not alter the size of its genus of PH20 polypeptides. Claims 7-9 specify types of "therapeutic agents" to be administered with the PH20 polypeptide (*e.g.*, an antibody or small molecule drug), while claims 10-11 specify parenteral or subcutaneous administration of pharmaceutical compositions.

The specification explains that "sequence identity can be determined by standard alignment algorithm programs …"[46] and provides an example, explaining a polypeptide that is "'at least 90% identical to' refers to percent identities from 90 to 100% relative to the reference polypeptide" where "no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides."[47]

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[46] EX1001, 60:14-16.

[47] EX1001, 60:49-58.

It further explains that "differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence" and that "[d]ifferences are defined as [] amino acid substitutions, insertions or deletions."[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 of the 19 alternative amino acids).[49] Except for position 320, no language in the claims restricts ***where*** substitutions can occur within the modified PH20 sequence, or ***which*** of 19 other amino acids can be substituted at those positions.

The sequence identity parameters capture an immense number of modified PH20 polypeptides, each with a unique amino acid sequence.[50] The polypeptides may have up to 17-23 total changes but must have one substitution at position 320. Several claims permit four position 320 alternatives (H, K, R, S) while others permit one (K) (calculations shown below):[51]

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48 EX1001, 60:59-67; *see also id.* at 5:1-2, 47:43-47, 56-58.

49 EX1001, 130:21-28; *see also id.* at 135:38-40.

50 EX1003, ¶¶ 122, 124.

51 EX1004, ¶¶ 168-171, Appendix F.

Claims	*Max Length*	*Sequence Identity %*	*Max Changes*	*Pos. 320 Choices*	*# of Distinct Polypeptides*
1, 5-11	465	95	23	4	1.35×10^{66}
2	465	95	23	1	3.36×10^{65}
3	433	96	17	1	1.53×10^{49}
4	430	95	21	1	4.40×10^{59}

2. The Claims Encompass Use of One Particular Mutant: D320K $PH20_{1\text{-}447}$

Claims 1-11 capture a method of administering a modified $PH20_{1\text{-}447}$ polypeptide having only one amino acid substitution: aspartic acid at position 320 to lysine (K) ("D320K"). This single-replacement $PH20_{1\text{-}447}$ mutant is: (i) 99.7% identical to SEQ ID NO: 3 (1 change / 447 residues), (ii) 96.5% identical to SEQ ID NO: 35 (15 changes / 433 residues), and (iii) 95.9% identical to SEQ ID NO: 32 (18 changes / 430 residues).[52]

3. The Claims Require Use of "Active Mutants"

All claims require use of a modified PH20 polypeptide in a "method for increasing delivery of a therapeutic agent." The common disclosure unequivocally attributes the ability of a modified PH20 to cause "increased delivery" to its ability to hydrolyze hyaluronic acid. The claims thus require use of ***enzymatically active*** modified PH20 polypeptides.

[52] EX1003, ¶ 143.

(a) Increased Delivery Requires the PH20 to Enzymatically Degrade HA in the Extracellular Matrix

Most directly, in the section that describes the claimed method of increasing delivery of therapeutic agents, the common disclosure explains:

> … ***hyaluronidase*** is a spreading or diffusing substance that ***modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid***, a polysaccharide found in the intercellular ground substance of connective tissue, and of certain specialized tissues, such as the umbilical cord and vitreous humor.[53]

Likewise, the introduction of the "methods of treatment and combination therapy" section of the common disclosure refers to "any of PH20 polypeptides provided herein ***that exhibit the ability to degrade*** glycosaminoglycan(s) such as ***hyaluronan***" and explains:

> *…**[d]ue to such activity***, the modified PH20 polypeptides can be used as a spreading factor **to *increase the delivery and/or bioavailability*** of subcutaneously administered therapeutic agents.[54]

Further, in a section describing the prior art, the common disclosure explains that "[t]he ***hyaluronidase activity of PH20 accounts for the spreading activity***

[53] EX1001, 175:24-29.

[54] EX1001, 174:22-28 (emphasis added); EX1003, ¶¶ 130-132.

observed in animal testes extracts that have been used clinically for decades to ***increase the dispersion and absorption*** [i.e. delivery] of drugs."[55]

The vividly clear explanations in the common disclosure thus establish that a modified PH20 polypeptide's ability to increase delivery of another therapeutic agent derives from its ability to degrade the hyaluronic acid (HA) within the extracellular matrix to a degree sufficient to enable the other therapeutic agent to diffuse through that matrix:

> Since HA is a major component of the interstitial barrier, hyaluronan-degrading enzymes (e.g., hyaluronidase) increase tissue permeability and therefore can be used to increase the dispersion and delivery of therapeutic agents.[56]

Thus, ***at a minimum***, to be used in the claimed methods, a modified PH20 polypeptide must be able to ***hydrolyze*** HA (*i.e.*, possess "hyaluronidase activity"). The common disclosure, however, indicates that enzymatic activity alone may be

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[55] EX1001, 73:22-26 (citing EX1080); EX1080, 230-231 ("'Spreading agents' derived from animal testes extracts containing interstitial matrix-degrading enzymes have been used clinically for over 50 years to facilitate the dispersion and absorption of drugs [7]. The ***active agent*** in these testes extracts was later ***associated with hyaluronidase activity*** [8].").

[56] EX1001, 4:33-40.

insufficient. It thus instructs skilled artisans to ***further test*** modified PH20 polypeptides to determine if they act as a "spreading or diffusing agent" by injecting each under the surface of the skin of a mouse and measuring "the ability of the PH20 polypeptide to act as a spreading agent."[57]

Unsurprisingly, the disclosure provides no suggestion that (much less examples of) ***inactive*** modified PH20 polypeptides (*i.e.*, those without the ability to degrade hyaluronan) can be used to increase delivery of therapeutic agents.[58] Indeed, there is no scientifically plausible theory by which such "inactive mutants" could do so—per the common disclosure, hyaluronidase activity is ***required***.

(b) The Preamble Informs the Requirements of the Claimed Methods

It is unnecessary for the Board to determine whether the preamble ("method of increasing delivery of a therapeutic agent to a subject") limits the scope of the claims. That is because the common disclosure unequivocally requires use of "active" mutants in the claimed methods, and broadening the scope of the claims to encompass use of inactive mutants only exacerbates the § 112 deficiencies of the claims.[59]

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[57] EX1001, 172:37-45; EX1003, ¶ 183.

[58] EX1003, ¶ 136.

[59] *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019).

If the Board believes a construction of the preamble is necessary, it should find that the preambular phrase "*increasing delivery of a therapeutic agent*" limits the claims to methods that administer a modified PH20 polypeptide "*for the purpose of modifying the permeability of connective tissue through the hydrolysis of hyaluronic acid*." That aligns precisely with the explanation in the specification of ***why*** a modified PH20 is administered with another therapeutic agent, and ***how*** it achieves increased delivery of that other agent. And reading the preamble in this manner reflects the "intended purpose" of the method as well as the "essence of the invention" as it is described in the specification.[60]

This construction also makes clear the claimed methods must use ***enzymatically active*** PH20 polypeptides. The common disclosure is explicit and consistent in explaining that hyaluronidase activity is prerequisite for a PH20 (modified or native) to increase delivery of another therapeutic agent.[61]

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[60] *Apotex, Inc. v. Regeneron Pharms., Inc.*, IPR2021-00881, Paper 94 at 17-19 (PTAB Nov. 9, 2022).

[61] *See* § IV.D.3(a); EX1001, 174:22-28, 4:33-40; EX1003, ¶¶ 134-136.

(c) The Claims As a Whole Are Limited to the "Active Mutant" Embodiment of Modified PH20 Polypeptides

When a specification discloses alternative embodiments, the claim language may limit the claims to one.[62] That is true here: the specification describes two distinct categories of modified PH20 polypeptides ("active mutants" vs. "inactive mutants"), each with distinct (alleged) utilities, but the claims are limited to methods that use only one of those categories of modified PH20 polypeptides—"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)."[63]
- "***Inactive mutants***" are modified PH20 polypeptides that "generally exhibit less than 20% … of the hyaluronidase activity of a wildtype or

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

63 EX1001, 75:47-52; *see also id.* at 79:29-33 ("active mutants" "can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide …"); *id.* at 79:26-29.

> reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7."[64]

Mutants are then classified into tables of "active" or "inactive" mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).[65]

The common disclosure reports no examples of an "active mutant" modified PH20 with two or more replacements.[66] It also reports no examples of an enzymatically active $PH20_{1\text{-}447}$ that incorporates: (i) a mutation that preserved activity in Tables 3 and 9 ("active mutants") ***plus*** (ii) a second mutation that eliminated activity in Tables 5 and 10 ("inactive mutants"). And, critically here, it nowhere describes administering "inactive mutants" to increase delivery of another therapeutic agent.

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

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[64] EX1001, 115:40-49. *See also id*. at 262:24-28 (mutants with <20% activity "were rescreened to confirm that the dead mutants are inactive" in Table 10).

[65] EX1001, 80:60-82:10, 227:15-17, 116:42-67, 262:51-54 ("reconfirmed inactive mutants are set forth in Table 10."); EX1003 ¶¶ 101, 103-104, 110.

[66] *E.g.*, EX1003, ¶¶ 148, 184.

- "Active mutants" are portrayed as being therapeutically useful ***because they possess hyaluronidase activity***.[67]
- "Inactive mutants" are portrayed as being therapeutically useful ***because they lack hyaluronidase activity***.[68]

The only utility identified for inactive mutants is "as antigens in contraception vaccines," which, while implausible (*see* § V.C), only requires them to lack activity. "Active mutants" also are not portrayed as having contraceptive utility; they are used ***in combination*** with contraceptive agents.[69]

In addition to the preamble, additional claim language reinforces that each claim is limited to "active mutants."

First, each requires modified PH20 polypeptides with 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). All

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67 EX1001, 174:22-28; *see also id*. at 4:33-36, 73:33-47, 174:22-187:48; EX1003, ¶ 111.

68 EX1001, 72:60-62; *see also id.* at 187:49-50, 75:56-58, 187:48-67 (for "contraception" "the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2."); EX1003, ¶ 112.

69 EX1001, 150:38-51; EX1060, 1711.

four are identified as "Active Mutants" in Table 3 and all have >100% activity per Table 9.[70]

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 amino acid modification," but can also "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity.***"[71] This aligns with the specification's prophetic methodology for discovering PH20 polypeptides with multiple changes, which selects "active mutants" with one substitution, randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity.[72] This also tracks the claims, which require one substitution and permit others.

Fourth, claim 1 requires the modified PH20 polypeptide to be in a composition with a "therapeutic agent." As the disclosure explains, such

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70 EX1001, 85 (Table 3), 252 (Table 9), 97:34-46; EX1003, ¶¶ 133-135.

71 EX1001, 48:38-53; *see also id*. at 47:61-65, 76:5-8, 76:67-77:7, 81:1-82:10; EX1003, ¶ 136.

72 EX1001, 135:5-16; *see also id*. at 42:48-55.

compositions can be formulated "so that the components, ***particularly the PH20*** … ***remain active*** or are ***stable***" "(*i.e.*, it [PH20] ***retains*** activity…)."[73]

Finally, Patentee may contend the claims should be read as encompassing both alternative embodiments (*i.e.*, "active" and "inactive" mutants). Reading the claims in that manner is incorrect. It also exacerbates the § 112 problems, as every claim still necessarily includes (and thus must describe and enable) the full sub-genus of "active mutants" in claim 1 defined by claims 5 and 6, and the common disclosure provides no indication that inactive modified PH20 polypeptides can play any role in influencing the delivery of another therapeutic agent.[74]

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

Claims 1-11 are unpatentable because each lacks written description in and was not enabled by the common disclosure of the '185 Patent and the '731 Application in 2011.

Per § IV.D.1, the claim language defines methods that encompass use of enormous genera of modified PH20 polypeptides: between 10^{49} and 10^{66} distinct polypeptides. Their real-world scope is absurd. A collection of one molecule of

[73] EX1001, 32:25-40 (emphasis added).

[74] EX1003, ¶¶ 136-1372, 139-141.

each polypeptide in the smallest genus would consume an aggregate mass (~1.37 x 10^{27} kg) that exceeds the mass of the Earth (~6 x 10^{24} kg).[75]

Relative to this broad scope, the ’185 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 and their potential to be used in methods of increased delivery. But the common disclosure nowhere demonstrates possession of methods that use the unknown number of this vast remainder of multiply-modified polypeptides in the claims’ scope. And to practice the claimed method’s full scope requires a skilled artisan to make-and-test at least ~10^{49} mutants to know if each is active or inactive and whether it causes increased spreading. But testing every polypeptide within the claims’ scope in search of “active mutants” is impossible—literally.

A. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.[76] “To fulfill the written description requirement, a patent owner must

[75] EX1003, ¶¶ 125, 202; *see also, e.g.*, EX1039, 136-37 (10^{390} forms of a polypeptide possible from 300 residue sequence).

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

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."[77] 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."[78]

"[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus."[79] "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

[77] *Idenix Pharm., LLC v. Gilead Scis., Inc.,* 941 F.3d 1149, 1163 (Fed. Cir. 2019) (internal quotation marks omitted).

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

[79] *Idenix*, 941 F.3d at 1164.

described the genus sufficiently to show that the inventor invented, or had possession, of the genus."[80]

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).[81] And "merely drawing a fence around the outer limits of a purported genus" is insufficient.[82] 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."[83]

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

> Although the number of the described species appears high quantitatively, the described species are all of the similar type

[80] *AbbVie*, 759 F.3d at 1299-1300.

[81] *Idenix*, 941 F.3d at 1164.

[82] *Ariad*, 598 F.3d at 1350-54.

[83] *Id.* at 1349.

> and do not qualitatively represent other types of antibodies encompassed by the genus.[84]

It also criticized the prophetic description as being "only a research plan, leaving it to others to explore the unknown contours of the claimed genus" and a "trial and error approach."[85]

Second, *Idenix* addressed method of treatment claims using a broad genera of compounds defined by formulas: "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").[86] The court criticized the specification's failure to indicate which of the thousands of compounds would be effective, and found that "provid[ing] lists or examples of supposedly effective 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

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

85 *Id.*

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

direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV."[87]

Finally, the Board in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found.*, PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) considered claims employing "90% sequence homology" language that captured "broad genus of amino acid sequence homologues" but which (like here) imposed no restrictions where particular replacements could be made, thereby causing the claim "to cover, at minimum, thousands of amino acid sequences."[88] The Board found fatal the specification's failure to "explain what, if any, structural features exist (*e.g.*, remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification" and required by certain dependent claims, and noted the homology limitation "serves to merely draw a fence around the outer limits of a purported genus [which] is not an adequate substitute for describing a variety of materials constituting the genus" for purposes of section 112(a).[89]

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[87] *Id.* at 1164.

[88] *Boehringer*, at 16. The claims included methods of using proteins. *Id.* at 6.

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

The deficiencies of the present claims dwarf those in these three cases. They define much larger, much less predictable, and much more diverse genera, and the common disclosure is far more limited. Because the common disclosure neither discloses a representative number of species, nor identifies sufficient structural features common to the members of each claimed genus, it fails to demonstrate possession of the genera defined by the claims of the '185 Patent.

1. Claims 1-4 Lack Written Description

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

The genera of modified PH20 polypeptides that claims 1 to 4 specify use of are not only immense, but structurally and functionally diverse. They capture PH20 mutants with 2, 3, or more substitutions up to a number set by the sequence identity boundary (*i.e.*, 17 for the narrowest claims (*i.e.*, claim 3) to 23 for the broadest (*e.g.*, claim 1)). The optional substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, and arranged in any manner.[90] They thus capture a mutant with 5 substituted hydrophobic

[90] EX1003, ¶ 121; EX1001, 60:59-65, 47:43-47, 47:56-58, 42:3-9.

residues clustered in a small region, as well as one with up to 23 substitutions that mix polar, charged, aliphatic, and aromatic amino acids together in any manner.[91]

Each claim also encompasses use of PH20 polypeptides having substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 36 alternative sequences that terminate at positions 430 to 465. The claims' sequence identity language also captures PH20 polypeptides that terminate at positions before 430. For example, claims referencing SEQ ID NO: 32 that allow up to 21 changes (with any mixture of deletions and substitutions) capture a PH20 terminating at position 416 or below. But removing so many residues from the C-terminus of PH20 can render it inactive, and the disclosure does not describe or suggest that position 320 substitutions would restore activity.[92] The claims, however, encompass use of such polypeptides in the specified method.

(b) The Claims Specify Use of Modified PH20 Polypeptides the Common Disclosure Says to Avoid or Not Make

The claims' unconstrained sequence identity language captures categories of PH20 mutants a skilled artisan would understand the disclosure to be saying to avoid. Each raises unique questions relative to the remainder of the genus and are thus distinct "sub-genera" of PH20 mutants that are not representative of other

[91] EX1003, ¶¶ 121-22.

[92] EX1003, ¶¶ 170-73.

"sub-genera" within the claimed genera. But instead of providing guidance that navigates this confusing landscape, the patent simply instructs the skilled artisan "to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein."[93] The common disclosure thus does not describe any of the polypeptides within these sub-genera being claimed.

(i) Substitutions to Avoid in Active Mutants

The common disclosure indicates that active mutant modified PH20 polypeptides (*i.e.*, those potentially useful in methods of increasing delivery of another therapeutic agent) should not incorporate amino acid substitutions that rendered $PH20_{1-447}$ inactive, stating:

> ***To retain hyaluronidase activity***, modifications typically ***are not made*** at those positions that are less tolerant to change or required for hyaluronidase activity.[94]

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.[95] It does not limit this observation to

[93] EX1001, 78:33-38; EX1003, ¶ 206.

[94] EX1001, 80:13-15 (*emphases added*).

[95] EX1001, 80:15-55.

single-replacement $PH20_{1-447}$ mutants, or suggest that any of these substitutions that render $PH20_{1-447}$ inactive should be included in enzymatically active, multiply-modified PH20 polypeptides (much less identify specific combinations including them).[96] 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*** methods requiring use of enzymatically active multiply-modified PH20 polypeptides do not and should not use PH20 mutants that include any of the individual mutations that rendered the $PH20_{1-447}$ polypeptide an inactive mutant.[97] The sequence identity claim parameters, however, capture such mutants.

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

The common disclosure does not describe and provides no guidance concerning "active mutant" PH20 polypeptides having fewer than 447 residues, particularly multiply-modified PH20 mutants terminating significantly before that position.[98]

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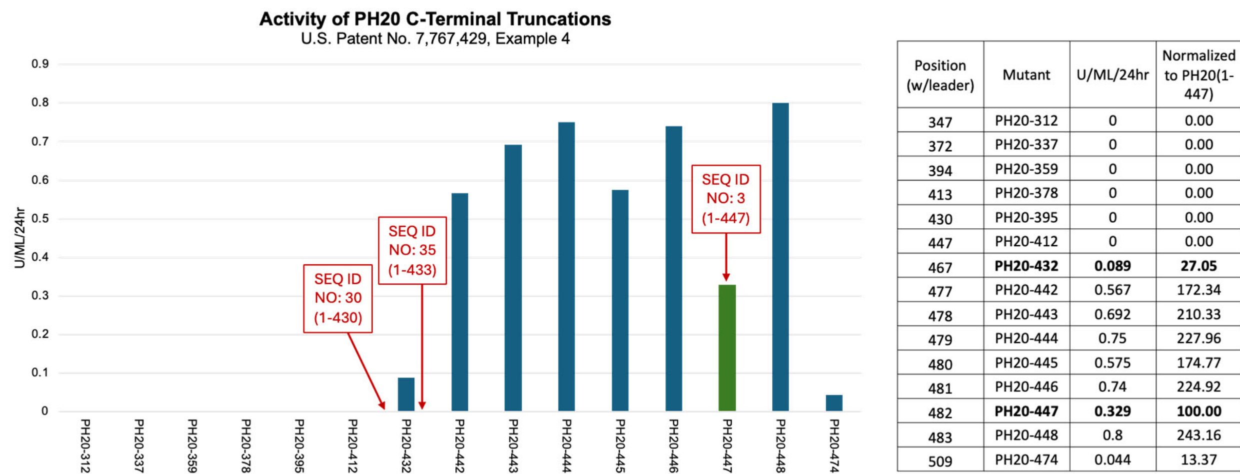
96 EX1003, ¶¶ 158, 168-69, 175.

97 EX1003, ¶¶ 155-58, 169; EX1001, 80:13-55, 70:46-56.

98 EX1003, ¶¶ 97, 100, 173-75; EX1001, 74:9-15.

The common disclosure and the prior art do report that wild-type PH20 polypeptides terminating at or below position 442 have ***significantly reduced or no*** hyaluronidase activity. For example, Patentee's '429 Patent reported that PH20 mutants terminating below position 432 residues lacked hyaluronidase activity, while those terminating between positions 432 and 448 had widely varying activities (below):[99]



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

Patentee's '429 Patent also reported that "a very narrow range spanning … [437-447] … defined the minimally active domain" of human PH20, and elsewhere

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99 EX1005, 87:52-88:24 ($PH20_{1-442}$ activity "decreased to approximately 10%"); EX1013, Figure 2, 430-32 ("[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA"); EX1003, ¶ 94.

observed this "minimally active" human PH20 domain contains at least residues 1-429.[100]

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

> A mature PH20 polypeptide … containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue ***464*** of SEQ ID NO: 6 [position ***429*** without signal] … ***is the minimal sequence required for hyaluronidase activity***.[101]

In 2007, Chao reported that the C-terminal region of human hyaluronidases contains a unique domain ("Hyal-EGF") linked to a characteristic pattern of sequences.[102] In PH20, the Hyal-EGF domain runs from positions 337-409.[103] In

[100] EX1005, 6:65-7:7 ("… sHASEGP from amino acids 36 to Cys 464 [429] … comprise the minimally active human sHASEGP hyaluronidase domain"); EX1003, ¶ 93.

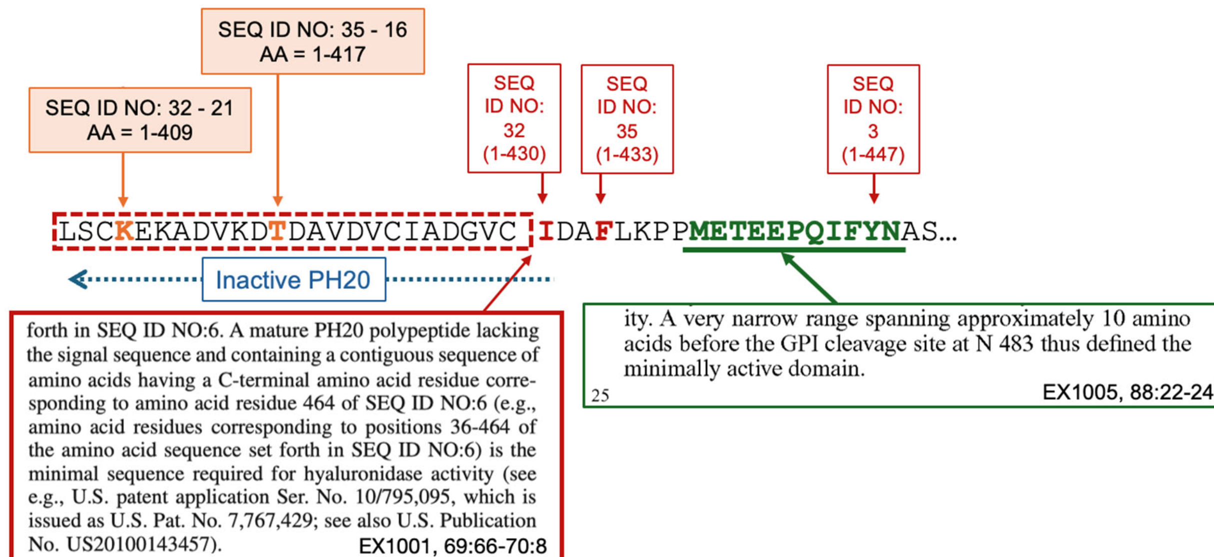
[101] EX1001, 69:66-70:8 (*emphases added*); *also* EX1003, ¶¶ 96, 159.

[102] EX1006, 6912; EX1003, ¶¶ 84, 87-88.

[103] EX1004, ¶¶ 97-99; EX1003, ¶ 95.

2009, Zhang showed the Hyal-EGF domain was necessary for hyaluronidase activity.[104]

The C-terminus of PH20 is illustrated below, showing (i) the positions where SEQ ID NOS: **3** (447), **32** (430) and **35** (433) terminate, (ii) the "minimally active domain" at 437-447, and (iii) residues below position 429.[105] Positions resulting from deletion of 21 or 16 residues from SEQ ID NOS: 32 and 35 end before position 429.

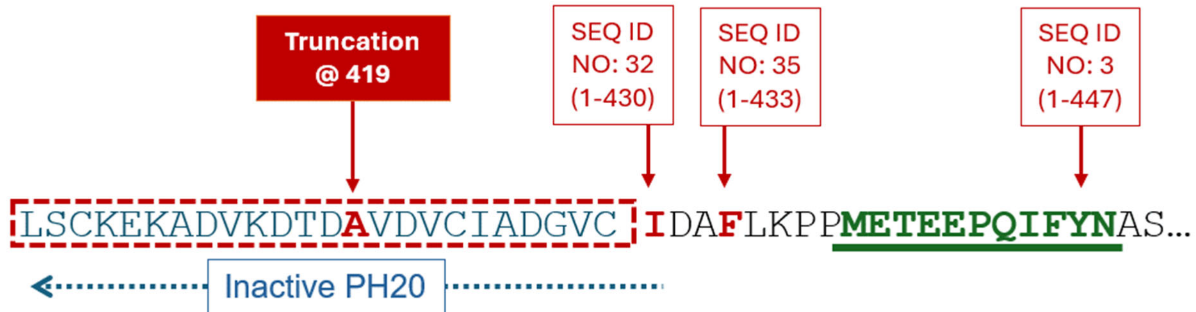


Consequently, a skilled artisan in 2011 would have believed that PH20 polypeptides that terminate before position 430 would be inactive (*e.g.*, at position 419, below), and therefore would not, if administered with another therapeutic

[104] EX1010, 9438; EX1003, ¶ 89.

[105] EX1003, ¶ 160.

agent, degrade HA in the extracellular matrix, and thus would not increase delivery of the other agent.[106]



The common disclosure provides no examples of (or guidance concerning) PH20 mutants truncated below position 447 with one or more substitutions and that are enzymatically active. It thus ignores the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433.[107] The claimed method nonetheless captures use of such modified PH20 polypeptides with truncations down to and beyond position 419.[108]

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

The empirical results in the common disclosure provide no predictive guidance to a skilled artisan about the structural features of multiply-modified

[106] EX1003, ¶¶ 95-96, 136, 171-172.

[107] EX1003, ¶¶ 95-96, 98, 100.

[108] EX1003, ¶¶ 170-72.

PH20 polypeptides within the claimed genera that are enzymatically active and can increase delivery of another therapeutic agent.

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

The common disclosure reports results from testing a portion of a randomly generated library of ~6,743 single-replacement $PH20_{1\text{-}447}$ polypeptides.[109] These mutants were generated via a mutagenesis process which substituted one of ~15 amino acids into random positions in $PH20_{1\text{-}447}$ "such that each member contained a single amino change."[110] Approximately 5,917 were tested, while ~846 were uncharacterized.[111] More than half (~57%) of these mutants were classified as "inactive mutants," while ~30% (1335) were reported to have less activity than

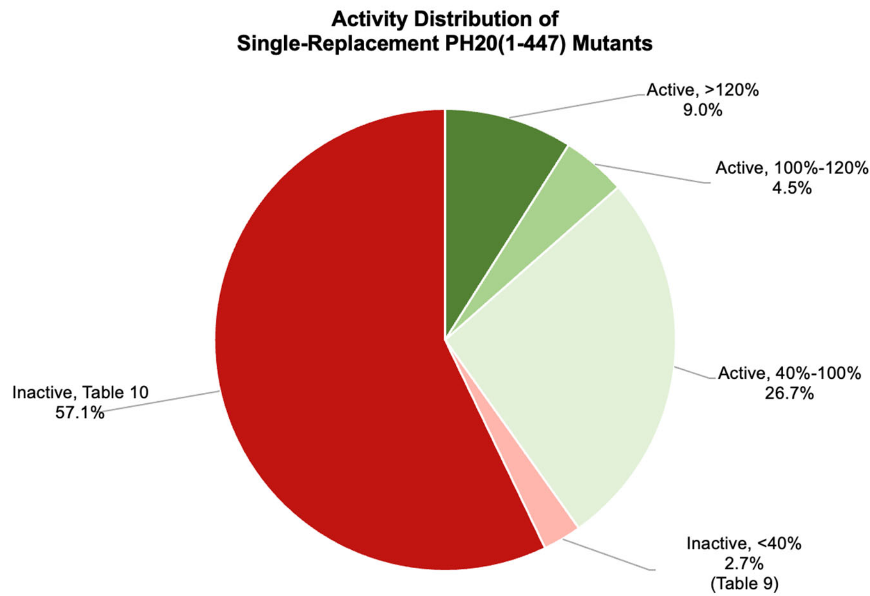
109 EX1001, 127:37-48, 194:46-48, 194:26-32.

110 EX1001, 194:26-35.

111 EX1003, ¶¶ 106-107. Inconsistent numbers and classifications of mutants are not explained: (i) Table 3 lists 2,516 single-replacement $PH20_{1\text{-}447}$ mutants as "active mutants," but Table 9 identifies only 2,376 mutants that exhibit >40% hyaluronidase activity; (ii) Tables 5 and 10 list 3,368 and 3,380 $PH20_{1\text{-}447}$ "inactive mutants," respectively.

unmodified $PH20_{1-447}$ (20%-100%).[112] In other words, ~87% of the single-replacement $PH20_{1-447}$ polypeptides had ***less*** activity than unmodified $PH20_{1-447}$.[113]

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%



112 EX1003, ¶ 108.

113 *Id.*

The measured activity of single-replacement $PH20_{1-447}$ mutants shows no trends or correlations even for single-replacement $PH20_{1-447}$ polypeptides.[114] Instead, numerous examples show that even introducing different amino acids at the same position in $PH20_{1-447}$ resulted in (i) increased activity, (ii) decreased activity, or (iii) inactive mutants (below).[115]

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

The data on activities of tested single-replacement $PH20_{1-447}$ mutants is not analyzed or explained in the common disclosure—it is simply presented. There is no attempt to extrapolate its results to any combinations of substitutions in PH20 polypeptides, or to assess the impact of a single substitution on the protein's structure.[116] The quality of the data is also questionable: no control values or

114 EX1003, ¶¶ 109, 149-50.

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

116 EX1003, ¶ 146.

statistical assessments are provided.[117] All the data shows is that most of the tested single-substitution mutants impaired PH20's activity.[118]

The results from single substitutions provide no insights into PH20 polypeptides with multiple concurrent mutations, which together can cause complex and unpredictable effects on a protein's structure and resulting function.[119] The patent's empirical test results thus provide no guidance to a skilled artisan about which of the many possible PH20 mutants with different sets of 2-42 substitutions will be enzymatically active, let alone which will be useful in increasing delivery of therapeutic agents (which would require yet further testing).[120]

(ii) Purported Stability Data Is Not Reliable or Probative

The common disclosure reports results in Tables 11 and 12 from two runs of "stability" testing of ~409 single-replacement $PH20_{1\text{-}447}$ polypeptides.[121] Table 11 reports the hyaluronidase activity of single-replacement $PH20_{1\text{-}447}$ mutants tested at

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[117] EX1003, ¶ 109.

[118] EX1003, ¶ 145.

[119] EX1003, ¶¶ 146, 149.

[120] EX1003, ¶¶ 147, 150, 168-169, 178, 183.

[121] EX1001, 273:30-275:37.

4° C and 37° C, and in the presence of a "phenolic preservative" (m-cresol),[122] while Table 12 compares relative activities under pairs of these conditions.[123]

The data in Tables 11 and 12 provides no meaningful insights.[124] For example, unsurprisingly, single-replacement $PH20_{1\text{-}447}$ polypeptides showed higher activity at 37° C than at 4° C, given that PH20 exists at the former temperature in humans.[125] And all that testing with m-cresol showed was that only a few mutants were able to resist its effects, with no explanation why.[126]

With one exception, there is no evidence the measured activity data was attributable to improved stability of PH20.[127] More directly, the common disclosure does not identify which ***combinations*** of substitutions improve

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[122] EX1001, 275:38-282:17 (Table 11).

[123] EX1001, 282:18-293:24 (Table 12).

[124] EX1003, ¶ 76.

[125] EX1003, ¶ 73; EX1001, 170:66-171:8.

[126] EX1003, ¶ 69.

[127] EX1003, ¶ 69.

stability.[128] It thus provides no probative insight regarding multiply-modified PH20 polypeptides with increased stability.[129]

The data is also largely meaningless, as many of their values fall within the range of activity observed for the positive control.[130] As the charts and table below show, the activity of unmodified $PH20_{1-447}$ varied by 97% and 87% in two rounds of testing.[131]

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

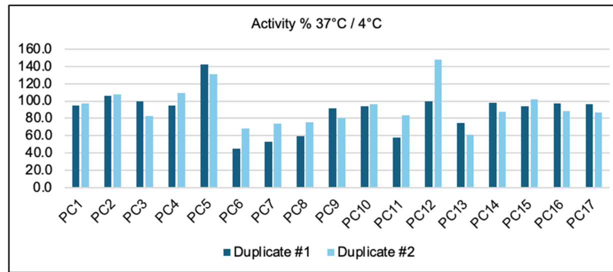
KEY
Coloration of Percent (%) Activity Values
n/a
>120
between 100 and 120
between 80 and 100
between 40 and 80
between 20 and 40
between 10 and 20
between 0 and < 10

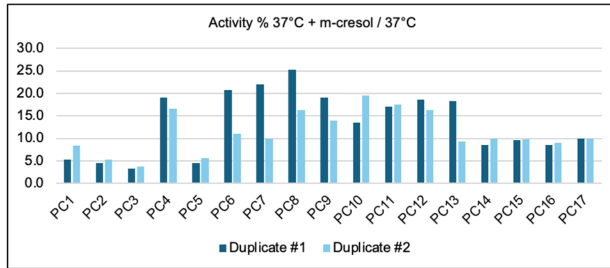
128 EX1003, ¶¶ 75-76.

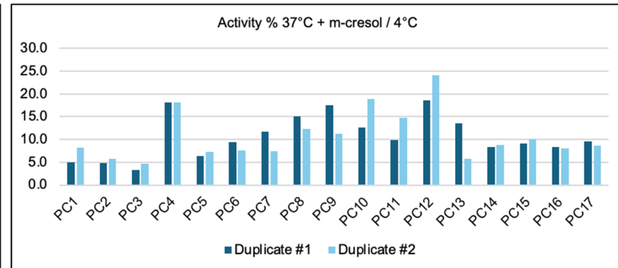
129 *Id.*

130 EX1003, ¶ 71; EX1001, 293 (Table 12).

131 EX1003, ¶ 71, Appendix A-7, A-8.







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

As Dr. Hecht observes, this "significant variation raises serious doubts about how probative or instructive the values of individual tested mutants that fall within the range of variability observed for the control can possibly be."[132] The data not only fails to identify specific combinations of substitutions that yield PH20

132 EX1003, ¶¶ 70-72; *see also* EX1001, 293:46-56 (positive control also varied).

mutants with increased resistance to or stability in denaturing conditions, it is unreliable.

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

The common disclosure does not describe any multiply-modified PH20 polypeptides that are "active mutants." Instead, it simply presents ***the idea*** of multiply-modified PH20 polypeptides. First, it observes that "[a] modified PH20 polypeptide can have up to 150 amino acid replacements," "[t]ypically" contains between 1 and 50 amino acid replacements and "can include any one or more other modifications**,** in addition to at least one amino acid replacement as described herein."[133] It also contends a modified PH20 polypeptide with "a sequence of amino acids that exhibits" between 68% and 99% sequence identity with any of unmodified SEQ 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)."[134]

None of these statements identify ***any*** actual multiply-modified PH20 polypeptides (*i.e.*, PH20 polypeptide sequences with particular combinations of

[133] EX1001, 48:43-53.

[134] EX1001, 96:53-67 (emphasis added).

specific amino acid substitutions), much less provide results from testing any or indicating which will increase delivery of therapeutic agents. They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides.

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

> The method provided herein [] is ***iterative***. In one example, after the method is performed, any modified hyaluronan-degrading enzymes identified as exhibiting stability … ***can be modified or further modified*** to increase or optimize the 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.[135]

[135] EX1001, 135:4-16 (*emphases added*); *see also id.* at 42:48-55, 128:16-22; EX1003, ¶¶ 185-189.

This prophetic research plan is effectively meaningless—it does not indicate that any active mutant multiply-modified PH20 polypeptides will be found, much less identify ***which*** multiply-modified PH20 polypeptides are active mutants.[136]

An alternative focus is then proposed: mutations can be "targeted near" "critical residues" which supposedly "can be identified because, when mutated, a normal activity of the protein is ablated or reduced."[137] But Tables 5 and 10 show that at least one substitution at each of 405 positions between positions 1 and 444 of $PH20_{1\text{-}447}$ resulted in an inactive mutant.[138] In other words, the common disclosure's guidance is to target locations "near" ~90% of the amino acids in $PH20_{1\text{-}447}$, which is no different than targeting every residue in the protein.[139] It is, like the first proposed "iterative" process, meaningless.

These prophetic research plans, based entirely on unfocused, iterative "make-and-test" experiments, provide no direction to the skilled artisan about which of the trillions and trillions of possible multiply-modified PH20

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136 EX1003, ¶¶ 185, 196-97, 200; EX1001, 44:1-2; *see generally id.*, 127:37-128:15, 128:25-130:3, 130:30-135:3.

137 EX1001, 135:17-42; EX1003, ¶¶ 187-88.

138 EX1003, ¶ 192, Appendix A-3.

139 EX1003, ¶ 192.

polypeptides are enzymatically active.[140] Instead, they require the skilled artisan to repeat the cycle of mutagenesis iteratively, screening and selecting until 10^{49} to 10^{66} modified PH20 polypeptides are produced and screened for activity.[141] That in no way demonstrates possession of the claimed genus.

The specification also incorrectly portrays the experimental readout—hyaluronidase activity—as a measure of "stability."[142] 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.[143] Activity may or may not be influenced by stability but is not itself a measure of stability.[144]

Finally, the common disclosure affirmatively addresses only six specific modified PH20 polypeptides with more than one substitution that is identified by position and identity of the amino acid substitution. But its guidance is to ***not***

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[140] EX1003, ¶ 203.

[141] EX1003, ¶¶ 187-89, 200-01; EX1001, 130:11-16, 130:4-28, 133:22-26, 133:37-42, 133:59-134:6.

[142] EX1003, ¶¶ 67, 69, 191.

[143] EX1003, ¶¶ 63-66.

[144] EX1003, ¶ 67.

make those polypeptides.[145] While none of these mutants fall within the scope of the claims, no explanation is provided ***why*** these particular combinations of substitutions should be avoided. Nevertheless, by identifying certain multiply-modified PH20 polypeptides to not make, the common disclosure demonstrates that the inventors knew how to identify particular multiply-modified mutants with specificity.

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

The common disclosure does not identify the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1\text{-}447}$ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.[146] Instead, it simply lists single replacements to random amino acids at random positions that were

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[145] EX1001, 77:45-57.

[146] EX1003, ¶¶ 146-47, 158.

classified as "active mutants" by a hyaluronidase assay; nothing is said about the effects (if any) of substitutions on the protein's structure.[147]

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.[148] Again, it simply reports activity data from testing randomly generated ***single***-replacement $PH20_{1\text{-}447}$ mutants.

The common disclosure's empirically identified examples of "active mutant" single-replacement $PH20_{1\text{-}447}$ mutants also do not ***by themselves*** identify any "structure-function" relationship between "active mutants" and the set of single-replacement modified $PH20_{1\text{-}447}$ polypeptides.[149] They certainly do not do so for the much larger genus of modified PH20 polypeptides of varying lengths and between 2 and 23 substitutions.[150]

Critically, the common disclosure ***does not even contend*** that a particular amino acid replacement at a particular position (*e.g.*, 320) that makes a $PH20_{1\text{-}447}$

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[147] EX1001, 227:15-43; EX1003, ¶¶ 146-47, 149.

[148] EX1003, ¶¶ 55, 149-50.

[149] EX1003, ¶¶ 61, 150, 164, 166.

[150] EX1003, ¶ 164.

an "active mutant" will make any other modified PH20 polypeptide with that same amino acid replacement (plus between 1 and 22 additional replacements or truncations) an "active mutant."[151] 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.[152] Thus, even the inventors did not view their compilation of test results as identifying a structure-function correlation for multiply-modified PH20 polypeptides.[153]

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,[154] and thus cannot satisfy the written description requirement of § 112(a) as a disclosure that links a functional property to a particular structure ***shared*** by the members of the genus.

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[151] EX1003, ¶¶ 174, 204-205.

[152] EX1003, ¶¶ 56-57.

[153] Notably, three of the six multi-substituted mutants the disclosure instructs ***not*** to make includes a substitution—N219A—that showed 129% activity when made a single substitution in $PH20_{1-447}$. EX1001, 77:45-57, 245 (Table 9).

[154] EX1003, ¶ 164.

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

The ~2,500 active mutant single-replacement $PH20_{1\text{-}447}$ polypeptides in the disclosure are not representative of the structural and functional diversity of the modified PH20 polypeptides within the genera of polypeptides the claims specify use of in methods of increasing delivery of another therapeutic agent.[155]

First, these single-replacement $PH20_{1\text{-}447}$ examples are not representative of the trillions and trillions of $PH20_{1\text{-}447}$ polypeptides having between ***2 and 23 substitutions*** at any of hundreds of positions within the protein.[156] The latter group of proteins is structurally distinct from single replacement PH20 polypeptides, both as to their sequences and as to the various secondary structures and structural motifs within the folded proteins that result when multiple amino acid substitutions are incorporated and from the distinct interactions they can cause with neighboring residues.[157] The effects of numerous substitutions on the PH20 protein's various secondary structures and structural motifs are not described or discussed in the common disclosure, and the magnitude of structural changes resulting from the

[155] EX1003, ¶¶ 61, 150, 162, 166.

[156] *See* § IV.D.1; EX1003, ¶¶ 61, 150, 166.

[157] EX1003, ¶¶ 55-56, 58, 60, 163, 166.

concurrent substitutions encompassed by the claims was unknowable in 2011.[158] 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.[159]

More specifically, introducing a first amino acid substitution often affects the neighbors of that original/replaced amino acid by, for example, (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, and/or (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).[160] Introducing a second substitution in that region may reverse those interactions (or not) with each neighboring residue, and a third substitution may do the same, with up to 16 rounds permitted by even the narrowest claims, each potentially impacting each interaction.[161] The data associated with a single amino acid substitution thus cannot be representative of the properties of any of these downstream, multiply-substituted mutants, which will have an unknowable

[158] EX1003, ¶¶ 164-65, 242.

[159] EX1003, ¶¶ 61, 148.

[160] EX1003, ¶¶ 56-58.

[161] EX1003, ¶¶ 58-60, 149.

combination of substitutions that each uniquely impact the properties of the mutated protein.[162]

Enzymatically active single-replacement $PH20_{1-447}$ polypeptides also are not representative of multiply modified PH20 polypeptides that additionally incorporate changes that rendered the wild-type PH20 protein inactive (*e.g.*, truncations terminating below position 429, or single substitutions that render $PH20_{1-447}$ inactive).[163] That is because the ***active*** single-replacement $PH20_{1-447}$ polypeptides in the disclosure do not contain the distinct structural features that rendered the latter types of PH20 polypeptides enzymatically ***inactive***. For example, an enzymatically active $PH20_{1-447}$ protein with a single amino acid substitution (*e.g.*, D320K) would not be considered representative of a PH20 terminating between positions 409 and 433 that also additionally contains the D320K substitution.[164] For example, the common disclosure does not identify and a skilled artisan could not have predicted from the single-replacement $PH20_{1-447}$ polypeptides examples in the common disclosure whether enzymatic activity could

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162 EX1003, ¶¶ 150, 166.

163 EX1003, ¶¶ 168-70.

164 EX1003, ¶¶ 173-75.

be restored to the truncated PH20 mutants, much less the precise additional changes necessary to do so.[165]

The common disclosure thus provides a very narrow set of working examples relative to the diversity of modified PH20 polypeptides that the claims specify use of in methods of increasing delivery of another therapeutic agent.[166] The examples of modified PH20 polypeptides in the common disclosure are restricted to ***one type of change*** (a single amino acid replacement) in ***one type of PH20 polypeptide*** (SEQ ID NO: 3).[167] By contrast, the claims encompass use of modified PH20 polypeptides having changes within 36 different unmodified PH20 sequences, and include, in addition to one identified replacement at position 320, anywhere from 1 to 22 (claims 1-2) or 20 (claim 4) or 16 (claim 3) additional changes.[168] A simple illustration demonstrates how ***non-representative*** the examples are: all of the examples of single-replacement $PH20_{1\text{-}447}$ mutants fit into one box of the array below.

[165] EX1003, ¶ 174.

[166] EX1003, ¶ 162.

[167] EX1003, ¶¶ 100, 102, 106.

[168] EX1003, ¶¶ 118-22.

	Number of Changes																					
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
3																						
32																						
33																						
34																						
35																						
36																						
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Consequently, a skilled artisan would not have viewed the Patents' examples of individual single amino acid replacements in PH20$_{1\text{-}447}$ as being ***representative*** of the diversity of modified PH20 polypeptides to be used in the claimed methods.[169]

[169] EX1003, ¶ 150.

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

Patentee's position on the breadth of the claims is unknown. However, by their literal language, they capture use of several sub-genera of modified PH20 polypeptides with changes that the common disclosure says rendered the $PH20_{1\text{-}447}$ mutants inactive (*i.e.*, single replacements in Tables 5/10 or in PH20 sequences terminating before position 429). The claims thus improperly capture use of multiply-modified PH20 polypeptides the common disclosure affirmatively excludes from the genus of enzymatically active PH20 polypeptides that can cause increased delivery of another therapeutic agent.

The common disclosure provides no exemplification of using multiply-modified species of PH20 polypeptides in the claimed methods, much less use of modified PH20 polypeptides that, per the common disclosure's limited guidance, would be expected to be inactive mutants.[170] For example, there is no explanation of substitutions that might be made to restore activity to a PH20 mutant, that, under the logic of the common disclosure, will result in enzymatically inactive PH20 polypeptides.[171] Yet the claims encompass use of such proteins.

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[170] EX1003, ¶ 168.

[171] EX1003, ¶ 174.

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

(h) The Common Disclosure Does Not Identify Multi-Modified Mutants That Increase Delivery of a Therapeutic Agent

All claims concern methods of "increasing delivery of a therapeutic agent to a subject" (*e.g.*, an antibody) by administering any of the PH20 polypeptides within claim 1's genus with the other agent.

The common disclosure attributes a PH20 protein's capacity to "increase delivery" capability to its ability to cause "spreading" or "diffusion," and indicates this "spreading" / "diffusion" capability requires, at a minimum, a PH20 with hyaluronidase activity.[172] But, as explained above, the common disclosure does not identify which of the trillions of modified PH20 polypeptides within claim 1's genus have hyaluronidase activity. Nor does it identify which of those trillions of

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[172] EX1001, 174:19-28, 175:23-35, 73:22-47.

polypeptides also possess "spreading" / "diffusion" activity—it identifies only one (F204P $PH20_{1-447}$).[173]

The modified PH20 polypeptides within claim 1's genus also include those with multiple substitutions in the Hyal-EGF region of PH20. Before 2011, it was believed the Hyal-EGF domain mediated protein-protein interactions, and mutations to the Hyal-EGF domain substantially eliminated hyaluronidase activity in otherwise unaltered PH20 polypeptides.[174] Making multiple substitutions to the Hyal-EGF domain can alter its structure and thereby disrupt not only PH20's hyaluronidase activity but any protein-protein interactions that might be involved in PH20's spreading activity *in vivo*.[175]

All claims thus lack written description not only because the common disclosure does not identify which of the trillions of modified PH20 polypeptides with multiple substitutions will be active mutants, but because they also do not identify those that preserve the Hyal-EGF domain so as to retain the ability to

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[173] EX1001, 308:29-311:16.

[174] EX1003, ¶¶ 85-86, 89-90, 98; EX1006, 6912, 6913, 6916-17; EX1010, 9439; EX1005, 87:52-88:24; EX1079, 84.

[175] EX1003, ¶¶ 98-100, 176-180.

cause “spreading”/diffusion necessary to increase delivery of another therapeutic agent.[176]

2. Dependent Claims 5-11 Lack Written Description

(a) Claims 5-6

Claims 5 and 6 add additional functional requirements to the genus defined by claim 1: that the modified PH20 polypeptides being administered exhibit increased (>100% (claim 5) or >120% (claim 6)) hyaluronidase activity relative to unmodified $PH20_{1-447}$.

The reasons provided in § V.A.1 explaining why the claims generally lack written description apply with full force to claims 5 and 6.

First, the identification of four single-substitution $PH20_{1-447}$ mutations at position 320 that exhibited increased activity compared to unmodified $PH20_{1-447}$ is not representative of each claim’s genus of PH20 polypeptides having 1 to 22 additional substitutions and/or truncations.[177]

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides (if any) exhibiting the recited >100% or >120% activity and also have the ability to increase delivery of other

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[176] EX1003, ¶ 181.

[177] EX1001, 252 (Table 9); EX1003, ¶¶ 204-205.

therapeutic agents.[178] The mere presence of a single substitution at position 320 in a modified PH20 certainly does not demonstrate possession of any multiply-modified PH20 polypeptide with increased activity having that position 320 substitution, and the common disclosure does not contend otherwise.[179]

The common disclosure does not describe any multiply-modified PH20 polypeptides having the claimed substitutions at position 320, much less those with 1 to 22 additional substitutions, and that exhibit increased enzymatic activity.[180] Indeed, the common specification does not identify any multiply-modified PH20 polypeptides with any level of hyaluronidase activity.[181]

Claims 5 and 6 lack written description in the common disclosure.

(b) Claims 7-11

Claims 7-11 do not alter the number of PH20 polypeptides within the genus of claim 1. They instead employ claim 1's definition of the genus of modified PH20 polypeptides and specify classes of therapeutic agents (claims 7-9) or how the pharmaceutical composition is administered (claims 10-11) in claim 1's

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[178] EX1003, ¶¶ 164, 178-179, 197, 203.

[179] EX1003, ¶¶ 151, 174, 197.

[180] EX1003, ¶¶ 147, 197, 203-206.

[181] EX1003, ¶¶ 137, 184.

method of increasing delivery of a therapeutic agent. Claims 7-11 therefore lack written description for the same reasons explained in § V.A.1.[182]

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

"If a patent claims an entire class of … compositions of matter, the patent's specification must enable a person skilled in the art to make and use the ***entire*** class," *i.e.*, "the ***full scope*** of the invention," and so the "more one claims, the more one must enable."[183] "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."[184] "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."[185]

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[182] *Idenix*, 941 F.3d at 1155, 1165; *Boehringer*, PGR2020-00076, Paper 42, at 40-41.

[183] *Amgen*, 598 U.S. at 610 (*emphases added*).

[184] *Idenix*, 941 F.3d at 1159.

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

Although not required, enablement may be assessed using the *Wands* factors, which consider: "(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention."[186]

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."[187]

Here, the common disclosure utterly fails to enable use of the immense genus of modified PH20 polypeptides specified in the claimed methods to increase delivery of another therapeutic agent. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to

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

[187] *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).

identify which of the 10^{49}+ PH20 polypeptides having multiple amino acid replacements and/or truncations specified by the sequence identity language of the claims are "active mutant" PH20 polypeptides that can be used in the claimed methods of increasing delivery of a therapeutic agent.[188]

1. Claims 1-4 Are Not Enabled

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

(a) Extreme Scope of the Claims

As explained in § IV.D.1, each of claims 1-4 specifies use of a modified PH20 polypeptide falling within immense and diverse genera of between 10^{49} and 10^{66} modified PH20 polypeptides in a method of increasing delivery of another therapeutic agent. Practicing the full scope of the claimed methods, however, raises substantial scientific questions left unanswered by the common disclosure:

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[188] EX1003, ¶¶ 182-184, 203.

(i) The claims encompass use of many modified PH20 polypeptides that terminate below position 429.[189] The common disclosure and the prior art, however, report that unmodified human PH20 must include residues through position 429 to have hyaluronidase activity.[190]

(ii) Several claims (1-2, 5-11) encompass use of modified PH20 polypeptides that, per the common disclosure's guidance, would be expected to be insoluble because they include all or some of the GPI anchor sequence.[191]

(iii) The mathematical "sequence identity" boundaries set by the claim language cause the claims to capture (without restriction) use of modified PH20 polypeptides with 2 to 23 amino acid replacements that the common disclosure instructs "are less tolerant to change or required for hyaluronidase activity."[192]

In other words, the claims capture use of massive genera of modified PH20 polypeptides, most of which would have unknowable properties (particularly with

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[189] EX1003, ¶¶ 161, 170-172.

[190] EX1001, 69:66-70:8; EX1003, ¶¶ 96, 159-60.

[191] EX1001, 46:27-29, 72:8-9, 74:19-25, 75:16-18; EX1005, 2:56-61, 3:57-62.

[192] EX1001, 80:13-15.

respect to their ability to increase delivery of other therapeutic agents) absent individual production and testing.[193]

Claims that capture use of a massive and diverse genus of proteins have routinely been found non-enabled. For example, the claims in *Amgen* covered "millions" of different, untested antibodies,[194] while in *Idenix*, a skilled artisan would "understand that 'billions and billions' of compounds literally meet the structural limitations of the claim."[195] In both cases (as here), the enormous claim scope was contrasted to limited working examples in the patent, the field found unpredictable, and an immense quantity of experimentation was needed to practice the claims' full scope (*Wands* Factors 1, 3, 4, and 7). As the *Idenix* court also observed, one cannot rely on the knowledge and efforts of a skilled artisan to try to "fill the gaps in the specification" regarding which of the "many, many thousands" of possible compounds should be selected for screening, and which in this case is impossible.[196]

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[193] EX1003, ¶¶ 163-165.

[194] 598 U.S. at 603.

[195] 941 F.3d at 1157.

[196] *Id.* at 1159.

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

The common disclosure provides an extremely narrow set of working examples: ~5,917 randomly generated single-replacement $PH20_{1\text{-}447}$ polypeptides, of which ~2500 were “active mutants.”[197] Those examples of active mutant PH20 polypeptides are a tiny fraction of the 10^{49} to 10^{66} modified PH20 polypeptides whose use in the increased delivery method is 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 and identify modified PH20 polypeptides that can be used to increase delivery of another therapeutic agent; indeed, none of the examples incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.[198]

The common disclosure provides no credible guidance on the full scope of the claimed methods of administering PH20 polypeptides with multiple combinations of changes to increase delivery of another therapeutic agent.[199] Instead, it describes explicitly prophetic and “iterative” processes for ***discovering***

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[197] EX1003, ¶¶ 106-107.

[198] EX1003, ¶¶ 162-166, 173.

[199] EX1003, ¶¶ 138, 146.

active mutant PH20 polypeptides that might be useful in the claimed methods. *See* § V.A.1.d.

This prospective research plan requires a skilled artisan to engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of ***randomized*** mutations (up to 22 rounds under the broadest claim parameters) to ***discover*** which of the 10^{49}+ possible modified PH20 polypeptides the claims encompass use of might possess hyaluronidase activity.[200]

Second, it provides no meaningful guidance about 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";

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[200] EX1003, ¶¶ 191-93; *see also* EX1018, 382 ("combinatorial randomization of only five residues generates a library of 205 possibilities (3.2 x 10^6 mutants), too large a number for manual screening"). Chica credited a "ground-breaking" predictive molecular modeling technique that was later shown to be false. EX1018, 384, 382; EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

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

(iii) it does not identify any regions or residues that are "associated with the activity and/or stability of the molecule" or "'critical residues involved in structural folding or other activities' of the molecule" when two or more concurrent replacements have been made.[201]

From the common disclosure and their knowledge in 2011, a skilled artisan could not predict whether a particular multiply-modified PH20 polypeptide will be enzymatically active without making and testing each one.[202]

As discussed in § IV.D.3(a), the common disclosure also explains that, while necessary, hyaluronidase activity may not be ***sufficient*** for a modified PH20 polypeptide to be able to increase delivery of another therapeutic agent.[203] It thus instructs testing of modified PH20 polypeptides in a particular, *in vivo* assay to determine if they cause "spreading"/"diffusion," which is necessary to enable increased delivery of another therapeutic agent.[204] As the common disclosure

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[201] EX1003, ¶¶ 151, 165, 184, 196-197.

[202] EX1003, ¶¶ 202-203, 206.

[203] EX1001, 174:19-28, 175:23-35, 73:22-47.

[204] *See* § V.A.2.d; EX1001, 174:19-28, 175:23-35, 73:22-47.

explains: "[t]he ability of a PH20 polypeptide … to act as a spreading or diffusing agent can be assessed" using a specified *in vivo* experiment in a mouse.[205] Notably, this is a different test than the *in vitro* assay used to detect hyaluronidase activity.[206] And, the common disclosure identifies only one mutant as having this "spreading" capability responsible for PH20's ability to increase delivery of a therapeutic agent.[207]

In other words, to determine which of the trillions of modified PH20 polypeptides within claims 1's structural parameters can be used in the claimed method of increasing delivery of a therapeutic agent, a skilled artisan must make and test each of the mutants twice—once to determine if it is an active mutant, and then to determine if that active mutant possesses the ability to cause spreading/diffusion to the degree necessary to increase delivery of another therapeutic agent.[208] Practicing the full scope of the claimed methods, thus, would require a skilled artisan to engage in an impossible amount of "make and test" experiments.

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[205] EX1001, 172:37-57, 298:2-35; EX1003, ¶¶ 177-178, 180.

[206] EX1001, 189:1-16, 224:55-226:51; EX1003, ¶ 195.

[207] EX1001, 308:29-311:15.

[208] EX1003, ¶ 198.

Regardless whether individual rounds of "iterative" production and testing might be considered "routine," the process described in the common disclosure is indistinguishable from the "***iterative, trial-and-error process[es]***" that have consistently been found to not enable broad genus claims to modified proteins.[209] 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.[210]

(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.[211] Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary

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

[210] EX1003, ¶¶ 178, 195-197, 202.

[211] EX1003, ¶ 61.

structures or structural motifs within the protein that are important to its biological activity (*e.g.*, catalysis, ligand binding, etc.) and/or stability.[212]

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.[213] 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.[214]

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.[215] Introducing ***multiple*** concurrent changes into a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity and/or stability,

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[212] EX1003, ¶¶ 61, 204-205.

[213] EX1003, ¶ 207.

[214] EX1003, ¶¶ 20, 49.

[215] EX1003, ¶¶ 165, 242.

and can even introduce new ones into the protein.[216] Replacing multiple amino acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.[217]

The cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure in 2011. The further away the modeled amino acid sequence gets from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model became.[218] 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.[219] And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.[220]

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[216] EX1003, ¶¶ 59-60, 197.

[217] EX1003, ¶¶ 55, 58, 61.

[218] EX1003, ¶¶ 165, 203, 242; EX1004, ¶¶ 161-162.

[219] EX1003, ¶¶ 165, 242; EX1004, ¶¶ 151-153; EX1012, 4, 8.

[220] EX1003, ¶¶ 51, 203; EX1059, 1225-26; EX1018, 378.

Consequently, a skilled artisan could not have used conventional rational design techniques to identify, much less predict the outcome of attempts to make, the enormous number of PH20 polypeptide sequences that incorporate the myriad possible combinations of between 2 and up to 23 substitutions the claims encompass.[221] 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 capable of increasing delivery of another agent, 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.[222]

(d) Other Wands Factors and Conclusion

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

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed.[223]

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[221] EX1003, ¶¶ 61, 165, 242.

[222] EX1003, ¶¶ 165, 203.

[223] EX1003, ¶¶ 165, 242.

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

Practicing the full scope of claims 1-4 thus would have required a skilled artisan to engage in undue experimentation, which renders those claims non-enabled.

2. Dependent Claims 7-11 Are Not Enabled

(a) Claims 5-6

Claims 5 and 6 require the modified PH20 polypeptides used in the claimed method to have specific levels of increased activity (*i.e.*, >100% or >120% of unmodified PH20).

Claims 5 and 6 are not enabled for the same reasons that claims 1-4 are not enabled (*see* § V.B.1). Specifically, a skilled artisan could not have predicted which of the trillions of PH20 polypeptides having up to 22 changes beyond a required change at position 320 would exhibit greater than 100% or 120% of the

hyaluronidase activity relative to unmodified PH20.[224] Instead, a skilled artisan would need to make-and-test each molecule in order to practice the "full scope" of the claims.[225]

(b) Claims 7-11

Claims 7-11 employ the genus definition used in claim 1 and additionally recite classes of therapeutic agents or details regarding the method of administration. They do not add requirements that limit the numbers of polypeptides in the claim 1 genus. They are therefore not enabled for at least the same reasons that claim 1 is.[226]

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

Patentee may contend the claims encompass use of modified PH20 polypeptides that are "inactive mutants." Such a contention is directly refuted by the common disclosure, which unequivocally explains that to increase delivery of another therapeutic agent, a modified PH20 polypeptide must be able to ***hydrolyze HA***—it must possess sufficient hyaluronidase enzymatic activity. *See* § IV.D.3(a).

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224 EX1003, ¶¶ 197, 203.

225 *Id.*

226 *See, e.g.*, *Idenix*, 941 F.3d at 1155, 1165.

Moreover, dependent claims 5 and 6 require PH20 polypeptides with >100% activity of an unmodified PH20. This means claim 1 must necessarily include in its scope modified PH20 polypeptides that are "active mutants." *See* § V.B.2.a. Even if claim 1 were to be read as encompassing methods that used enzymatically inactive PH20 polypeptides, the failure of the common disclosure to enable or describe the subgenus corresponding to methods that use PH20 polypeptides with activity >100% (*i.e.*, those within the scope of claims 5 and 6) demonstrates that claim 1 is unpatentable.[227]

The common disclosure also identifies zero correlation between "inactive mutants" and the claimed methods.[228] To discover if any inactive mutant could (implausibly) increase delivery of another agent, a skilled artisan must perform trial-and-error testing of each of the 10^{49}+ candidate polypeptides within the claims' scope to determine (i) which are "inactive mutants" and (ii) which can increase "spreading" using the mouse spreading experiment.[229]

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227 *ABS Glob., Inc. v. Inguran*, 914 F.3d 1054, 1070, 1074 (7th Cir. 2019) (citing *Alcon Research, Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1367-68 (Fed. Cir. 2012)).

228 EX1003, ¶ 151.

229 EX1001, 171:22-172:36, 172:37-57; EX1003, ¶¶ 132, 180, 182-83, 193-97.

The only putative utility identified for "inactive" polypeptides is as "antigens in contraception vaccines."[230] That putative utility is irrelevant to the claimed methods of increasing delivery of another therapeutic agent. It also is not scientifically credible. While the specification cites two studies in guinea pigs,[231] it ignores numerous publications before 2011 that showed that immunizing mammals with PH20 did ***not*** cause contraception.[232] Moreover, Patentee reported clinical studies of unmodified human $PH20_{1\text{-}447}$ in 2018 showed that "[a]lthough some antisperm antibodies are associated with decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-

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230 EX1001, 75:56-58, 187:48-67.

231 EX1001, 187:48-67; EX1022, 1142-43; EX1023, 1133-34.

232 *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 …").

positive subjects of either sex."[233] A skilled artisan thus would have expected "inactive mutant" PH20 polypeptides to have no utility at all.[234]

The common disclosure identifies ***no*** inactive PH20 mutants that exhibit contraceptive effects in humans.[235] It provides no guidance about which epitopes (if any) on the PH20 protein might induce contraceptive effects, much less show that "inactive mutants" preserve such epitopes.[236] Thus, a skilled artisan could not have reasonably predicted from the common disclosure whether any "inactive mutant" PH20 polypeptides would contain such (unidentified) epitopes or induce antibody production sufficient to confer contraceptive effects.[237] The common disclosure at best presents only a "research proposal" to discover "inactive

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[233] EX1024, 87-88; *see also* EX1061, 1154; EX1003, ¶¶ 113-14.

[234] EX1003, ¶¶ 113-16; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App'x. 26, 30 (Fed. Cir. 2007); *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

[235] EX1003, ¶ 116.

[236] *Id.*

[237] EX1003, ¶¶ 115-16.

mutants" with contraceptive utility, which is insufficient and, in any event, unrelated to the claimed methods.[238]

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 '185 Patent are substantially identical, and neither supports the challenged claims as § 112(a) requires. The claims are both PGR eligible and unpatentable under § 112(a).

The original claims of the '731 Application provide no additional guidance demonstrating written description or enablement of the claimed genera of multiply-modified PH20 polypeptides. Those original claims claimed equivalently broad genera via sequence identity language (*e.g.*, 85% to SEQ ID NOS: 3, 7, or 32-66) (claims 1-3) or having up to "75 or more amino acid replacements" (claim 4). Dependent claims listed single positions (claim 12) or replacements (claims 13-16) in those polypeptides. And, while certain claims contemplated 2-3 particular combinations of amino acid replacements (from dozens listed), others

[238] *See Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009).

encompassed substitutions at unspecified locations.[239] The original claims do not provide § 112 support for the challenged claims.[240]

VI. Challenged Claims 1-4 and 7-11 Are Unpatentable Under § 103

The methods of claims 1-4 define use of genera of modified PH20 polypeptides that encompass one specific modified PH20 polypeptide: D320K $PH20_{1\text{-}447}$. *See* § IV.D.2. Because this mutant and its use in a method of increasing delivery of therapeutic agents would have been obvious from the ’429 Patent in view of Chao and the knowledge of a skilled artisan, each of those claims is unpatentable. Claims 7-11 are also obvious, as each recites attributes met by D320K $PH20_{1\text{-}447}$, or is suggested by the ’429 Patent alone or with other prior art.

A. The Prior Art

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

Chao (EX1006) was published in “Biochemistry” in 2007. Chao is not discussed in the common disclosure of the ’185 Patent and ’731 Application and was not cited during examination.

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[239] EX1026, at 335.

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

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. Claims 1-4 Are Obvious

Patentee's '429 Patent would have motivated a skilled artisan to produce modified $PH20_{1\text{-}447}$ polypeptides having a single amino acid substitution in non-essential regions of the protein and use them to increase delivery of other therapeutic agents. Guided by her familiarity with rational protein design and the teachings of the '429 Patent and Chao, the artisan would have readily identified single amino acid substitutions in non-essential regions of $PH20_{1\text{-}447}$ that would have been tolerated (*i.e.*, a $PH20_{1\text{-}447}$ with that single substitution would retain its enzymatic activity). D320K $PH20_{1\text{-}447}$ is one such example. Because claims 1-4 encompass use of this obvious variant of $PH20_{1\text{-}447}$, each is unpatentable.

1. Patentee's '429 Patent Motivates a Skilled Artisan to Make and Use Single Amino Acid Substitutions in Non-Essential Regions of $PH20_{1\text{-}447}$

Patentee's '429 Patent, filed in 2003, describes its invention as soluble PH20 hyaluronidase glycoproteins ("sHASEGPs") that are enzymatically active at neutral pH.[241] It exemplifies and claims one such "sHASEGP" that terminates at

[241] EX1005, 6:4-10, 10:30-59.

position 447 (positions 36-482 of SEQ ID NO: 1).[242] It also defines sHASEGPs as including wild-type $PH20_{1-447}$ and "equivalent" proteins "with amino acid substitutions that do not substantially alter activity" of the protein:[243]

> 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 …[244]

The '429 Patent also explains that single amino acid substitutions can include "conservative" substitutions in Table 1, but that "[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions."[245]

The '429 Patent thus teaches making a ***particular*** type of modification (a single amino acid substitution) in ***particular*** locations (non-essential regions of

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

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

[244] EX1005, 16:14-22.

[245] EX1005, 16:24-36.

PH20) in a ***particular*** PH20 sequence ($PH20_{1-447}$) to yield equivalents of $PH20_{1-447}$ (*i.e.*, those that do not substantially alter the activity or function of $PH20_{1-447}$).[246]

The ’429 Patent also motivates skilled artisans to undertake this effort to design and produce such single-amino acid substituted $PH20_{1-447}$ proteins because it assures them their efforts will be successful.[247] As it states, skilled artisans recognized that such “single amino acid substitutions in non-essential regions” of $PH20_{1-447}$ “do not substantially alter biological activity” of $PH20_{1-447}$.[248] As such, a skilled artisan would have expected a $PH20_{1-447}$ mutant with a single amino acid substitution in a non-essential region to have the same utility, therapeutic applications, and other characteristics that the ’429 Patent identifies for wild-type $PH20_{1-447}$ and other sHASEGPs.[249]

2. Patentee’s ’429 Patent Teaches Use of Modified PH20 Polypeptides to Increase Spreading of Other Agents

The ’429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, in pharmaceutical compositions that contain other therapeutic

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[246] EX1003, ¶ 219; EX1004, ¶ 32.

[247] EX1003, ¶ 220.

[248] EX1005, 16:4-21.

[249] EX1003, ¶¶ 211-215, 220, 236.

agents (*e.g.*, antibodies, chemotherapeutics).[250] It describes and illustrates administering such compositions parentally and subcutaneously.[251]

The ’429 Patent also teaches and exemplifies the methods claimed here—administering compositions containing sHASEGPs (modified PH20 polypeptides with at least one substitution) with other therapeutic agents to “increase spreading” of those agents, including antibodies:[252]

> …the sHASEGP polypeptides provided herein can be used as a delivery or “spreading” agent in combination with a second active compound, such as a therapeutically effective agent, including, but not limited to a drug or a prodrug, to facilitate delivery of or to enhance the activity of the second active ingredient.[253]

$PH20_{1\text{-}447}$ was approved by the FDA as Hylenex® in 2005.[254] The ’429 Patent’s teachings combined with the status of $PH20_{1\text{-}447}$ as an approved human

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[250] EX1005, 8:25-9:4, 54:38-55:34, 73:4-20, 75:12-24.

[251] EX1005, 56:36-56, 57:22-36, 63:41-61, 74:10-29.

[252] EX1005, 8:25-37, 54:40-45, 56:36-57:21,73:4-19, 97:36-98:18, 98:49-99:24, 100:7-47; EX1003, ¶¶ 213-214.

[253] EX1005, 56:66-57:5. *Also id.* 97:33-100:47.

[254] EX1049, 1.

therapeutic before 2011 would have induced a skilled artisan to focus on this particular PH20 polypeptide.[255]

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

In 2011, a skilled artisan looking to implement the '429 Patent's suggestion to make a single-amino acid modification in a non-essential region of $PH20_{1-447}$ would have recognized such changes could best be accomplished using rational design—determining (i) which regions are non-essential in PH20, and (ii) which single amino acids to substitute into positions in those non-essential regions.[256]

In 2011, a skilled artisan would have looked for additional published insights into the structure of human hyaluronidase enzymes like PH20, like Chao (EX1006).[257] Chao reported an experimentally determined structure for human HYAL1 and provided new insights into the shared characteristics of human hyaluronidase enzymes.[258]

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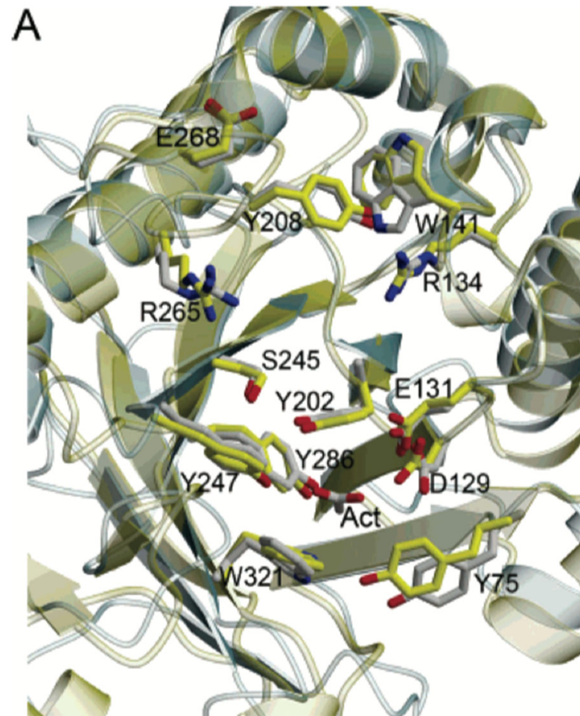
[255] EX1003, ¶ 208.

[256] EX1003, ¶¶ 225-27.

[257] EX1003, ¶¶ 88, 222-224; EX1004, ¶ 88.

[258] EX1003, ¶¶ 81-88; EX1004, ¶ 88; EX1006, 6912-17.

First, Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues in it that interact with HA.[259]



The ’429 Patent also used this comparative technique to identify critical residues in PH20,[260] and reported that hyaluronidase domains share similarity among species, including residues necessary for enzymatic activity.[261]

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

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

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

Second, using an alignment of five human hyaluronidases, Chao identified predicted secondary structures (*e.g.*, β-sheets, α-helices) (Figure 3, below), as well as invariant conserved positions (blue), residues involved in catalysis (red), conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).[262]

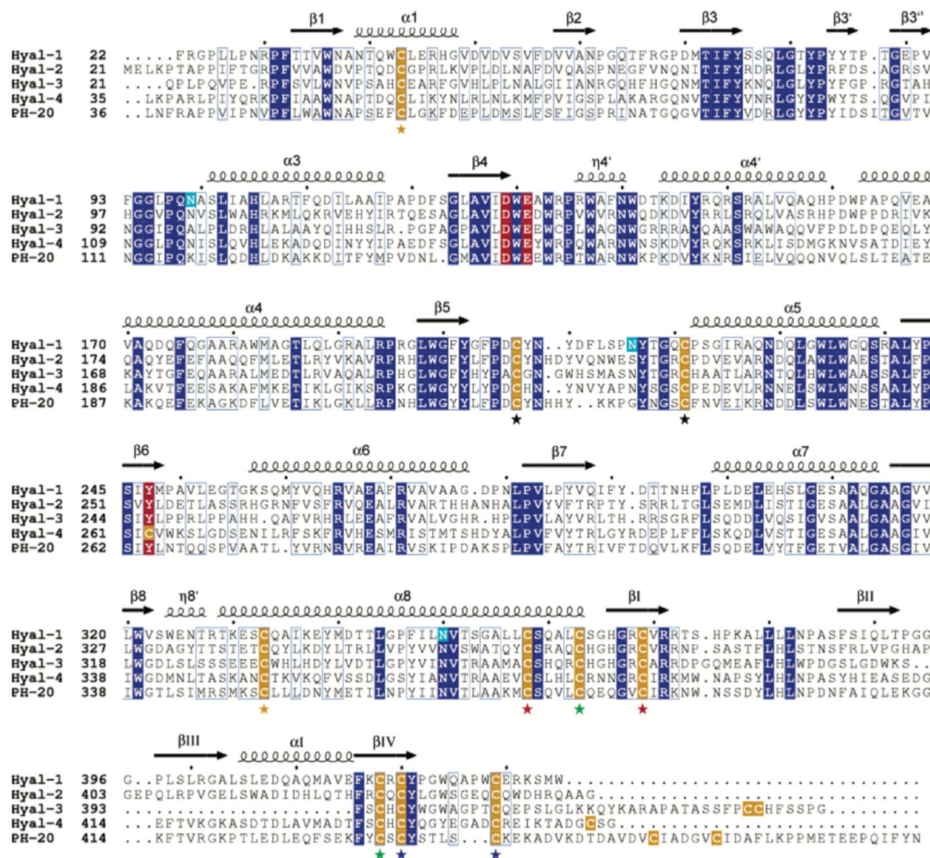

FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative 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.

[262] EX1006, 6916; EX1003, ¶¶ 83, 224; EX1004, ¶ 92.

Third, Chao reported the presence of "a novel, EGF-like domain" in the C-terminal region of human hyaluronidases that was "closely associated" with the catalytic domain (discussed above, § V.A.1.b.ii), and identified a characteristic pattern for the Hyal-EGF domain in PH20 at positions 337-409.[263]

4. A Skilled Artisan Would Have Identified Position 320 as Being in a Non-Essential Region of $PH20_{1-447}$ in 2011

To implement the '429 Patent's suggestion to produce and use modified $PH20_{1-447}$ polypeptides with single amino acid substitutions in non-essential regions that retain hyaluronidase activity, the skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011.[264] The artisan would have done that using conventional sequence alignment tools in conjunction with the information in the '429 Patent and in Chao, as well as information publicly known in 2011.[265]

Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps. He prepared and used a multi-sequence alignment (MSA) of 88 homologous hyaluronidase sequences published by December 29, 2011 to identify essential (Appendix D-3)

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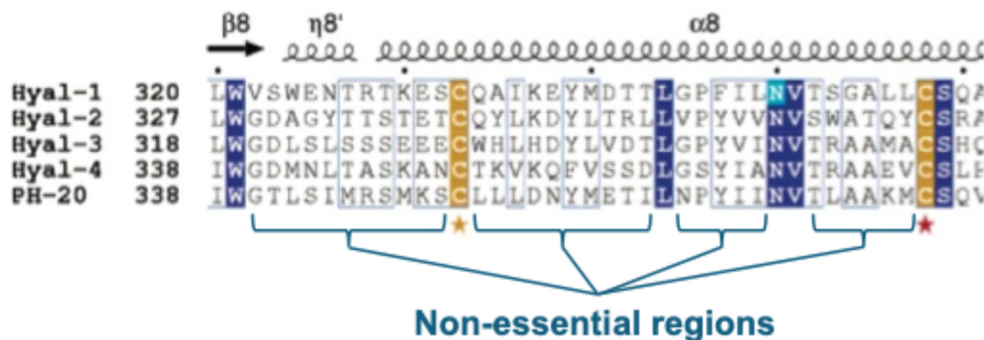
[263] EX1006, 6911; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84, 87.

[264] EX1003, ¶¶ 225-227; EX1004, ¶¶ 22, 25-30, Appendix D-3.

[265] EX1003, ¶¶ 20-21, 226-228; EX1004, ¶¶ 22-24; EX1017, 224-26.

and non-essential (Appendix D-2) residues, as Chao did with the five human hyaluronidases.[266]

MSAs identify non-essential regions in PH20—the sequences between essential residues—and positions at which variations occur at a frequency above ~5% (illustrated below).[267]



Dr. Park's analysis and by Chao's Figure 3 show that position 320 is within a non-essential region of $PH20_{1\text{-}447}$, as it is between the same bounding essential residues (*i.e.*, C316 and L327) (below).[268]

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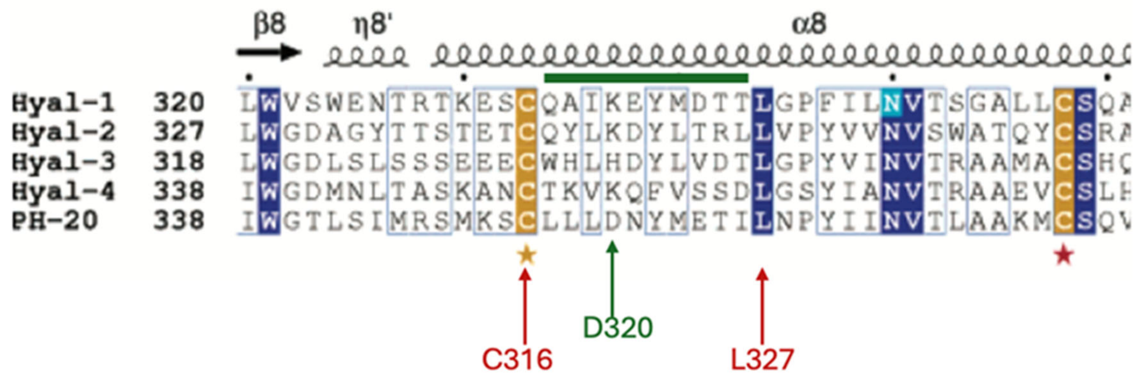
[266] EX1004, ¶¶ 27-32, 143-148, Appendix D; EX1053; EX1054; EX1055; EX1056; EX1057; EX1058; EX1043, 1-2, 4-5; EX1064, 1, 4, 10, 23-28; EX1065, 1, 4.

[267] EX1004, ¶¶ 31-32, Appendix D-2; EX1003, ¶¶ 226-227; EX1006, 6916.

[268] EX1003, ¶ 230; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.



Thus, from ’429 Patent and Chao, and information publicly available in December 2011 using conventional sequence analysis tools, a skilled artisan would have identified position 320 as a position in a non-essential region $PH20_{1\text{-}447}$.[269]

5. Lysine Would Be Seen as an Obvious Single Amino Acid Substitution at Position 320 of $PH20_{1\text{-}447}$

The MSA reveals a second powerful insight: it identifies ***which*** amino acids have been tolerated at specific positions in homologous naturally occurring hyaluronidase enzymes.[270] That is because evolutionary selection principles

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[269] EX1003, ¶ 234; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

[270] EX1003, ¶ 227; EX1004, ¶¶ 21-22.

eliminate from the genome of organisms sequence variations that do not yield stable and active forms of a protein.[271]

Using the MSA, a skilled artisan can readily compile a list of amino acids tolerated at positions within non-essential regions of PH20.[272] Dr. Park did this: using his MSA of 88 hyaluronidase proteins known by December 2011, he identified which amino acids occur at positions corresponding to position 320 in PH20 (and their frequency) in homologous hyaluronidases (below).[273]

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

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
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% of occurrence of AA in set of proteins

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[271] EX1003, ¶ 227; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 (evolutionarily conserved sequences useful for determining protein structure and function); EX1014, 351.

[272] EX1003, ¶¶ 227-228; EX1004, ¶¶ 21-22.

[273] EX1004, ¶¶ 30-32, 41-43, 106, 116, Appendix D-1; EX1003, ¶¶ 228, 230-231.

A skilled artisan would have considered position 320 to be a position within a non-essential region of $PH20_{1-447}$ at which a single amino acid substitution could be made pursuant to the guidance in the '429 Patent.[274]

The skilled artisan also would have selected lysine (K) for such a single substitution at position 320 in $PH20_{1-447}$.[275]

First, lysine is the most prevalent amino acid at positions corresponding to 320 in PH20: it occurs in nearly 60% of the 88 homologous hyaluronidase enzymes known by 2011 (51 different naturally occurring hyaluronidase enzymes) and in 3 of the 5 human hyaluronidases (shown in Chao Figure 3, above).[276] Lysine's high frequency at positions corresponding to 320 in naturally occurring hyaluronidases indicates it is likely to be tolerated in PH20, and makes it an obvious amino acid to substitute into position 320 of PH20.[277]

Second, lysine was known to be favored in sequences that form α-helix secondary structures due to its high helix propensity.[278] Chao identified the "α8"

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[274] EX1003, ¶¶ 230, 234.

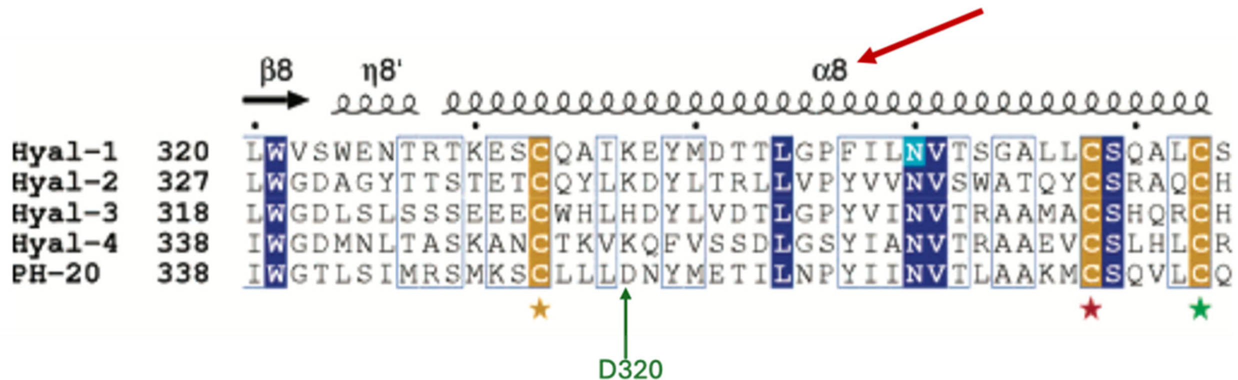
[275] EX1003, ¶¶ 234-235; EX1004, ¶¶ 41-42, 106, 116.

[276] EX1004, ¶¶ 43, 106, 116; EX1003, ¶¶ 231, 234.

[277] EX1003, ¶ 235; EX1004, ¶ 116.

[278] EX1050, 422-24, Table 2; EX1003, ¶ 233; EX1004, ¶¶ 69-70.

helix sequence as one such α-helix forming sequence in PH20, and position 320 is within the α8 helix sequence in PH20 (below).[279]



Consequently, a skilled artisan would have viewed lysine as a logical (and thus obvious) single amino acid substitution for aspartic acid at position 320 in PH20$_{1\text{-}447}$ pursuant to the guidance in the ’429 Patent.[280]

6. D320K PH20$_{1\text{-}447}$ Would Be Expected to Be Enzymatically Active and Useful in Methods for Increasing Delivery of Other Therapeutic Agents

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

Replacing the aspartic acid at position 320 with lysine yields a PH20$_{1\text{-}447}$ with a single amino acid substitution in a non-essential region of the polypeptide.[281] In its ’429 Patent, Patentee stated:

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279 EX1006, 6916, Figure 3; EX1003, ¶ 205; EX1004, ¶¶ 32, 108.

280 EX1003, ¶ 233-235; EX1004, ¶¶ 32, 108.

281 *See* § VI.B.3; EX1003, ¶ 230; EX1004, ¶ 32.

> 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.[282]

Patentee also secured claims in the '429 Patent to modified $PH20_{1-447}$ proteins with at least one substitution (*e.g.*, claim 1), without examples of PH20 proteins with substitutions. Patentee, thus made and relied on its statements that a skilled artisan would have expected ***any*** single amino acid substitution in ***any*** non-essential position in $PH20_{1-447}$ to not substantially affect the activity of the enzyme. Patentee should not be permitted to now contend a skilled artisan would not have reasonably expected that the 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 the D320K Substitution to be Tolerated in $PH20_{1-447}$

Independently, a skilled artisan would have reasonably expected the D320K substitution to not substantially alter the hyaluronidase activity of $PH20_{1-447}$. Both experts noted that many naturally occurring, enzymatically active homologous hyaluronidase proteins contain lysine at positions corresponding to position 320 in

[282] EX1005, 16:17-20.

PH20 (including lysine in three human hyaluronidases (Chao)), which suggests lysine would be tolerated at that position in PH20.[283]

Dr. Park's sequence alignment shows that many (8) different amino acids occur in homologous proteins at positions corresponding to position 320 in PH20.[284] The diversity of characteristics of those amino acids at that position (*e.g.*, large or small side chains, high or low helix propensities, net positive, negative, or zero charges, etc.) suggests that many different kinds of amino acids can be tolerated at position 320 in PH20.[285]

In view of the above, as skilled artisan would have reasonably expected the D320K substitution to be tolerated as a single substitution in $PH20_{1\text{-}447}$.[286]

(c) A PH20 Structural Model Confirms that $PH20_{1\text{-}447}$ Would Tolerate Lysine at Position 320

Dr. Park assessed whether single amino acid substitutions in $PH20_{1\text{-}447}$ would be tolerated, including D320K, using a PH20 protein structural model generated by SWISS-MODEL using Chao's HYAL1 structure as the template, as

283 EX1003, ¶¶ 231-232, 231; EX1004, ¶¶ 106, 116.

284 EX1004, ¶ 106.

285 EX1003, ¶ 232; EX1004, ¶ 106.

286 EX1003, ¶¶ 234-235; EX1004, ¶¶ 116, 70.

would have been done in 2011 by a skilled artisan.[287] He explains that his PH20 model was reliable in the region of position 320 of PH20 based on QMEAN values,[288] and would be very similar to a PH20 model generated by SWISS-MODEL in 2011 (*e.g.*, it used 165 conserved positions in the backbone of the two proteins).[289] He also devised a consistent, objective methodology for assessing substitutions using the $PH20_{1\text{-}447}$ model.[290] Factors he considered included, *inter alia*, the number of neighboring residues at position 320 (*i.e.*, those within 5 Å), the various possible interactions between neighbors (*e.g.*, hydrophobic, charged, van der Walls, steric, etc.), and solvent accessibility.[291] Where interactions were

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[287] EX1004, ¶¶ 39-40, 149-150; EX1003, ¶¶ 237-241; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

[288] EX1004, ¶¶ 151-153 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

[289] EX1004, ¶¶ 154-155, 159; EX1038, 3382-4; EX1017, 229-230; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

[290] EX1004, ¶¶ 102-103; *see generally id.* at § IV.C (description of Dr. Park's methodology); EX1003, ¶¶ 228-229.

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

observed, Dr. Park assessed the impact of them (*e.g.*, hydrophobic-hydrophilic, effects on secondary structures, size related issues such as steric clashes or creation/filling of "holes" in the structure).[292]

Dr. Park visually assessed the environment of position 320 by comparing the wild-type and D320K forms of PH20 using functionality within the PyMol viewer (PyMol) and with a modeled sequence generated in SWISS-MODEL using the D320K $PH20_{1\text{-}447}$ sequence.[293] These technologies were available in 2011.[294] He also used this methodology to assess substitutions representing diverse interactions, and confirmed it provided a consistent, objective and unbiased evaluation of substitutions.[295]

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed (below).[296]

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292 EX1004, ¶¶ 62-63, 85.

293 EX1004, ¶¶ 61, 107, 115, 118, 122, 138, 140, 164-166; EX1003, ¶¶ 238, 240.

294 EX1004, ¶¶ 149, 154-155, 163, 165-167; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4; EX1003, ¶¶ 20-22.

295 EX1004, ¶¶ 102-103; EX1003, ¶¶ 228-229.

296 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 it would be expected to confer improved stability.[297] 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.[298] He also observed a negative surface charge at position 320 that creates electrostatic repulsion with the charged carboxyl group of D320.[299] When the lysine was substituted in position 320: (i) it introduces a stabilizing salt-bridge with E324 (left image), and a hydrogen bond to the main carbonyl group of P32, (ii) the long aliphatic chain of lysine participates in hydrophobic interactions with P32 and L317 residues (right image), and (iii) its positive charge offsets nearby negative charges.[300] Overall, Dr. Park found that the D320K substitution

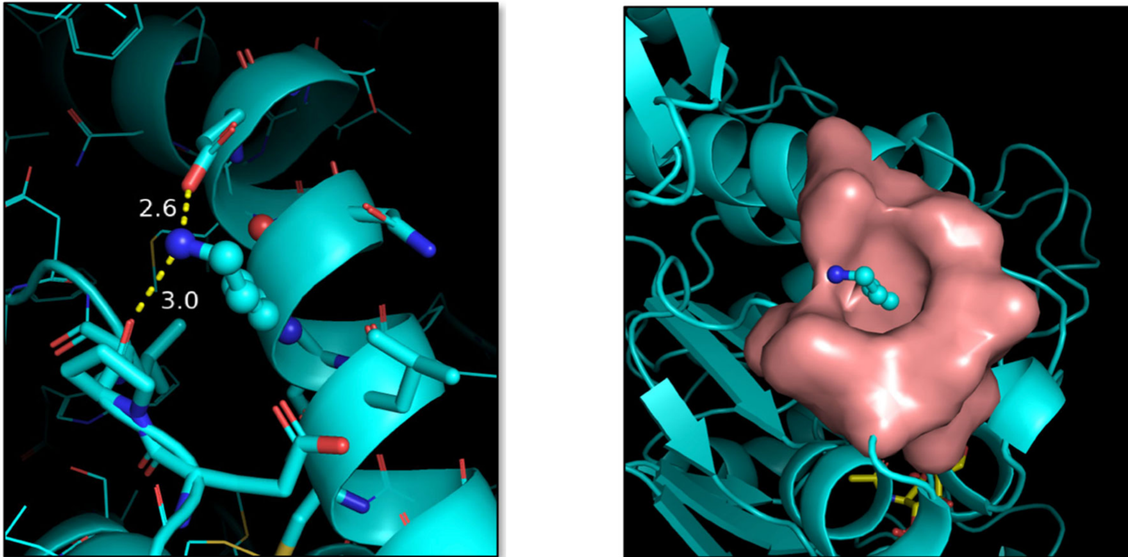
[297] EX1004, ¶ 123, Appendix C.

[298] EX1004, ¶ 110.

[299] EX1004, ¶¶ 112-114.

[300] EX1004, ¶¶ 119-121, 123.

would be stabilizing, meaning that D320K $PH20_{1-447}$ would be expected to retain the hyaluronidase activity of the unmodified $PH20_{1-447}$.[301]



Dr. Park's visualization-based assessment was a prevalent technique used in 2011.[302] Similarly, his technique of assessing interactions between neighbors and

[301] EX1004, ¶ 123.

[302] EX1017, 228 ("… a structural biologist's intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this."); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 239-241.

assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications.[303]

Dr. Hecht reviewed Dr. Park's analysis and conclusions concerning the D320K single substitution and agreed with them.[304] He concluded that lysine would likely have been tolerated at position 320 as a single substitution in $PH20_{1-447}$ because lysine would have a stabilizing effect due to (i) its compatibility with the solvent-exposed pocket at position 320, and (ii) formation of a salt bridge with E324.[305]

The common disclosure defines an "active mutant" as a modified PH20 polypeptide with at least ~40% of the activity of unmodified $PH20_{1-447}$.[306] Drs. Hecht and Park each independently concluded that the D320K substitution would have been tolerated by $PH20_{1-447}$.[307] A skilled artisan thus would have reasonably

303 EX1004, ¶¶ 48-52; EX1031, 459, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 241.

304 EX1003, ¶¶ 240, 243.

305 EX1003, ¶ 244.

306 EX1001, 75:47-52; *also id.* at 79:29-33.

307 EX1003, ¶¶ 243-244, 246; EX1004, ¶¶ 17, 123, 141.

expected that the D320K $PH20_{1-447}$ polypeptide would exhibit at least 40% of the activity of unmodified $PH20_{1-447}$.[308]

Further, a $PH20_{1-447}$ polypeptide with only a D320K substitution would be expected to cause spreading comparably to unmodified $PH20_{1-447}$ as claim 1 specifies.[309] Notably, the claims impose no minimum degree of "increased delivery."[310] And the amino acids that are spatially close to position 320 are not within the Hyal-EGF domain.[311]

A skilled artisan would have found the D320K $PH20_{1-447}$ mutant polypeptide to have been obvious before 2011. The '429 Patent teaches that single substitution mutants of the native $PH20_{1-447}$ polypeptide would be expected to retain the activity of unmodified PH201-447. It also teaches that administration of "sHASGEP" mutants (including PH20 mutants) in a pharmaceutical composition

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[308] EX1003, ¶ 246.

[309] EX1003, ¶¶ 215, 236.

[310] EX1003, ¶¶ 215, 220, 235-236.

[311] EX1004, ¶¶ 97-99, 107, Appendix E-3; EX1003, ¶ 95 (PH20 Hyal-EGF runs from 337-409).

containing another therapeutically active agent to increase delivery of that other agent.[312]

Because the D320K $PH20_{1\text{-}447}$ polypeptide would be expected to have a comparable structure and activity as unmodified $PH20_{1\text{-}447}$, a skilled artisan would have believed each would be equivalently useful as the unmodified $PH20_{1\text{-}447}$ in pharmaceutical compositions and methods of administration described in the '429 Patent.[313] Indeed, in the '429 Patent, Patentee secured claims encompassing pharmaceutical compositions containing PH20 polypeptides with 1+ substitutions and chemotherapeutic agents despite the absence of any exemplification.[314] The claims also impose no restrictions on the makeup of the pharmaceutical composition.

Claims 1-4 therefore encompass a method of using D320K $PH20_{1\text{-}447}$ that is suggested by and thus obvious from the '429 Patent in conjunction with Chao and information known in 2011. Each of claims 1 to 4 is unpatentable.

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312 *See* § VI.B.2.

313 EX1003, ¶¶ 212-215, 236.

314 EX1005, claims 29, 30, 50.

C. Dependent Claims 7-11 Are Obvious

Each of claims 7-11 defines subject matter that would have been obvious to a skilled artisan. Claims 7-9 specify a method of using a pharmaceutical composition comprising any modified PH20 polypeptide in the genus of claim 1 and provides categories for the "therapeutic agent" that include antibodies (i), and small molecule drugs (7, 9). Claims 10 and 11 specify that the pharmaceutical composition comprising any modified PH20 polypeptide in the genus of claim 1 is administered parenterally (10) or subcutaneously (11).

The '429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*, $PH20_{1\text{-}447}$), alone or with other therapeutic agents including antibodies and other small molecule drugs used in treating cancer and hyaluronan-associated disease.[315] It similarly describes and claims methods of administering them subcutaneously using formulations that combine an enzymatically active "sHASEPGs" (*e.g.*, $PH20_{1\text{-}447}$ with one substitution) with another therapeutic agent, which together

[315] EX1005, 8:60-9:4, 54:40-55:35, 56:28-57:21, 55:61-56:9, 56:66-57:21, 63:41-44, 73:4-74:29, claims 14, 29, 33; EX1003, ¶¶ 212-214.

enable increasing delivery of the therapeutic agent after injection.[316] It likewise explains that the therapeutic agent and the PH20 can be subcutaneously administered together or sequentially.[317]

A skilled artisan thus would have found the methods of claims 7-11 to have been obvious before 2011.[318]

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

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

Patentee is likely to dispute that the D320K $PH20_{1\text{-}447}$ substitution is obvious. For example, Patentee may contend that the variant has unexpectedly high hyaluronidase activity as a single substitution mutant. Demonstrating that result for one mutant out of the ~10^{49} and 10^{66} modified PH20 polypeptides

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316 EX1005, 8:25-38, 54:40-65, 56:28-56, 57:22-36, 58:59-59:12, 63:40-64:4, 73:4-20, 76:18-77:37, claim 27; EX1003, ¶ 215.

317 EX1005, 8:25-37, 8:60-9:4, 75:25-50, 76:19-77:33, 99:27-100:47; EX1003, ¶¶ 213-214.

318 EX1003, ¶¶ 212-215, 220, 236.

encompassed by the claims utterly fails to establish a nexus between that evidence and the claims. As explained in § V.A.1, the single-substitution D320K $PH20_{1-447}$ mutant is not representative of the numerous, structurally different proteins encompassed by the claims, particularly those expected to be inactive. No evidence or explanation is provided in the common disclosure that resolves this confusion.

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

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

No litigation involving the '185 Patent is pending, making discretionary denial unwarranted under the factors in *Apple Inc. v. Fintiv, Inc.,* IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020).

The examination record also does not warrant the Board exercising its discretion to not institute. As explained in § IV.C, no obviousness rejections were raised during prosecution.[319] The present obviousness grounds also rely on Chao (EX1006), which was not cited or considered during examination, and are

[319] EX1002, 650-71, 682-701, 731-40.

supported by evidence not available to the Examiner (*e.g.*, expert testimony of Drs. Hecht and Park).

Also, while certain indefiniteness and enablement rejections were imposed and overcome by claim amendments,[320] the Examiner erred by not rejecting the claims for lack of written description and non-enablement for the claimed method of administering an immense genus of modified PH20 polypeptides (or any substantially similar arguments) during prosecution. *See* §§ V.A and V.B.

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

VIII. CONCLUSION

For the foregoing reasons, the challenged claims are unpatentable.

Dated: March 28, 2025

Respectfully Submitted,

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[320] EX1002, 704-06, 753-55.

EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,104,185
1002	File History of U.S. Patent No. 12,104,185
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," Biochemistry, 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," Chem. Rev. 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," Proteins: Structure, Function and Bioinformatics, 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," J. Biol. Chem., 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," Eur. J. Biochem., 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," Nature Protocols, 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," Expert Opinion on Drug Delivery, 4(4):427-440 (2007)
1014	Branden & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '185 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]
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1045	Redline Comparison of the ’731 and ’185 Specifications
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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
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No.	Exhibit Description
1080	Bookbinder et al., "A Recombinant Human Enzyme for Enhanced Interstitial Transport of Therapeutics," J. Controlled Release, 114:230-241 (2006)

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 18,536 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: March 28, 2025

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Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 28th day of March, 2025, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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