

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00009
U.S. Patent No. 12,123,035

PETITION FOR POST GRANT REVIEW

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35 U.S.C. § 1201, 2, 5

35 U.S.C. § 1215

I. Introduction

Petitioner Merck Sharp & Dohme LLC (“Merck”) requests post grant review of claims 1-34 of U.S. Patent No. 12,123,035 (“’035 Patent”).

The ’035 Patent claims are unpatentable for three independent reasons.

The first two are linked to the extreme breadth of the claims, which, due to their unconstrained language, encompass between 10^{59} and 10^{112} different enzymatically active human hyaluronidase (“PH20”) polypeptides. Each defines a genus of PH20 polypeptides that (i) *must have one* amino acid substitution at position 312, and (ii) *may have* between 20 and 41 additional substitutions at *any* of 430+ positions, and to *any* of 19 other amino acids. The scale of these genera is unfathomable. A collection of one molecule of each polypeptide in the smallest genus exceeds the weight of the Earth, and practicing the full scope of the narrowest claimed genus would require many lifetimes of “making and testing” using the patent’s methodology.

These immensely broad claims, measured against the common disclosure of the ’035 Patent and its ultimate parent ’731 Application,¹ utterly fail the written description and enablement requirements of § 112(a). That renders every claim of the ’035 Patent unpatentable. It also precludes the claims from a valid § 120

¹ 13/694,731 (’731 Application) (EX1026).

benefit claim to the '731 Application, the only non-provisional application filed before March 16, 2013, thus making the '035 Patent PGR eligible.

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by the enzymatically active, multiply-modified PH20 polypeptides within each claimed genus. The disclosed examples also are not representative of those structurally diverse genera: each has only *one* amino acid substitution in *one* PH20 sequence (1-447), while the claims encompass PH20 proteins with myriad *undescribed* combinations of 5, 10, 15, or 20+ substitutions anywhere within PH20 sequences of varying length. The claims even capture mutated PH20 polypeptides the disclosure says to avoid (*e.g.*, PH20₁₋₄₄₇ mutants rendered inactive by a single substitution, inactive truncated forms). The disclosure is nothing more than a research plan, lacking any blaze marks, and does not describe the claimed genera.

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

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

Finally, each of claims 1-2 and 5-34 are unpatentable each captures one or both of two obvious PH20₁₋₄₄₇ mutants that change a *single* amino acid—the serine at position 312—to either threonine (“S312T”) or asparagine (“S312N”). But Patentee’s ’429 Patent (EX1005) directs artisans to make such single amino acid substitutions in non-essential regions of PH20₁₋₄₄₇ (and expressly claimed them). Skilled artisans implementing that guidance in 2011 would have found Chao (EX1006)—a 2007 paper ignored in the common disclosure and never cited to the Office. That artisan, from their knowledge and the collective teachings of Chao and the ’429 Patent, would have (i) readily identified position 312 as being in a non-essential region of PH20, and (ii) found it obvious to change serine to threonine or asparagine at position 312. They also would have reasonably expected both mutants to retain enzymatic activity because that is what Patentee said in its ’429 Patent (“Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not

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

substantially alter biological activity”).³ Because the claims capture these obvious species, they are unpatentable, along with the dependent claims.

The '035 Patent claims are unpatentable. The Board should institute trial.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the '035 Patent's issuance. Petitioner certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '035 Patent.

The '035 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

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

³ EX1005, 16:17-22.

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

Only one of the applications to which the '035 Patent claims benefit under 35 U.S.C. § 120 and/or § 121—U.S. Application No. 13/694,731 (the '731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011) and WO 01/3087 (“WO087”). The '731 Application, however, alters several passages of the provisional disclosures, adds new examples and tested mutants and makes other changes.⁴

The '731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '035 Patent (§§ V.A, V.B). The same is true for the '035 Patent, whose

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

disclosure relative to the claims is generally identical to the '731 Application.⁵

The '035 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the '731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

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

2. Related Proceedings

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

3. Counsel and Service Information

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⁵ The “common disclosure” refers to the shared disclosure of the '035 Patent and the '731 Application (EX1026). Citations are to the '035 Patent; EX1015 correlates citations to the '731 Application. The '035 Patent alters the classification of one mutant (“I083K” PH20₁₋₄₄₇) relative to the '731 Application. EX1045, 215; EX1068, ¶ 6.

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

III. Grounds

The grounds advanced in this Petition are:

- (a) Claims 1-34 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.
- (b) Claims 1-34 are unpatentable under 35 U.S.C. § 112 as not being enabled.
- (c) Claims 1-2 and 5-34 are unpatentable as obvious under 35 U.S.C. § 103 based on the '429 Patent (EX1005), Chao (EX1006) and knowledge held by a person of ordinary skill in the art.

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

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

⁶ EX1003, ¶ 15.

a sequence of 1-n residues in PH20 (*e.g.*, PH20₁₋₄₄₇ is SEQ ID NO: 3), and “AxxxB” is used to identify the position of a substitution (*e.g.*, “S312T”).

IV. Background on the '035 Patent

A. Field of the Patent

The '035 Patent concerns the human PH20 hyaluronidase enzyme, and structurally altered forms of that protein that retain enzymatic activity.⁷

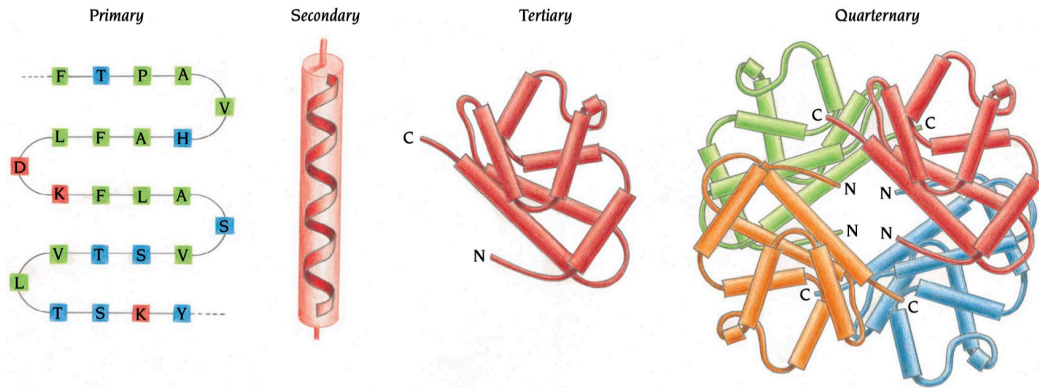
1. Protein Structures

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

⁷ EX1001, 4:16-20.

⁸ EX1003, ¶ 36.

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



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

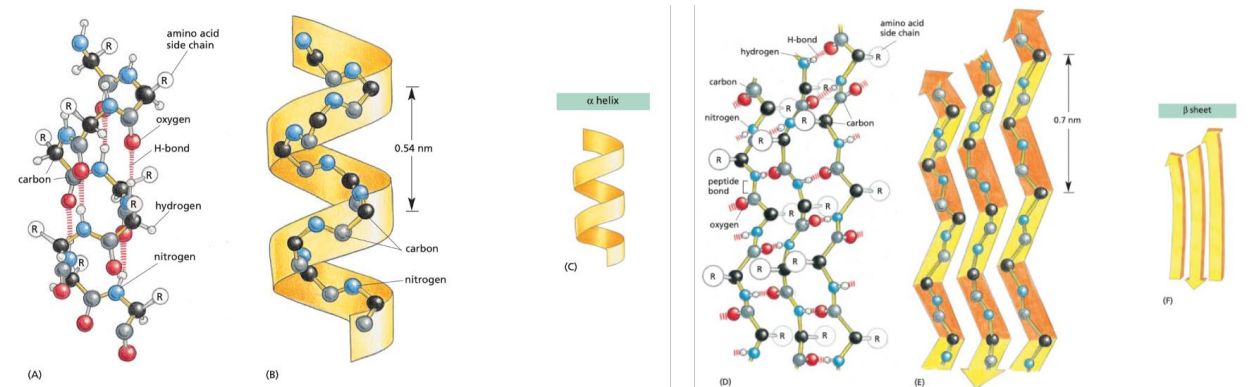


Figure 3-7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. **<GTAG> <TGCT>** (A, B, and C) The α helix. The N-H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the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

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

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

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

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

¹¹ EX1003, ¶¶ 44-46; EX1014, 21-22.

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

¹³ EX1003, ¶ 158.

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

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

2. Hyaluronidase Enzymes

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

¹⁵ EX1003, ¶¶ 57-59.

¹⁶ EX1003, ¶¶ 50, 158, 190, 228; EX1004, ¶¶ 142-144.

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

¹⁸ EX1003, ¶ 77; EX1008, 819.

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

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

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

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

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

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

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

²⁴ EX1006, 6914-18.

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

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

3. Protein Engineering

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

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

²⁷ EX1003, ¶ 47.

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

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

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

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

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

³¹ EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶ 37, *also id.* 33-36; EX1003, ¶¶ 223, 225.

³² EX1003, ¶¶ 50, 158; EX1004, ¶¶ 142-144.

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

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

whether it exists and its sequence are unknown.³⁵ Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale of experimentation this approach requires.³⁶ The '035 Patent embodies this approach.³⁷

B. Person of Ordinary Skill in the Art

While the '035 Patent claims priority to provisional applications dating to December 30, 2011 and benefit to the '731 Application (filed December 28, 2012), they are not supported as § 112(a) requires by those earlier-filed applications. *See* §§ II.A, V.A, V.B. Regardless, the prior art of the grounds was published before December 2011, and the obviousness grounds use that date to assess the knowledge and perspectives of the skilled artisan.

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

³⁵ EX1003, ¶ 184.

³⁶ EX1003, ¶¶ 52-53.

³⁷ EX1003, ¶¶ 138, 173, 183, 186.

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

C. Prosecution History

One Office action issued during examination of the '035 Patent. In it, the Examiner rejected certain dependent claims directed to post-translational modifications and conjugation for indefiniteness.³⁹ Patentee overcame each rejection by amending the claims as the Examiner suggested.⁴⁰

D. The Challenged Claims

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

³⁸ EX1003, ¶ 13.

³⁹ EX1002, 465-67.

⁴⁰ EX1002, 538-41.

mutant PH20 polypeptides that is neither adequately described in nor enabled by the common disclosure of the '731 Application and the '035 Patent.

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

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

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

- **must** contain **one** amino acid replacement at position 312 (*i.e.*, from S to any of G, K, L, N, and T); and
- **may** contain **additional** modifications, provided each polypeptide retains **at least 91% sequence identity** to one of the 37 unmodified sequences (SEQ ID NOs: 3, 7 or 32-66), ranging in length from 430 (SEQ ID NO: 32) to 474 residues (SEQ ID NO: 7).

Certain dependent claims restrict these parameters: (i) claims 2 and 24-25 limit (*inter alia*) sequence identity to 95%, (ii) claims 8-14 narrow the comparator

⁴¹ EX1001, 48:38-43. Dependent claims 23-34 reference genera of PH20 polypeptides defined by claims 1 or 6.

unmodified sequences (*e.g.*, removing SEQ ID NO: 7 or requiring only SEQ ID NOs: 35 or 32), (iii) claims 6 and 7 require the position 312 substitutions to be T or N, respectively (S312T or S312N), and (iv) claims 3-5 and 15 add functional requirements (*e.g.*, increased “stability” or activity, solubility).

Claims 16-23 and 26-34 depend from claim 1 but do not alter the parameters governing the number of PH20 polypeptides in each genus. Claims 16-22 specify additional features of the PH20 polypeptides (*e.g.*, glycosylation) while claims 23 and 26-34 define pharmaceutical compositions and methods of use.

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

It further explains that “differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence” and that

⁴² EX1001, 60:14-16.

⁴³ EX1001, 60:49-58.

“[d]ifferences are defined as [] amino acid substitutions, insertions or deletions.”⁴⁴

Also, “amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids” (e.g., 10-18 of the 19 alternative amino acids).⁴⁵ Likewise, except for position 312, no language in the claims restricts *where* substitutions can occur within the modified PH20 sequence, or *which* of 19 other amino acids can be substituted at those positions.

The claim parameters cause them to encompass an immense number of distinct polypeptides, each with a unique amino acid sequence.⁴⁶ In particular, the sequence identity limitations capture modified PH20 polypeptides with up to 21-42 total changes but require only one: a substitution at position 312, with either 5 alternatives (claims 1-5, 8, 10-11, 15-23, 26-34) or one (“T” (claims 6, 9, 12-14, 24-25), or “N” (claim 7)). Dr. Park’s calculations show each claim’s parameters capture an immense number of distinct polypeptides:⁴⁷

⁴⁴ EX1001, 60:59-67; *see also id.* at 5:1-2; 47:43-47, 56-58.

⁴⁵ EX1001, 127:29-36; *see also id.* at 132:49-51.

⁴⁶ EX1003, ¶¶ 120, 122.

⁴⁷ EX1004, ¶¶ 150-154, Appendix F.

<i>Claims</i>	<i>Max Length</i>	<i>Max Changes</i>	<i>Pos. 312 Choices</i>	<i># of Distinct Polypeptides</i>
1, 3-5, 15-23, 26-34	474	42	5	3.16×10^{112}
2	474	23	5	2.59×10^{66}
6-7	474	42	1	6.32×10^{111}
8, 21	465	41	5	7.06×10^{109}
9, 14	465	41	1	1.41×10^{109}
10	433	38	5	5.01×10^{101}
11	430	38	5	3.83×10^{101}
12	433	38	1	1.00×10^{101}
13	430	38	1	7.66×10^{100}
24	430	21	1	4.40×10^{59}
25	433	21	1	5.08×10^{59}

2. The Claims Encompass Two Particular PH20₁₋₄₄₇ Mutants: S312T and S312N PH20₁₋₄₄₇

The claims' parameters also cause them to capture one or both of two modified PH20₁₋₄₄₇ polypeptides that change the serine at position 312 to either threonine (T) ("S312T") or asparagine (N)("S312N"). These single-replacement PH20₁₋₄₄₇ mutants are: (i) 99.7% identical to SEQ ID NO: 3 (1 change / 447 residues), (ii) 96.5% identical to SEQ ID NO: 35 (15 changes / 433 residues), and

(iii) 95.9% identical to SEQ ID NO: 32 (18 changes / 430 residues).⁴⁸ Both satisfy claims 1-5, 8-13, and 15-34, the S312T mutant satisfies claims 6 and 14, and the S312N mutant satisfies claim 7.

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

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

According to the specification:

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

⁴⁸ EX1003, ¶ 136.

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

polypeptide not containing the amino acid modification (e.g., amino acid replacement).”⁵⁰

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

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

The common disclosure reports no examples of an “active mutant” modified PH20 with two or more replacements.⁵³ Notably, it reports no examples of an

⁵⁰ EX1001, 75:47-52; *see also id.* at 79:29-33 (“active mutants” “can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide ...”); *id.* at 79:26-29.

⁵¹ EX1001, 115:58-67. *See also id.* at 259:11-15 (mutants with <20% activity “were rescreened to confirm that the dead mutants are inactive” in Table 10).

⁵² EX1001, 80:60-82:10, 224:15-17, 116:58-118:7, 260:17-20 (“reconfirmed inactive mutants are set forth in Table 10.”); EX1003 ¶¶ 98, 104-105, 107, 126-28.

⁵³ *E.g.*, EX1003, ¶¶ 141, 172.

enzymatically active PH20₁₋₄₄₇ that incorporates: (i) a mutation that preserved activity in Tables 3 and 9 (“active mutants”) plus (ii) a second mutation that eliminated activity in Tables 5 and 10 (“inactive mutants”).

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

- “Active mutants” are portrayed as being therapeutically useful *because they possess hyaluronidase activity*. For example, the specification explains that *due to* having hyaluronidase activity, “the modified PH20 polypeptides can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents.”⁵⁴
- “Inactive mutants” are portrayed as being therapeutically useful *because they lack hyaluronidase activity*. Their only identified utility

⁵⁴ EX1001, 171:27-33; *see also id.* at 4:33-36, 73:33-47, 171:27-184:54; EX1003, ¶ 108.

is “as antigens in contraception vaccines,” which is implausible (*see* § V.C) but ostensibly requires them to lack activity.⁵⁵

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

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

First, every claim requires modified PH20 polypeptides with one of five replacements at position 312 that yielded an “active mutant” as a single-replacement PH20₁₋₄₄₇ polypeptide (*i.e.*, S312G, S312K, S312L, S312N, or S312T). All 5 mutants are identified as “Active Mutants” in Table 3, and have at least ~40% activity per Table 9.⁵⁷

⁵⁵ EX1001, 72:60-62; *see also id.* at 184:55-56, 75:56-58, 184:54-185:6 (for “contraception” “the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.”).

⁵⁶ EX1001, 147:50-63; EX1003, ¶ 113; EX1060, 1711.

⁵⁷ EX1001, 85 (Table 3), 248 (Table 9), 97:49-61; EX1003, ¶¶ 127-128.

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

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

Patentee may contend the claims should be read as encompassing both alternative embodiments (*i.e.*, “active” and “inactive” mutants). Reading the

⁵⁸ Claim 3 requires mutants with increased resistance to or stability in denaturing conditions. The specification portrays increased stability as an additional attribute of an “active mutant.” EX1001, 52:41-47, 124:28-47, 170:15-18, 310:36-311:59.

⁵⁹ EX1001, 48:38-53; *see also id.* at 47:61-65, 76:5-8, 76:67-77:7, 81:1-82:10.

⁶⁰ EX1001, 132:14-26; *see also id.* at 42:48-55.

claims in that manner is incorrect. It also exacerbates the § 112 problems, as every claim still necessarily includes (and thus must describe and enable) the full sub-genus of “active mutants” in claim 1 defined by claim 4.⁶¹

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

Claims 1-34 are unpatentable because each lacks written description in and was not enabled by the common disclosure of the '035 Patent and the '731 Application in 2011.

As explained in § IV.D.1, the claim language defines enormous genera: between 10^{59} and 10^{112} distinct polypeptides. To illustrate the real-world absurdity of those claims, consider what practicing the claims' full scope requires.

Excluding single-replacement PH20₁₋₄₄₇ mutants, and only considering multiply-substituted mutants of PH20₁₋₄₄₇, a skilled artisan would need to make-and-test at least $\sim 10^{59}$ mutants. Producing only one molecule of each mutant—each must be made and tested to see if it is active or inactive (and also exhibits increased stability per claim 3)—would require consuming an aggregate mass ($\sim 3.93 \times 10^{37}$

⁶¹ EX1003, ¶ 135.

kg) that exceeds the mass of the Earth ($\sim 6 \times 10^{24}$ kg).⁶² Testing every polypeptide within the claims' scope in search of "active mutants" is impossible—literally.

In support of that broad scope, the '035 Patent and the '731 Application provide only a meager disclosure: *singly*-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones. It nowhere demonstrates possession of the vast remainder of multiply-modified polypeptides in the claims' scope, nor does it enable a skilled artisan to practice that full-range of mutant polypeptides without undue experimentation.

A. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.⁶³ "To fulfill the written description requirement, a patent owner 'must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by

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

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

disclosure in the specification of the patent.”⁶⁴ If the claims define a genus, the written description must “show that one has truly invented a genus ...,” “[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus.”⁶⁵

“[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.”⁶⁶ “One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent ... [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus.”⁶⁷

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

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

⁶⁶ *Idenix*, 941 F.3d at 1164.

⁶⁷ *AbbVie*, 759 F.3d at 1299-1300.

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

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

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

It also criticized patentee’s attempt to use a prophetic description for the remaining claim scope, portraying it as “only a research plan, leaving it to others to explore

⁶⁸ *Idenix*, 941 F.3d at 1164.

⁶⁹ *Ariad*, 598 F.3d at 1350-54.

⁷⁰ *Ariad*, 598 F.3d at 1349.

⁷¹ *AbbVie*, 59 F.3d at 1300-1301.

the unknown contours of the claimed genus” and a “trial and error approach.”⁷²

Both criticisms apply to the present disclosure, which exemplifies only singly-substituted PH20 mutants and provides only a prophetic research plan, yet claims all multiply-modified PH20 mutants with many additional substitutions.

Second, *Idenix* addressed claims to methods of treatment with a broad genera of compounds defined by formulas analogous to the challenged claims here: “eighteen position-by-position formulas describing ‘principal embodiments’ of compounds that may treat HCV,” each with “more than a dozen options” at each position (totaling “more than 7,000 unique configurations”).⁷³ The court criticized the specification’s failure to indicate which of the thousands of compounds would be effective, and found that “providing lists or examples of supposedly effective nucleosides,” without “explain[ing] what makes them effective, or why” deprives a skilled artisan “of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result” because they “fail to provide sufficient blaze marks to direct a POSA to the specific subset of 2’-methyl-up nucleosides that are effective in treating HCV.” That logic resonates strongly with the deficiencies of the common disclosure here.

⁷² *Id.*

⁷³ *Idenix*, 941 F.3d at 1158-64.

Finally, the Board in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found.*, PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) considered claims that used “90% sequence homology” language to capture “a broad genus of amino acid sequence homologues” but (like here) imposed no restrictions on where particular amino acids replacements could be made, thus causing the claim “to cover, at minimum, thousands of amino acid sequences.”⁷⁴ The Board found the specification’s failure to “explain what, if any, structural features exist (*e.g.*, remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification” was fatal, and the homology limitation “serves to merely draw a fence around the outer limits of a purported genus [which] is not an adequate substitute for describing a variety of materials constituting the genus” for purposes of section 112(a).⁷⁵

The deficiencies of the claims here dwarf those in these three cases. They define much larger, much less predictable and much more diverse genera of modified PH20 polypeptides, and the common disclosure is far more limited. Because the common disclosure neither discloses a representative number of

⁷⁴ *Boehringer*, at 16. The claims were directed to compositions and methods of using proteins. *Id.* at 6.

⁷⁵ *Id.* at 35-36.

species within each immense claimed genus, nor identifies sufficient structural features common to the members of each claimed genus, it fails to demonstrate possession of the genera defined by the claims of the '035 Patent.

1. Claims 1-2, 6-15, and 24-25 Lack Written Description

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

The sequence identity language in claims 1-2, 6-14, and 24-25 define genera of modified PH20 polypeptides of varying size that are not only immense, but are structurally and functionally diverse. These genera capture PH20 mutants with 2 substitutions, 3 substitutions and so on up to a number set by the sequence identity boundary (*i.e.*, 21 for the narrowest claims (*e.g.* claims 24 and 25) to 42 for the broadest (claim 1)). The optional substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, and arranged in any manner.⁷⁶ They thus capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with up to 42 substitutions that mix polar, charged, aliphatic, and aromatic amino acids together in any manner.⁷⁷

⁷⁶ EX1003, ¶ 119; EX1001, 60:59-66, 47:43-47, 47:56-58, 42:3-9.

⁷⁷ EX1003, ¶¶ 119-20.

Each claim also encompasses substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 37 alternative sequences that terminate at positions 430 to 474. The claims' sequence identity language, however, also causes them to capture PH20 polypeptides that terminate at positions well before 430. For example, claims referencing SEQ ID NO:32 require one substitution at position 312 but permit between 20 and 41 additional changes, which can be any mixture of deletions and other substitutions (e.g., the 312 substitution, 5 more substitutions, and 14 deletions, yielding a PH20 terminating at position 416). But removing many residues from the C-terminus of wild-type PH20 can render it inactive, and nothing in the common disclosure shows (much less suggests) that adding the S312T mutant restores activity to such mutants. Patentee nonetheless claims all these polypeptides.⁷⁸

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

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

⁷⁸ EX1003, ¶¶ 164-67.

that navigates this confusing landscape, the patent simply instructs the skilled artisan “to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein.”⁷⁹ In other words, it directs the skilled artisan to blindly make-and-test all such candidate mutants using trial-and-error experimentation.⁸⁰

(i) Multiply-Modified PH20 Mutants to Not Make

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

[W]here the modified PH20 polypeptide contains only two amino acid replacements, the amino acid replacements are ***not*** P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A or N333A/N358A. In a further example, where the modified PH20 polypeptide contains only three amino acid replacements, the amino acid replacements are ***not*** N47A/N131A/N219A.⁸¹

No explanation is provided why these particular combinations of replacements should be avoided, and nor any data testing their activity or other

⁷⁹ EX1001, 78:34-38.

⁸⁰ EX1003, ¶ 193.

⁸¹ EX1001, 77:45-57 (emphases added).

characteristics.⁸² The substitutions are not included in Tables 5 and 10 (i.e., “inactive mutants”) and N219A PH20₁₋₄₄₇ showed increased activity (129%).⁸³ Nothing in the claim language excludes these combinations.

(ii) Substitutions to Avoid in Active Mutants

The common disclosure indicates that active mutant modified PH20 polypeptides should not incorporate amino acid substitutions that rendered PH20₁₋₄₄₇ inactive, stating:

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

It identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10 that are made at other positions.⁸⁵ It does not limit this observation to single-replacement PH20₁₋₄₄₇ mutants, or suggest including any of the substitutions that rendered PH20₁₋₄₄₇ inactive into enzymatically active, multiply-modified PH20

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

⁸³ EX1001, 242 (Table 9).

⁸⁴ EX1001, 80:13-15 (emphases added).

⁸⁵ EX1001, 80:15-55 (“For example, generally modifications are not made at a position corresponding to position ...”).

polypeptides (much less identify specific combinations including them).⁸⁶ Instead, by stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that the ***claimed*** enzymatically active multiply-modified PH20 polypeptides do not and should not contain them.⁸⁷

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

The common disclosure describes no multiply-modified “active mutant” PH20 polypeptides having fewer than 447 residues (or even unmodified PH20s with such lengths) and provides no guidance about making such multiply-modified, truncated and enzymatically active PH20 mutants.⁸⁸

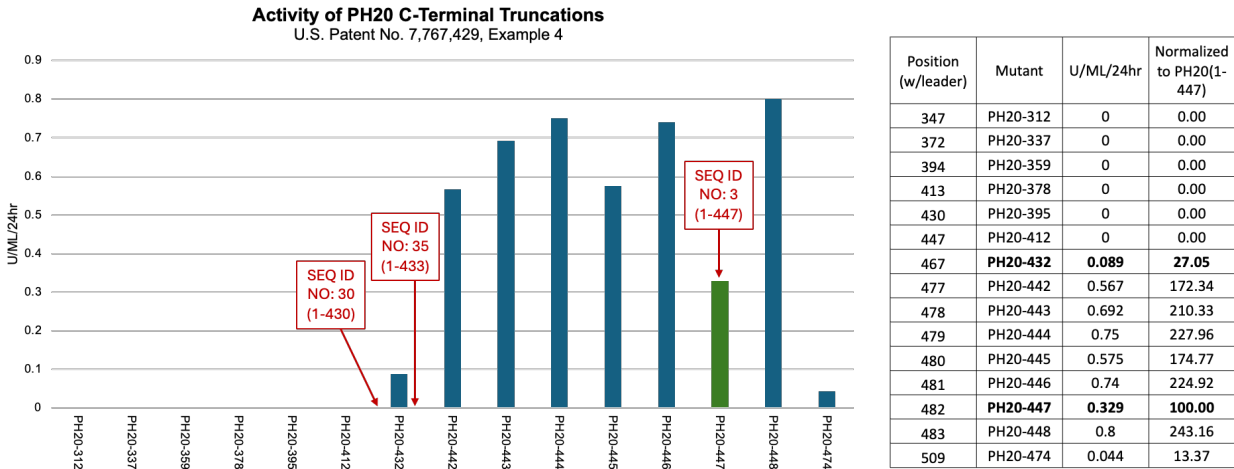
These omissions create significant uncertainty because both the common disclosure and the prior art report that truncations that yield PH20 polypeptides that terminate at or below position 442 have ***significantly reduced or no*** hyaluronidase activity. For example, Patentee’s ’429 Patent reported that PH20 mutants terminating below position 432 residues lacked hyaluronidase activity,

⁸⁶ EX1003, ¶¶ 151, 161-62, 169.

⁸⁷ EX1003, ¶¶ 148-51, 162; EX1001, 80:13-55, 70:46-56.

⁸⁸ EX1003, ¶¶ 94, 97, 167-69; EX1001, 74:9-15.

while those terminating between positions 432 and 448 had widely varying activities (below):⁸⁹



The '429 Patent also reported that “a very narrow range spanning ... [437-447] ... defined the minimally active domain” of human PH20, and elsewhere observed this “minimally active” human PH20 domain contains at least residues 1-429.⁹⁰ The common disclosure agrees, stating that PH20 polypeptides must extend to at least position 429 to exhibit hyaluronidase activity:

⁸⁹ EX1005, 87:52-88:24 (PH20₁₋₄₄₂ activity “decreased to approximately 10%”); EX1013, Figure 2, 430-32 (“[I]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA”).

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

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

In 2007, Chao reported that the C-terminal region of PH20 contained a unique domain (“Hyal-EGF”) linked to a characteristic pattern of sequences.⁹² In PH20, the Hyal-EGF domain runs from positions 337-409, and in 2009 it was shown to be necessary for hyaluronidase activity.⁹³

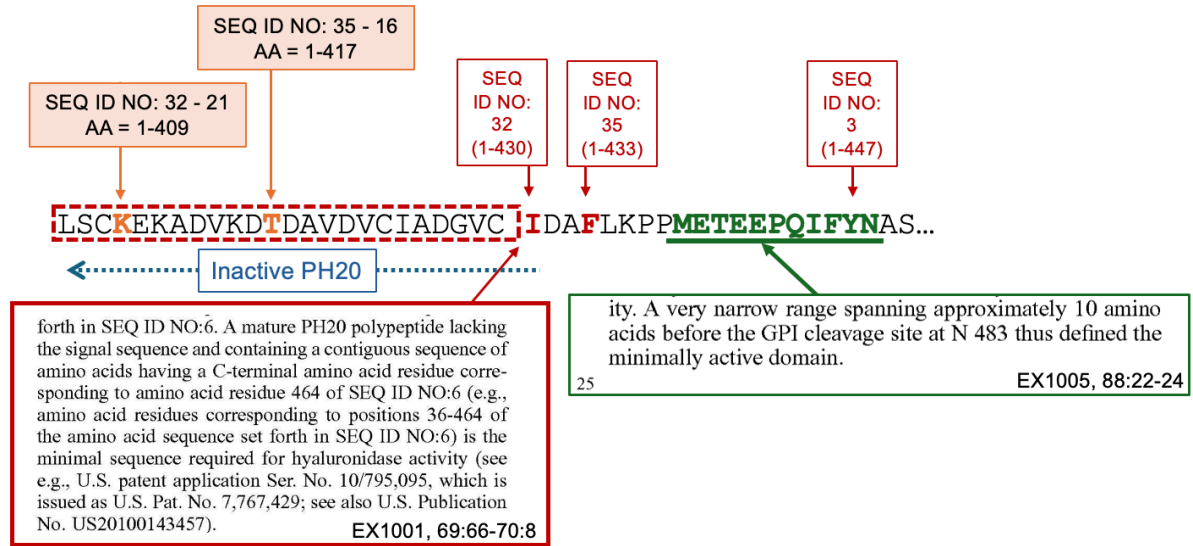
The C-terminus of PH20 is illustrated below, showing (i) the positions where SEQ ID NOS: **3** (447), **32** (430) and **35** (433) terminate, (ii) the “minimally active domain” at 437-447, and (iii) residues below position 429.⁹⁴ Positions resulting from deletion of 21 or 16 residues from SEQ ID NOS: 32 and 35 end before position 429.

⁹¹ EX1001, 69:66-70:8 (emphases added).

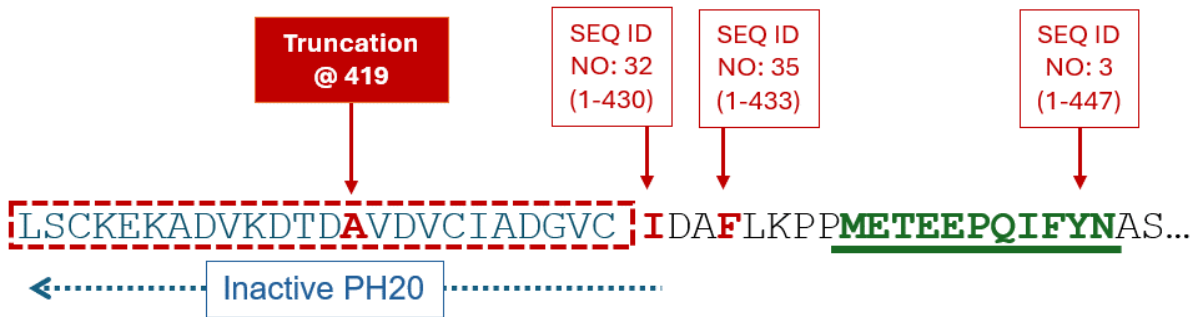
⁹² EX1006, 6912; EX1003, ¶¶ 84-96, 153.

⁹³ EX1004, ¶¶ 97-99; EX1010, 9438; EX1003, ¶¶ 95-97.

⁹⁴ EX1003, ¶ 153.



Thus, a skilled artisan in 2011 would have believed that C-terminal deletions yielding PH20 polypeptides terminating before position 430 would be inactive (below).⁹⁵



The common disclosure provides no examples of (or guidance concerning) PH20 mutants truncated below position 447 with one or more substitutions and that are enzymatically active. It thus ignores the uncertainty existing in 2011 about

⁹⁵ EX1003, ¶¶ 92-93, 97, 165-167.

PH20 truncation mutants that terminate between positions 419 to 433.⁹⁶ The claims nonetheless expressly encompass modified PH20 polypeptides with truncations down to and beyond position 419.⁹⁷

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

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

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

The common disclosure reports results from testing a portion of a randomly generated library of ~6,743 single-replacement PH20₁₋₄₄₇ polypeptides.⁹⁸ These mutants were generated via a mutagenesis process which substituted one of ~15 amino acids into random positions in PH20₁₋₄₄₇ “such that each member contained a single amino change.”⁹⁹ Approximately 5,917 were tested, while ~846 were

⁹⁶ EX1003, ¶¶ 143, 159, 167-69.

⁹⁷ EX1003, ¶¶ 160-65.

⁹⁸ EX1001, 124:48-59, 192:14-16, 191:10-16.

⁹⁹ EX1001, 191:10-192:3.

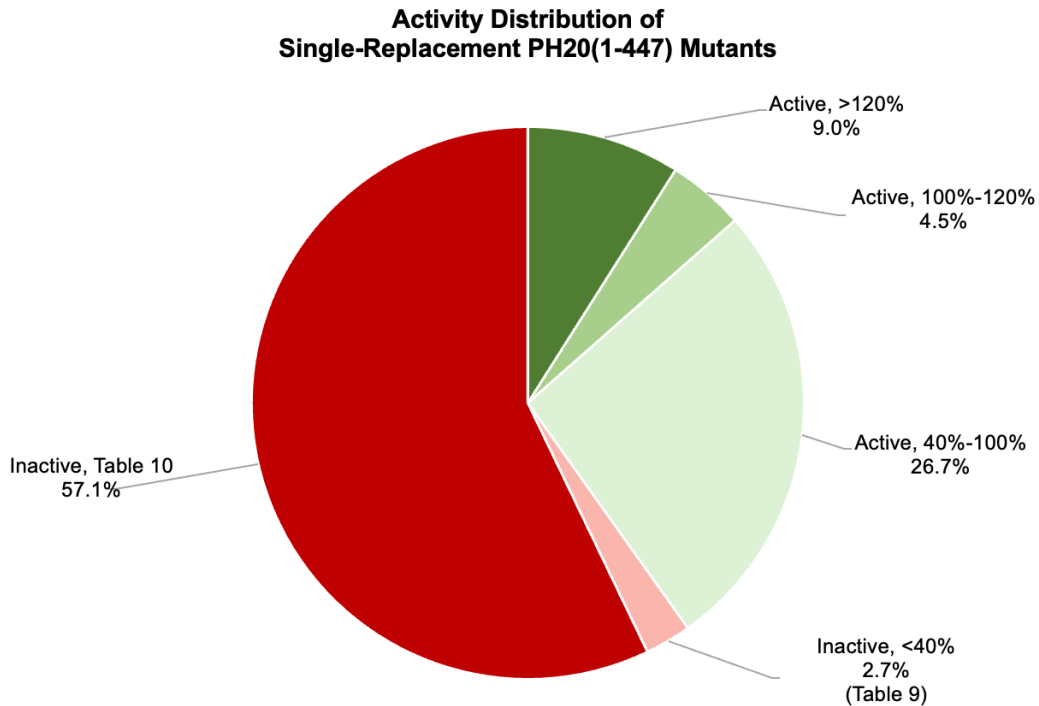
uncharacterized.¹⁰⁰ More than half (~57%) of these mutants were classified as “inactive mutants,” while ~30% (1335) were reported to have less activity than unmodified PH20₁₋₄₄₇ (20%-100%).¹⁰¹ In other words, ~87% of the single-replacement PH20₁₋₄₄₇ polypeptides had *less* activity than unmodified PH20₁₋₄₄₇.¹⁰²

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

¹⁰⁰ EX1003, ¶¶ 103-104. Inconsistent numbers of tested mutants and classifications of mutants are reported but not explained: (i) Table 3 lists 2,516 single-replacement PH20₁₋₄₄₇ 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 PH20₁₋₄₄₇ “inactive mutants,” respectively.

¹⁰¹ EX1003, ¶ 105.

¹⁰² *Id.*



The measured activity of single-replacement PH20₁₋₄₄₇ mutants shows no trends or correlations even for single-replacement PH20₁₋₄₄₇ polypeptides.¹⁰³ Instead, numerous examples show that even introducing different amino acids at the same position in PH20₁₋₄₄₇ resulted in (i) increased activity, (ii) decreased activity, or (iii) inactive mutants (below).¹⁰⁴

¹⁰³ EX1003, ¶¶ 106, 142-43.

¹⁰⁴ Data from Tables 3, 5, 9, 10.

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

The data on activities of tested single-replacement PH20₁₋₄₄₇ mutants is not analyzed or explained in the common disclosure—it is simply presented. There is no attempt to extrapolate its results to any combinations of substitutions in PH20 polypeptides, or to assess the impact of a single substitution on the protein's structure.¹⁰⁵ The quality of the data is also questionable: no control values or statistical assessments are provided.¹⁰⁶ All the data shows is that most of the tested single-substitution mutants impaired PH20's activity.¹⁰⁷

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

¹⁰⁵ EX1003, ¶ 139.

¹⁰⁶ EX1003, ¶ 106.

¹⁰⁷ EX1003, ¶ 138.

function.¹⁰⁸ The patent's empirical test results thus provide no guidance to a skilled artisan about which of the many possible PH20 mutants with different sets of 2-42 substitutions will be enzymatically active.¹⁰⁹

(ii) Purported Stability Data Is Not Reliable or Probative

The common disclosure reports results in Tables 11 and 12 from two runs of “stability” testing of ~409 single-replacement PH20₁₋₄₄₇ polypeptides.¹¹⁰ Table 11 reports the hyaluronidase activity of single-replacement PH20₁₋₄₄₇ mutants tested at 4° C and 37° C, and in the presence of a “phenolic preservative” (m-cresol),¹¹¹ while Table 12 compares relative activities under pairs of these conditions.¹¹²

The data in Tables 11 and 12 provides no meaningful insights.¹¹³ For example, unsurprisingly, single-replacement PH20₁₋₄₄₇ polypeptides showed higher activity at 37° C than at 4° C, given that PH20 exists at the former temperature in

¹⁰⁸ EX1003, ¶¶ 139, 142.

¹⁰⁹ EX1003, ¶¶ 140, 143.

¹¹⁰ EX1001, 269:60-272:47.

¹¹¹ EX1001, 272:50-283:25 (Table 11).

¹¹² EX1001, 283:26-295:50 (Table 12).

¹¹³ EX1003, ¶ 76.

humans.¹¹⁴ And all that testing with m-cresol showed was that only a few mutants were able to resist its effects, with no explanation why.¹¹⁵

With one exception, there is no evidence the measured activity data was attributable to improved stability of PH20.¹¹⁶ More directly, the common disclosure does not identify which *combinations* of substitutions improve stability.¹¹⁷ It thus provides no probative insight regarding multiply-modified PH20 polypeptides with increased stability.¹¹⁸

The data is also largely meaningless, as many of their values fall within the range of activity observed for the positive control.¹¹⁹ The charts and table below show that the positive control had activity that varied by 97% and 87% in two rounds of testing.¹²⁰

¹¹⁴ EX1003, ¶ 73; EX1001, 168:4-13.

¹¹⁵ EX1003, ¶ 69.

¹¹⁶ EX1003, ¶ 69.

¹¹⁷ EX1003, ¶¶ 75-76.

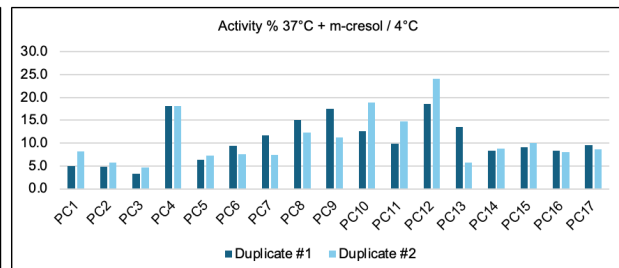
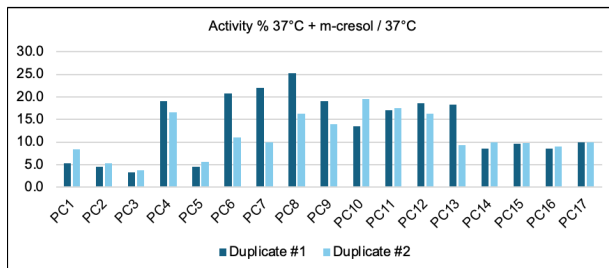
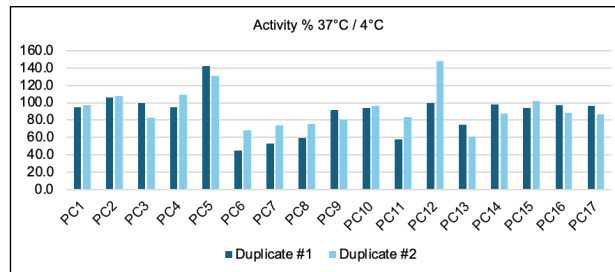
¹¹⁸ *Id.*

¹¹⁹ EX1003, ¶ 71; EX1001, 295 (Table 12).

¹²⁰ EX1003, ¶ 71, Appendix A-7, A-8.

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

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



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

As Dr. Hecht observes, this “significant variation raises serious doubts about how probative or instructive the values of individual tested mutants that fall within the range of variability observed for the control can possibly be.”¹²¹ The data not only fails to identify specific combinations of substitutions that yield PH20 mutants with increased resistance to or stability in denaturing conditions, it is unreliable.

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

Instead of describing any multiply-modified PH20 polypeptides that are “active mutants,” the common disclosure provides only a prophetic research plan based on iterative rounds of “make-and-test” experiments that were never

¹²¹ EX1003, ¶¶ 70-72; *see also* EX1001, 295:57-67 (positive control also varied).

performed. This prophetic method provides absolutely no insights into which multiply-modified PH20 polypeptides are active mutants.¹²²

The common disclosure merely outlines *the idea* of multiply-modified PH20 polypeptides. It declares that “[a] modified PH20 polypeptide can have up to 150 amino acid replacements,” “[t]ypically” contains between 1 and 50 amino acid replacements and “can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.”¹²³ In addition to PH20 polypeptides with single amino acid replacements, it contends that a modified PH20 polypeptide “having a sequence of amino acids that exhibits” between 68% and 99% sequence identity with any of unmodified Sequence ID Nos. 74-855 “*can* exhibit altered, such as improved or increased, properties or activities compared to the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement).”¹²⁴

None of these statements identify *any* actual multiply-modified PH20 polypeptides (*i.e.*, particular sets of specific amino acid substitutions), much less

¹²² EX1003, ¶¶ 173, 184-85, 190; EX1001, 44:1-3; *see generally id.*, 124:48-125:26, 125:35-127:10, 127:38-132:12.

¹²³ EX1001, 48:43-53.

¹²⁴ EX1001, 97:1-15 (emphasis added).

provide results from testing any. They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides.

The common disclosure instead outlines a prophetic, “iterative” make-and-test research plan for discovering modified PH20 polypeptides with multiple substitutions that might exhibit hyaluronidase activity, stating:

The method provided herein [] is *iterative*. In one example, after the method is performed, any modified hyaluronan-degrading enzymes identified as exhibiting stability ... *can be modified or further modified* to increase or optimize the stability. A secondary library *can be* created by introducing additional modifications in a first identified modified hyaluronan-degrading enzyme. ... The secondary library *can be* tested using the assays and methods described herein.¹²⁵

The guidance in this research plan is effectively meaningless. It says to make mutants, test them to find activity and/or stability, and keep repeating the process until you find something via screening. It does not indicate that any useful multiply-modified PH20 polypeptides will be found, much less what their specific characteristics or activities are.¹²⁶

¹²⁵ EX1001, 132:13-26 (emphases added); *see also id.* at 42:48-55, 125:27-32; EX1003, ¶¶ 173-177.

¹²⁶ EX1003, ¶¶ 187-90.

The specification also incorrectly portrays the experimental readout—hyaluronidase activity—as a measure of “stability.”¹²⁷ As Dr. Hecht explains, to assess a protein’s stability directly one performs experiments that measure the energy associated with the protein’s transition between its folded and unfolded states.¹²⁸ Activity may or may not be influenced by stability but is not itself a measure of stability.¹²⁹

An alternative focus is then proposed: mutations can be “targeted near” “critical residues” which supposedly “can be identified because, when mutated, a normal activity of the protein is ablated or reduced.”¹³⁰ But Tables 5 and 10 show that at least one substitution at each of 405 positions between positions 1 and 444 of PH20₁₋₄₄₇ resulted in an inactive mutant.¹³¹ In other words, the common disclosure’s guidance is to target locations “near” ~90% of the amino acids in

¹²⁷ EX1003, ¶¶ 67, 69, 179.

¹²⁸ EX1003, ¶¶ 63-66.

¹²⁹ EX1003, ¶ 67.

¹³⁰ EX1001, 132:27-53; EX1003, ¶¶ 178-79.

¹³¹ EX1003, ¶ 180, Appendix A-3.

PH20₁₋₄₄₇, which is no different than targeting every residue in the protein.¹³² It is, like the first proposed “iterative” process, meaningless.

These prophetic research plans, based entirely on unfocused, iterative “make-and-test” experiments, provide no direction to the skilled artisan about which of the trillions and trillions of possible multiply-modified PH20 polypeptides are “active mutant” PH20 polypeptides. Instead, they require the skilled artisan to repeat the cycle of mutagenesis iteratively, screening and selecting until 10⁵⁹ to 10¹¹² modified PH20 polypeptides are produced and screened for activity.¹³³ That in no way demonstrates possession of the claimed genus.

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

The common disclosure does not identify the structural significance of any of the ~2,500 mutations that yielded single residue “active mutant” PH20₁₋₄₄₇ 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

¹³² EX1003, ¶ 180.

¹³³ EX1003, ¶¶ 175-77, 181, 187-88; EX1001, 127:19-24, 127:11-36, 130:31-35, 130:46-51; 131:1-15.

polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.¹³⁴ Instead, it simply lists single replacements to random amino acids at random positions that were classified as “active mutants” by a hyaluronidase assay, without further explanation; nothing is said about the effects (if any) of substitutions on the protein’s structure.¹³⁵

The common disclosure also does not identify any *sets* of specific amino acid replacements that correlate to structural domains or motifs that positively or negatively influence hyaluronidase activity, much less *predictably* increase activity to defined thresholds.¹³⁶ Again, it simply reported activity data from testing randomly generated *single*-replacement PH20₁₋₄₄₇ mutants.

The common disclosure’s empirically identified examples of “active mutant” single-replacement PH20₁₋₄₄₇ mutants also do not *by themselves* identify any “structure-function” relationship between “active mutants” and the set of single-replacement modified PH20₁₋₄₄₇ polypeptides.¹³⁷ They certainly do not do so

¹³⁴ EX1003, ¶¶ 139-40, 151.

¹³⁵ EX1001, 224:15-43; EX1003, ¶¶ 139-40, 142.

¹³⁶ EX1003, ¶¶ 55, 142-43.

¹³⁷ EX1003, ¶¶ 61, 143, 157, 159.

for the much larger genus of modified PH20 polypeptides of varying lengths and between 2 and 42 substitutions.¹³⁸

Critically, the common disclosure *does not even contend* that a particular amino acid replacement at a particular position (*e.g.*, 312) that makes a PH20₁₋₄₄₇ an “active mutant” will make any other modified PH20 polypeptide with that same amino acid replacement (plus between 1 and 41 additional replacements or truncations) an “active mutant.”¹³⁹ Such an assertion would have no scientific credibility—the activity of a protein such as PH20 is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.¹⁴⁰ Thus, even the inventors did not view their compilation of test results as identifying a structure-function correlation for multiply-modified PH20 polypeptides.

The common disclosure, thus, does not identify to a skilled artisan *any* structural features shared by the many, diverse “active mutant” modified PH20 polypeptides within the scope of the claims,¹⁴¹ and thus cannot satisfy the written

¹³⁸ EX1003, ¶ 157.

¹³⁹ EX1003, ¶¶ 168, 192-93.

¹⁴⁰ EX1003, ¶¶ 56-57.

¹⁴¹ EX1003, ¶ 157.

description requirement of § 112(a) as a disclosure that links a functional property to a particular structure *shared* by the members of the genus.

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

The ~2,500 single-replacement PH20₁₋₄₄₇ polypeptides that are “active mutants” are not examples representative of the claimed genera of the claims, much less their various sub-genera captured in the dependent claims.¹⁴²

First, the single-replacement PH20₁₋₄₄₇ examples are not representative of the trillions and trillions of PH20₁₋₄₄₇ polypeptides with between **2 and 42 substitutions** at any of hundreds of positions within the protein.¹⁴³ The latter group of proteins is structurally distinct from single replacement PH20 polypeptides, both as to their sequence and due to the various structures within the folded protein that, when incorporating different amino acid substitutions, may alter their structures and their interactions with neighboring residues.¹⁴⁴ The effects of those numerous substitutions on a protein’s various secondary structures and structural motifs within the protein is not described in the common disclosure, and the magnitude of

¹⁴² EX1003, ¶¶ 61, 143, 155, 159.

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

¹⁴⁴ EX1003, ¶¶ 54-56, 58, 120, 156, 159.

concurrent substitutions encompassed by the claims was unknowable in 2011.¹⁴⁵

The overall activity of a protein with multiple substitutions also will not be due to one amino acid, but to the unique structure of each protein that reflects *the totality* of effects of those many substitutions.¹⁴⁶

More specifically, introducing a first amino acid substitution often affects the neighbors of that original/replaced amino acid by, for example, (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, and/or (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).¹⁴⁷ Introducing a second substitution in that region may reverse those interactions (or not) with each neighboring residue, and a third substitution may do the same, with up to 21 rounds permitted by even the narrowest claims, each potentially impacting each interaction.¹⁴⁸ The data associated with a single amino acid substitution thus cannot be representative of the properties of any of these downstream, multiply-substituted mutants, which will have an unknowable

¹⁴⁵ EX1003, ¶ 228.

¹⁴⁶ EX1003, ¶¶ 36, 61, 140, 143, 151.

¹⁴⁷ EX1003, ¶¶ 56-58.

¹⁴⁸ EX1003, ¶¶ 58-60, 142.

combination of substitutions that each uniquely impact the properties of the mutated protein.¹⁴⁹

Enzymatically active single-replacement PH20₁₋₄₄₇ polypeptides also are not representative of enzymatically active, multiply modified PH20 polypeptides that incorporate changes that alone render PH20 proteins inactive (*e.g.*, truncations terminating below position 429, or single substitutions that render PH20₁₋₄₄₇ inactive).¹⁵⁰ That is because an *active* single-replacement PH20₁₋₄₄₇ polypeptide does not also contain the distinct structural features that render the latter types of PH20 polypeptides enzymatically *inactive*. For example, an enzymatically active PH20₁₋₄₄₇ protein with a single amino acid substitution (*e.g.*, S312T) would not be considered representative of a PH20 that combines that S312T substitution with truncations at the C terminus ending at positions between 409 to 433 because the common disclosure would have led a skilled artisan to expect that PH20 proteins terminating at those positions would be inactive.¹⁵¹ A skilled artisan could not have predicted—based on the examples in the common specification, all of which are limited to single-replacement PH20₁₋₄₄₇ polypeptides—whether enzymatic activity

¹⁴⁹ EX1003, ¶¶ 61, 142-43, 159, 169.

¹⁵⁰ EX1003, ¶¶ 161-64.

¹⁵¹ EX1003, ¶¶ 167-69.

could be restored to such severely truncated PH20 mutants, much less the precise additional changes that would do so.¹⁵²

The common disclosure thus provides a very narrow set of working examples relative to the diversity of modified PH20 polypeptides being claimed.¹⁵³ The examples are restricted to *one type of change* (a single amino acid replacement) in *one type of PH20 polypeptide* (SEQ ID NO: 3).¹⁵⁴ By contrast, the claims encompass changes in 37 different unmodified PH20 sequences, and include, in addition to one identified replacement at position 312, anywhere from 1 to 41 (claim 1) to 20 (claims 24-25) additional changes.¹⁵⁵ A simple illustration demonstrates how *non-representative* the examples are: all of the examples of single-replacement PH20₁₋₄₄₇ mutants fit into one box of the array below (claim 2).

¹⁵² EX1003, ¶ 168.

¹⁵³ EX1003, ¶ 155.

¹⁵⁴ EX1003, ¶¶ 97, 99, 103.

¹⁵⁵ EX1003, ¶¶ 115-20.

	Number of Changes																						
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3																							
7																							
32																							
33																							
34																							
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Unlike claim 2, which requires 95% sequence identity, claim 1 permits 91% sequence identity, thus capturing an even *larger* genus (up to 42 permitted changes) than depicted above.

Consequently, a skilled artisan would not have viewed the Patents’ examples of individual single amino acid replacements in PH20₁₋₄₄₇ as being *representative* of the diversity of modified PH20 polypeptides encompassed by the claims.¹⁵⁶

¹⁵⁶ EX1003, ¶ 143.

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

Patentee's position on the breadth of the claims is unknown. However, by their literal language, they capture several sub-genera of "active mutant" modified PH20 polypeptides that the common disclosure says caused single-replacement PH20₁₋₄₄₇ mutants to be inactive (*i.e.*, those with replacements in Tables 5/10 or in PH20 sequences terminated before position 429). Likewise, the claim language captures modified PH20 polypeptides with the six combinations of replacements the common disclosure explicitly says to not make: P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, N333A/N358A and N47A/N131A/N219A.¹⁵⁷ The claims thus improperly capture subject matter the common disclosure affirmatively excluded from the genus of enzymatically active modified PH20 polypeptides having multiple substitutions and other changes.

The common disclosure provides no exemplification of multiply-modified species of PH20 polypeptides that disregard these restrictions in the common disclosure.¹⁵⁸ Specifically, there is no explanation of the types of substitutions that might be made to restore activity that, under the logic of the common disclosure,

¹⁵⁷ See § V.A.2.a; EX1001, 77:45-57.

¹⁵⁸ EX1003, ¶ 161.

will result in enzymatically inactive PH20 polypeptides or which the specification teaches *not* to make.¹⁵⁹ Yet the claims encompass such proteins. The claims therefore independently violate the written description requirement for the reasons articulated by the Federal Circuit in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998)—if a disclosure “unambiguously limited” the invention, but the claims circumvent that limitation, those claims are “broader than the supporting disclosure” and are unpatentable.

2. Dependent Claims 3-5 and 15 Lack Written Description

a) *Claims 3 and 4*

Claims 3 and 4 specify additional functional properties of the modified PH20 polypeptides in the genus defined by claim 1: either (i) increased hyaluronidase activity (claim 4) or (ii) increased stability (claim 3) relative to unmodified PH20₁₋₄₄₇.

The reasons provided in § V.A.1 explaining why the claims generally lack written description apply with full force to claims 3 and 4. Stated simply, the common disclosure’s recitation of a *desired* level of stability or hyaluronidase activity in claims 3 and 4 does not identify *which* of the many trillions of PH20 polypeptides having 91% or 95% sequence identity with SEQ ID NOS: 3, 7, or 32-

¹⁵⁹ EX1003, ¶ 168.

66 and one of five replacements at position 312 will exhibit either of those functional properties.¹⁶⁰

First, the identification of one PH20₁₋₄₄₇ mutation at position 312 that exhibited increased activity (S312N) compared to unmodified PH20₁₋₄₄₇ is not representative of each claim's genus of PH20 polypeptides with 1 to 41 additional substitutions and/or truncations, and even other substitutions at position 312 that, when made as single-substitutions, did not result in increased activity.¹⁶¹ Notably, no test results are provided showing that a PH20 protein with a substitution at position 312 exhibits increased stability.

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides and exhibiting increased activity or stability.¹⁶² The mere presence of a position 312 replacement in a multiply-modified PH20 thus does not demonstrate possession of a modified PH20 polypeptide with increased activity or stability, and the common disclosure makes no claim that it does.¹⁶³

¹⁶⁰ EX1003, ¶¶ 185, 191-92.

¹⁶¹ EX1001, 248 (Table 9); EX1003, ¶¶ 191-92.

¹⁶² EX1003, ¶¶ 68-69, 76, 157, 185, 190.

¹⁶³ EX1003, ¶¶ 76, 143, 168, 185, 192-93.

The common disclosure also provides no description of multiply-modified PH20 polypeptides with the claimed substitutions at 312, much less one that identifies the 1 to 41 more substitutions that retain elevated enzymatic activity or exhibit increased stability.¹⁶⁴ Indeed, the common specification does not identify even one multiply-modified PH20 polypeptide with any level of hyaluronidase activity.¹⁶⁵ Similarly, even if the data reported in Tables 11 and 12 was not flawed and unreliable as a measure of “stability” (as discussed above, it is), it too is limited to single-substituted PH20 polypeptides, and, provides no “stability” data on multiply-modified PH20 polypeptides.¹⁶⁶

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

b) Claims 5 and 15

Claims 5 and 15 require an additional functional property: that the modified PH20 polypeptide be “soluble.” Each lacks written description support (i) for the same reasons identified for claim 1, and (ii) because they encompass modified PH20 polypeptides that the common disclosure suggests would be insoluble.

¹⁶⁴ EX1003, ¶¶ 140, 190-93.

¹⁶⁵ EX1003, ¶¶ 130, 172.

¹⁶⁶ EX1001, Tables 11, 12.

The common disclosure explains that “a soluble PH20 lacks all or a portion of a glycosphosphatidyl anchor (GPI) attachment sequence,”¹⁶⁷ which was known to be hydrophobic.¹⁶⁸ Citing prior art, it identifies the first residue of the GPI sequence in human PH20 as position 456 (position 491 in SEQ ID NO: 6).¹⁶⁹ It also states that a soluble PH20 “is a polypeptide that is truncated after amino acid 482 of ... SEQ ID NO: 6” (*i.e.*, 447 in SEQ ID NO:3).¹⁷⁰ It thus suggests that human PH20 sequences that terminate below position 448 are soluble and those that terminate above position 456 are insoluble.¹⁷¹

Claims 5 and 15 encompass PH20 polypeptides based on SEQ ID NOS:59-66, which terminate between positions at 457 to 464 respectively (*i.e.*, beyond position 456), and does not restrict where in the PH20 polypeptide changes are

¹⁶⁷ EX1001, 46:28-30, 72:8-9; 74:26-38.

¹⁶⁸ EX1001, 72:32-44; EX1005, 86:18-22.

¹⁶⁹ EX1001, 72:32-44; *also* EX1005, 2:56-61 (“Attempts to make human PH20 DNA constructs that would not introduce a lipid anchor into the polypeptide resulted in either a catalytically inactive enzyme, or an insoluble enzyme”) (citing EX1011).

¹⁷⁰ EX1001, 75:16-18; EX1005, 3:57-62.

¹⁷¹ EX1003, ¶¶ 89-90.

made, other than the replacement at position 312. Consequently, claims 5 and 15 capture modified PH20 polypeptides that are C-terminally truncated but, per the common disclosure, *are not* “soluble modified PH20 polypeptide[s]” because each contains “all or a portion of” the GPI attachment sequence.¹⁷²

Patentee may contend that some unidentified number of modified PH20 polypeptides based on SEQ ID NOS: 59-66 *may* be soluble, citing the common disclosure as suggesting that between 1-10 residues within the GPI anchor “can be retained, provided the polypeptide is soluble.”¹⁷³ But the common disclosure does not identify *which* modified PH20 polypeptides terminating above position 448 (and especially terminating between 457 and 464) *are* soluble, provides no examples of such soluble PH20 mutants, and provides no reason to expect that many modified PH20 polypeptides within the claim’s scope are soluble.

Thus, claims 5 and 15 are unpatentable for lack of written description for this additional, independent reason.

¹⁷² EX1001, 46:55-61.

¹⁷³ EX1001, 74:19-25.

3. The Remaining Dependent Claims Lack Written Description

The remaining dependent claims (16-23 and 26-34) do not meaningfully alter the number of PH20 polypeptides in the genus of claim 1.¹⁷⁴ They instead specify additional features (claims 16-22, 33-34), or pharmaceutical compositions or methods of treatment that reference the genus of claim 1. They lack written description for the same reasons explained in § V.A.1.¹⁷⁵

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

“If a patent claims an entire class of ... compositions of matter, the patent’s specification must enable a person skilled in the art to make and use the *entire* class,” *i.e.*, “the *full scope* of the invention” and so the “more one claims, the more

¹⁷⁴ Claim 21 omits reference SEQ ID NO:7.

¹⁷⁵ *Idenix*, 941 F.3d at 1155, 1165 (method of treatment claims involving immense genus of modified proteins invalid for lack of written description and non-enablement); *Boehringer*, PGR2020-00076, Paper 42, at 40-41 (methods of treatment claims found to lack written description because specification did not provide an adequate written description of compositions being administered).

one must enable.”¹⁷⁶ “It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.”¹⁷⁷ “Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation.”¹⁷⁸

Although not required, enablement may be assessed using the *Wands* factors, which consider: “(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention.”¹⁷⁹

Where the scope of the claims is large, there are few working examples disclosed in the patent, and the only guidance to practice “the full scope of the

¹⁷⁶ *Amgen*, 598 U.S. at 610 (emphases added).

¹⁷⁷ *Idenix*, 941 F.3d at 1159.

¹⁷⁸ *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

¹⁷⁹ *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims' functional limitations—the asserted claims are not enabled.”¹⁸⁰

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the 10^{59+} PH20 polypeptides having multiple amino acid replacements and/or truncations within the scope of the claims are “active mutant” PH20 polypeptides.¹⁸¹

1. The Genera of PH20 Polypeptides of Claims 1-2, 6-14, 21, and 24-25 Are Not Enabled

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

¹⁸⁰ *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, T., sitting by designation) *aff'd* 81 F.4th 1362 (Fed. Cir. 2023).

¹⁸¹ EX1003, ¶¶ 170-71, 190.

a) Extreme Scope of the Claims

As explained in § IV.D.1, each of claims 1-2, 6-14, 21, and 24-25 define an immense and diverse genus of between 10^{59} and 10^{112} enzymatically active modified PH20 polypeptides. Practicing that full genus, however, raises substantial scientific questions left unanswered by the common disclosure:

- (i) The claims encompass many modified PH20 polypeptides that terminate below position 429.¹⁸² The common disclosure and the prior art, however, report that unmodified human PH20 must include residues through position 429 to have hyaluronidase activity.¹⁸³
- (ii) Several claims (1-2, 6-9, 14, 21) encompass modified PH20 polypeptides that, per the common disclosure's guidance, would be expected to be insoluble because they include all or some of the GPI anchor sequence.¹⁸⁴
- (iii) The mathematical "sequence identity" boundaries set by the claim language cause the claims to capture (without restriction) modified PH20 polypeptides with 2 to 42 amino acid replacements that the

¹⁸² EX1003, ¶¶ 154, 164.

¹⁸³ EX1001, 69:66-70:8; EX1003, ¶¶ 93, 152-53.

¹⁸⁴ EX1001, 46:28-30, 72:8-9, 74:19-25, 75:16-18; EX1005, 2:56-61, 3:57-62.

common disclosure instructs “are less tolerant to change or required for hyaluronidase activity”¹⁸⁵ or which the common disclosure affirmatively says to not make.¹⁸⁶

In other words, the claims capture massive genera of modified PH20 polypeptides, most of which would have unknowable properties absent individual production and testing.¹⁸⁷

Claims that capture a massive and diverse genus of proteins have routinely been found non-enabled. For example, the claims in *Amgen* covered “millions” of different, untested antibodies,¹⁸⁸ while in *Idenix*, a skilled artisan would “understand that ‘billions and billions’ of compounds literally meet the structural limitations of the claim.”¹⁸⁹ In both cases, the enormous claim scope was found non-enabled after being contrasted to the limited working examples in the patent, the existence of unpredictability, and the quantity of experimentation needed to practice the full scope of the claims (*Wands* Factors 1, 3, 4, and 7). And, as the

¹⁸⁵ EX1001, 80:13-15.

¹⁸⁶ EX1001, 77:45-57.

¹⁸⁷ EX1003, ¶ 158.

¹⁸⁸ 598 U.S. at 603.

¹⁸⁹ 941 F.3d at 1157.

Idenix court observed, one cannot rely on the knowledge and efforts of a skilled artisan to try to “fill the gaps in the specification” regarding which of the “many, many thousands” of possible compounds should be selected for screening, and which in this case is impossible.¹⁹⁰

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

The common disclosure provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement PH20₁₋₄₄₇ polypeptides, of which ~2500 were “active mutants.”¹⁹¹ Those examples are a tiny fraction of the 10⁵⁹ to 10¹¹² modified PH20 polypeptides covered by the claims, and provide no guidance that would help a skilled artisan navigate the “trial-and-error” methodology the common disclosure describes using to make modified PH20 polypeptides; indeed, none incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.¹⁹²

The common disclosure provides no credible guidance on the full scope of the genus comprising multiple combinations of changes to PH20 polypeptides.¹⁹³

¹⁹⁰ *Id.* at 1159.

¹⁹¹ EX1003, ¶ 103.

¹⁹² EX1003, ¶¶ 155, 159, 167.

¹⁹³ EX1003, ¶¶ 131, 139.

Instead, it describes an explicitly prophetic and “iterative” process for *discovering* active mutant PH20 polypeptides. *See* § V.A.1.d.

The purely prospective research plan in the common disclosure demands that a skilled artisan engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of *randomized* mutations (up to 41 rounds per starting molecule under the broadest claims) to *discover* which of the 10^{59+} possible modified PH20 polypeptides having 2 to 41 replacements to any of 19 other amino acids in any of 35 starting PH20 sequences might possess hyaluronidase activity.¹⁹⁴

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

¹⁹⁴ EX1003, ¶¶ 188-90; *see also* EX1018, 382 (“combinatorial randomization of only five residues generates a library of 205 possibilities (3.2×10^6 mutants), too large a number for manual screening”). Chica also credited a supposed “ground-breaking” advancement in predictive molecular modeling techniques. EX1018, 384, 382. That supposed advancement, however, was later shown to be false. EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

- (i) it does not identify *any* specific combination of two or more replacements within any PH20 polypeptide that yield “active mutants”;
- (ii) it provides no data from testing *any* PH20 polypeptide with two or more substitutions; and
- (iii) it does not identify any regions or residues that are “associated with the activity and/or stability of the molecule” or “critical residues involved in structural folding or other activities’ of the molecule” when two or more concurrent replacements have been made.¹⁹⁵

From the common disclosure and their knowledge in 2011, a skilled artisan could not predict whether a particular multiply-modified PH20 polypeptide will be enzymatically active without making and testing each one.¹⁹⁶

Regardless whether individual rounds of “iterative” production and testing might be considered “routine,” the process described in the common disclosure is indistinguishable from the “*iterative, trial-and-error process[es]*” that have

¹⁹⁵ EX1003, ¶¶ 144, 158, 172, 184-85.

¹⁹⁶ EX1003, ¶ 190.

consistently been found to not enable broad genus claims to modified proteins.¹⁹⁷

Simply put, the common disclosure's prophetic, iterative and labor-intensive process requires making and screening an immense number of modified PH20 polypeptides, before which the skilled artisan will not know which multiply-modified PH20 polypeptides are within the claims' scope.¹⁹⁸

c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable

Like any protein, the activity of PH20 can be unpredictably influenced by changes to its amino acid sequence.¹⁹⁹ Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary structures or structural motifs within the protein that are important to its biological activity (*e.g.*, catalysis, ligand binding, etc.) and/or stability.²⁰⁰

¹⁹⁷ *Idenix*, 941 F.3d at 1161-63 (emphasis added); *see also Amgen*, 598 U.S. at 612-15; *Wyeth*, 720 F.3d at 1384-86; *Baxalta*, 597 F. Supp. 3d at 616-19; *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 n.2 (Fed. Cir. 2020).

¹⁹⁸ EX1003, ¶¶ 172, 183-85, 189.

¹⁹⁹ EX1003, ¶ 61.

²⁰⁰ *Id.*

As explained in § VI, below, by 2011, skilled artisans could have assessed whether certain *single* amino acid substitutions at certain positions would be tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.²⁰¹ That person, using a rational design approach, would have performed such an assessment by, *inter alia*, analyzing evolutionarily non-conserved positions and evaluating specific changed residues using a PH20 protein structure model using experimental evidence available before 2011 that is not disclosed in or referenced by the common disclosure.²⁰²

By contrast, the skilled artisan could *not* have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011.²⁰³ Introducing *multiple* concurrent changes into a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity and/or stability, and can even introduce new ones into the protein.²⁰⁴ Replacing multiple amino

²⁰¹ EX1003, ¶ 194.

²⁰² EX1003, ¶¶ 20-22, 49, 215-16, 220.

²⁰³ EX1003, ¶ 228.

²⁰⁴ EX1003, ¶¶ 59-60, 185.

acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.²⁰⁵

The cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure in 2011. For example, the further away the modeled amino acid sequence gets from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model became.²⁰⁶ In addition, depending on the structural template used to produce the model, regions of the protein not supported by a corresponding structure cannot be reliably used to assess particular changes.²⁰⁷ And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.²⁰⁸

Consequently, a skilled artisan could not have used conventional rational design techniques to identify, much less predict the outcome of attempts to make, the enormous number of PH20 polypeptide sequences that incorporate the myriad

²⁰⁵ EX1003, ¶ 58.

²⁰⁶ EX1003, ¶¶ 158, 190, 228; EX1004, ¶¶ 143-144.

²⁰⁷ EX1003, ¶¶ 158, 228; EX1004, ¶¶ 133-135; EX1012, 4, 8.

²⁰⁸ EX1003, ¶ 51, 190; EX1059, 1225-26; EX1018, 378.

possible combinations of between 5 and up to 42 substitutions the claims encompass.²⁰⁹ Stated another way, practicing the full scope of the claims would have been well beyond the ability of the skilled artisan's ability to reasonably predict which multiply-modified PH20 polypeptides would be enzymatically active, and, even if possible, doing so would have taken an extreme amount of time and effort even for a small handful of the vast universe of multiply-modified polypeptides within the claims.²¹⁰

d) Other Wands Factors and Conclusion

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

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed.²¹¹ Likewise, while there was significant knowledge in the public art about hyaluronidases, there was no solved structure of the PH20 protein, experimental reports generally reported on *loss of activity* from mutations, and did not

²⁰⁹ EX1003, ¶¶ 61, 158, 228.

²¹⁰ EX1003, ¶¶ 158, 190.

²¹¹ EX1003, ¶¶ 158, 228.

predictably teach how to introduce changes that *enhanced* stability or activity.

Indeed, the non-enabled patent disclosure at issue in *Amgen* dates to the same 2011 timeframe as the common disclosure.

Practicing the full scope of claims 1-2, 6-14, 21, and 24-25 thus would have required a skilled artisan to engage in undue experimentation, which renders those claims non-enabled.

2. Dependent Claims Additionally Are Not Enabled

a) Claims 3 and 4

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

The reasons why claims 1-2, 6-14, 21, and 24-25 are not enabled (*see* § V.B.1) establish why claims 3 and 4 are also not enabled. Specifically, a skilled artisan could not have predicted which of the trillions of PH20 polypeptides having up to 41 changes beyond a required change at position 312 would exhibit increased activity or stability compared to an unmodified PH20.²¹² Instead, a skilled artisan

²¹² EX1003, ¶¶ 185, 190.

would need to make-and-test each molecule in order to practice the “full scope” of the claims.²¹³

b) Claims 5 and 15

Because claims 5 and 15 encompass a substantial portion of the genus defined by claim 1, they are not enabled for the same reasons.

Additionally, as explained in § V.A.2.b, the common disclosure suggests that PH20 polypeptides (modified or unmodified) that extend past position 456 would be “insoluble.” Based on it and published literature, a skilled artisan would have expected the presence of the hydrophobic GPI sequence in the PH20 protein could cause aggregation, loss of activity, and/or reduced expression.²¹⁴ The common disclosure reinforces that these problems can occur, but provides no guidance as to how solve them and no examples of modified PH20 polypeptides extending past position 456 that are soluble. Claims 5 and 15 are thus not enabled.

c) Claims 16-20, 22-23, 26-34

The remaining claims employ the genus definition used in claim 1 and recite either further modifications to the modified polypeptides, pharmaceutical compositions, or methods of treatment using the claimed genus. These claims do

²¹³ *Id.*

²¹⁴ EX1003, ¶¶ 89-90, 196; EX1001, 51:2-4, 72:32-44; *also* EX1005, 2:56-61.

not add requirements that limit the numbers of polypeptides in the claim 1 genus.²¹⁵ They are therefore not enabled for the same reasons.²¹⁶

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

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

First, it ignores that at least *a portion* of the claimed genus *does* require the modified PH20 polypeptides to be an “active mutant.” *See* § V.B.2.b. Because dependent claim 4 requires the modified PH20 polypeptides to exhibit increased hyaluronidase activity, parent claim 1 necessarily encompasses a sub-genus comprised of “active mutant” modified PH20 polypeptides. A failure to enable or describe a subgenus within the scope of the claims demonstrates that the claim *as a whole* is unpatentable for lack of written description and non-enablement.²¹⁷

²¹⁵ Claim 21 limits the genus by removing SEQ ID NO:7, but defines an immense genus otherwise identical to claim 1.

²¹⁶ *See, e.g., Idenix*, 941 F.3d at 1155, 1165.

²¹⁷ *ABS Glob., Inc. v. Inguran*, 914 F.3d 1054, 1070, 1074 (7th Cir. 2019) (“If the specification failed to enable [a limitation] in the dependent claim, then [] the full scope of the invention is also not enabled in the independent claim, and

Second, the common disclosure fails to provide any correlation between changes to PH20 polypeptides and *either* active or inactive mutants.²¹⁸ Rather, it leaves to the skilled artisan the burdensome task of making and testing, through trial-and-error iteration, each of the 10⁵⁹+ candidate polypeptides within the claims' scope to determine which exhibit hyaluronidase activity and which are inactive mutants.²¹⁹

Third, the only putative utility identified for “inactive” polypeptides is as “antigens in contraception vaccines.”²²⁰ This assertion is not scientifically credible, but regardless, the common disclosure provides no guidance about which epitopes on the PH20 protein must be preserved in an “inactive mutant” (if any) to induce contraceptive antibody production in a human subject.²²¹ Notably, while the specification cites two studies in guinea pigs,²²² it ignores numerous

both claims are invalid for non-enablement”) (citing *Alcon Research, Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1367-68 (Fed. Cir. 2012)).

²¹⁸ EX1003, ¶ 143.

²¹⁹ EX1003, ¶¶ 173-74, 182-84.

²²⁰ EX1001, 75:56-58, 184:54-185:6.

²²¹ EX1003, ¶ 113.

²²² EX1001, 184:54-185:6; EX1022, 1142-43; EX1023, 1133-34.

publications before 2011 that showed that immunizing mammals with PH20 did *not* cause contraception.²²³ Moreover, Patentee’s own clinical studies of the unmodified PH20₁₋₄₄₇ protein reported in 2018 that, despite producing anti-PH20 antibodies, those anti-PH20 antibodies *did not affect fertility* in humans:

Although some antisperm antibodies are associated with decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex.²²⁴

Notably, Patentee reported this clinical result before filing the application that issued as the ’035 Patent.

Even if one considers the unlikely possibility that some epitope on human PH20 might induce contraceptive effects in a human, a skilled artisan could not have reasonably predicted from the common disclosure whether any “inactive mutant” modified PH20 polypeptides would preserve that epitope or induce

²²³ See EX1019, 325, 331-33 (“recombinant mPH20 is not a useful antigen for inclusion in immunocontraceptive vaccines that target mice”); EX1020, 179-81 (“immunization [of rabbits] with reproductive antigens ... are unlikely to result in reduced fertility ...”); EX1021, 30310, 30314 (“PH-20 is not essential for fertilization, at least in the mouse ...”).

²²⁴ EX1024, 87-88; *see also* EX1061, 1154; EX1003, ¶¶ 110-11.

antibody production that would confer (contrary to Patentee’s clinical evidence) contraceptive effects in humans.²²⁵ Indeed, a skilled artisan would have expected the vast majority of “inactive mutant” PH20 polypeptides would have no utility at all.²²⁶ Consequently, a skilled artisan would not have accepted the common disclosure’s assertion that “inactive mutants” are useful as contraceptive vaccines, particularly in humans.²²⁷

Finally, and most significantly, the common disclosure does not identify a single inactive PH20 mutant (with any number of substitutions) that was shown to have contraceptive effect.²²⁸ Therefore, at most, the common disclosure presents

²²⁵ EX1003, ¶¶ 112-13.

²²⁶ *Id.*; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App’x. 26, 30 (Fed. Cir. 2007).

²²⁷ EX1003, ¶¶ 112-13; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

²²⁸ EX1003, ¶ 113.

only a “research proposal” to discover such “inactive mutants.”²²⁹ It does not demonstrate possession of or enable the immense and diverse genus of PH20 polypeptides claimed, regardless of whether the claims are appropriately limited to “active mutants” or, instead, include “inactive mutants.”

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

The specifications of the pre-AIA ’731 Application and AIA ’035 Patent are substantially identical, and neither supports the challenged claims as § 112(a) requires by either. The claims are both PGR eligible and unpatentable under § 112(a).

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

²²⁹ See *Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) (“[t]he utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research”).

contemplated 2-3 particular combinations of amino acid replacements (from dozens listed), others encompassed substitutions at unspecified locations.²³⁰

Those the original claims do not provide § 112 support for the challenged claims.²³¹

VI. Challenged Claims 1-2 and 5-34 Are Unpatentable Under § 103

Claims 1-2, 6-14, 21, and 24-25 each define genera including one or both of two specific modified PH20 polypeptides: S312T PH20₁₋₄₄₇ and S312N PH20₁₋₄₄₇.

See § IV.D.2. Because both mutants would have been obvious from the '429

Patent in view of Chao and the knowledge of a skilled artisan, claims 1-2, 6-14 and

24-25 are unpatentable. Claims 5, 15-23, and 26-34 are also obvious: as each

recites attributes met by S312T or S312N PH20₁₋₄₄₇, or is suggested by the '429

Patent alone or with other prior art.

²³⁰ EX1026, at 335.

²³¹ *See, e.g., Ariad Pharms.*, 598 F.3d at 1349 (“original claim language” does not “necessarily disclose[] the subject matter that it claims”); *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993) (original claim amounted to no more than a “wish” or “plan” for obtaining the claimed DNA and “attempt[ed] to preempt the future before it has arrived”).

A. The Prior Art

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

Chao (EX1006) was published in "Biochemistry" in 2007. Chao is not discussed in the common disclosure of the '035 Patent and '731 Application and was not cited during examination.

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

B. Because S312T and S312N PH20₁₋₄₄₇ Would Have Been Obvious, Claims 1-2, 6-14, and 24-25 Are Unpatentable

Patentee's '429 Patent would have motivated a skilled artisan to produce modified PH20₁₋₄₄₇ polypeptides having a single amino acid substitution in non-essential regions of the protein. Guided by her familiarity with rational protein design and the teachings of the '429 Patent and Chao, the artisan would have readily identified single amino acid substitutions in non-essential regions of PH20₁₋₄₄₇ that would have been tolerated (*i.e.*, a PH20₁₋₄₄₇ with that single substitution would retain its enzymatic activity). S312T PH20₁₋₄₄₇ and S312N PH20₁₋₄₄₇ are two such examples. Because claims 1-2, 6-14 and 24-25 encompass at least one of these obvious variants of PH20₁₋₄₄₇, each is unpatentable.

1. Patentee's '429 Patent Motivates a Skilled Artisan to Make Single Amino Acid Substitutions in Non-Essential Regions of PH20₁₋₄₄₇

Patentee's '429 Patent, filed in 2003, describes its invention as soluble PH20 hyaluronidase glycoproteins ("sHASEGPs") that are enzymatically active at neutral pH.²³² It exemplifies and claims one such "sHASEGP" that terminates at position 447 (positions 36-482 of SEQ ID NO: 1).²³³

The '429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, in pharmaceutical compositions, and combined with other therapeutic agents (e.g., antibodies, chemotherapeutics), and illustrates administering such combinations subcutaneously to treat cancer and hyaluronidase disorders.²³⁴ PH20₁₋₄₄₇ was approved by the FDA as Hylenex[®] in 2005.²³⁵ The '429 Patent's teachings combined with the status of PH20₁₋₄₄₇ as an approved

²³² EX1005, 6:4-10, 10:30-59.

²³³ EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

²³⁴ EX1005, 8:25-9:4, 54:40-65, 56:34-57:36, 60:38-61:4, 63:41-61, 74:10-29, 76:19-77:36, 99:28-100:47.

²³⁵ EX1049, 1.

human therapeutic before 2011 would have induced a skilled artisan to focus on this particular PH20 polypeptide.²³⁶

Patentee's '429 Patent defines sHASEGPs as including wild-type PH20₁₋₄₄₇ and "equivalent" proteins "with amino acid substitutions that do not substantially alter activity" of the protein.²³⁷ It explains:

Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity ...²³⁸

The '429 Patent also explains that single amino acid substitutions can include "conservative" substitutions in Table 1, but that "[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions."²³⁹

²³⁶ EX1003, ¶ 195.

²³⁷ EX1005, 9:65-10:13; *see also id.* at 18:64-19:6 ("equivalent" proteins).

²³⁸ EX1005, 16:14-22.

²³⁹ EX1005, 16:24-36.

The '429 Patent thus teaches making a *particular* type of modification (a single amino acid substitution) in *particular* locations (non-essential regions of PH20) in a *particular* PH20 sequence (PH20₁₋₄₄₇) to yield equivalents of PH20₁₋₄₄₇ (*i.e.*, those that do not substantially alter the activity or function of PH20₁₋₄₄₇).²⁴⁰

The '429 Patent also motivates skilled artisans to undertake this effort to design and produce such single-amino acid substituted PH20₁₋₄₄₇ proteins because it assures them their efforts will be successful.²⁴¹ As it states, skilled artisans recognized that such “single amino acid substitutions in non-essential regions” of PH20₁₋₄₄₇ “do not substantially alter biological activity” of PH20₁₋₄₄₇. As such, a skilled artisan would have expected a PH20₁₋₄₄₇ 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 PH20₁₋₄₄₇ and other sHASEGPs.²⁴²

2. Chao Provides Information Useful for Engineering the Changes to PH20₁₋₄₄₇ 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 PH20₁₋₄₄₇

²⁴⁰ EX1003, ¶¶ 206-208; EX1004, ¶ 32.

²⁴¹ EX1003, ¶¶ 207-208.

²⁴² EX1003, ¶¶ 199-202, 207, 222.

would have recognized such changes could best be accomplished using rational design, which here involves determining (i) which regions are non-essential in PH20, and (ii) which single amino acids to substitute into positions in those non-essential regions.²⁴³

The '429 Patent was written eight years before 2011. Given that, a skilled artisan would have looked for additional published insights into the structure of human hyaluronidase enzymes like PH20.²⁴⁴ That would have led the person directly to Chao (EX1006), which reported an experimentally determined structure for human HYAL1, and provided new insights into the shared characteristics of human hyaluronidase enzymes.²⁴⁵

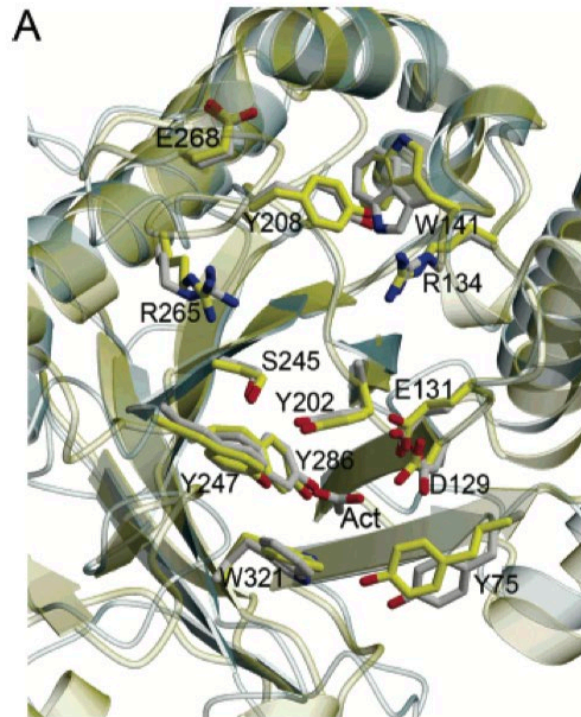
First, by superimposing the HYAL1 and bee venom hyaluronidase structures, Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues in it that interact with HA.²⁴⁶

²⁴³ EX1003, ¶¶213-14.

²⁴⁴ EX1003, ¶¶ 86, 209; EX1004, ¶ 88.

²⁴⁵ EX1003, ¶¶ 86, 209-11; EX1004, ¶ 88; EX1006, 6912-17.

²⁴⁶ EX1006, 6917 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1004, ¶¶ 89-91; EX1003, ¶¶ 81-82.



The '429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20,²⁴⁷ and taught that hyaluronidase domains share similarity among and between species, including residues necessary for enzymatic activity.²⁴⁸

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

²⁴⁷ EX1005, 4:12-22, 86:49-53, 88:14-24.

²⁴⁸ EX1005, 2:6-67, 4:11-22.

conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).²⁴⁹

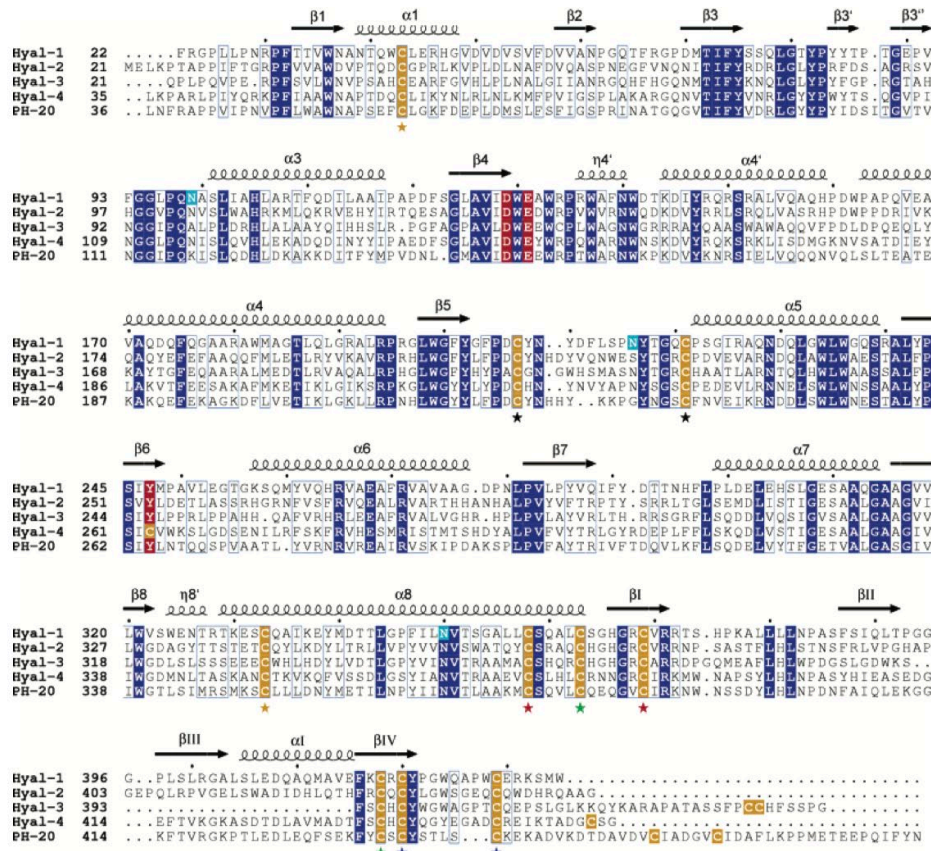


FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative replacements are blocked in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

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

²⁴⁹ EX1006, 6916; EX1003, ¶ 83; EX1004, ¶ 92.

catalytic domain (discussed above, § V.A.1.b.iii), and identified a characteristic pattern for the Hyal-EGF domain in PH20 at positions 337-409.²⁵⁰

3. A Skilled Artisan Would Have Identified Position 312 as Being in a Non-Essential Region of PH20₁₋₄₄₇ in 2011

To implement the '429 Patent's suggestion to produce modified PH20₁₋₄₄₇ polypeptides with single amino acid substitutions in non-essential regions that retain hyaluronidase activity, the skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011.²⁵¹ The person would have done that using conventional sequence alignment tools in conjunction with the information in the '429 Patent and in Chao, as well as information publicly known in 2011.²⁵²

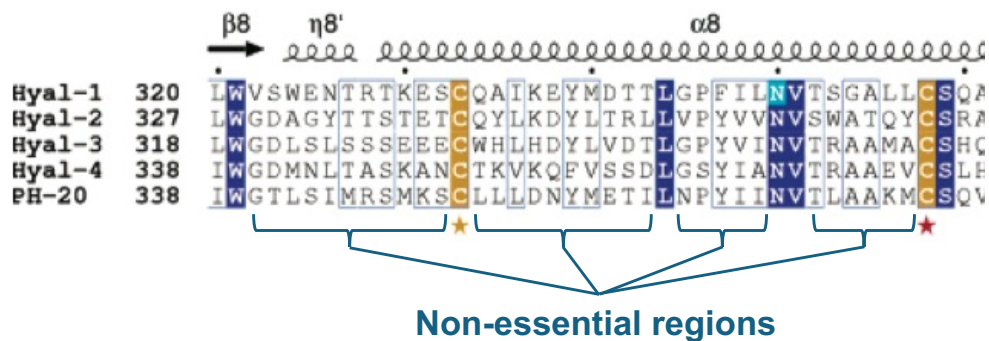
A multiple-sequence alignment identifies non-essential regions in PH20—they are the sequences between essential residues and are positions at which variations occur at a frequency above ~5% (illustrated using Chao below).²⁵³

²⁵⁰ EX1006, 6911; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84-85.

²⁵¹ EX1003, ¶¶ 212-214; EX1004, ¶¶ 22, 25-30, Appendix D-3.

²⁵² EX1003, ¶¶ 20-21, 213-215; EX1004, ¶¶ 22-24; EX1017, 224-26.

²⁵³ EX1004, ¶¶ 31-32, Appendix D-2; EX1003, ¶ 215; EX1006, 6916.

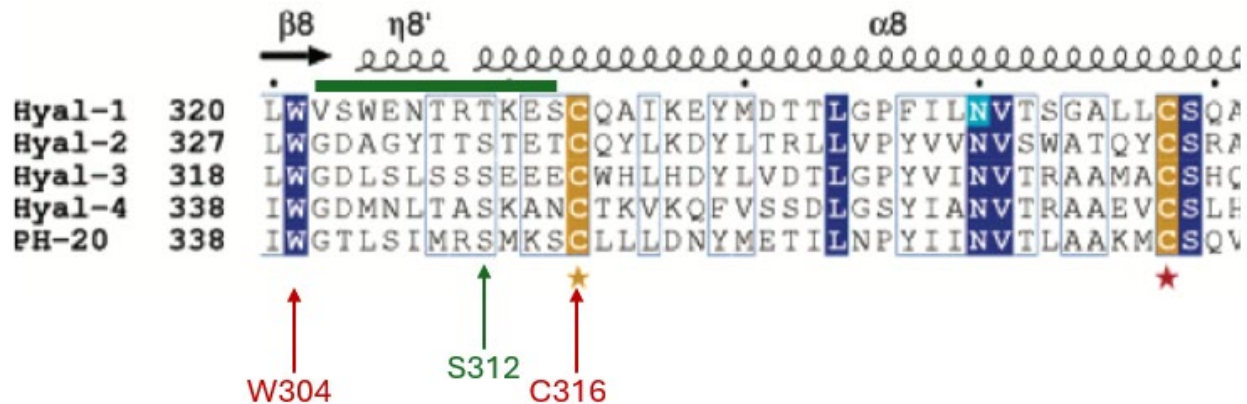


Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps. He first identified 88 homologous hyaluronidase protein sequences that had been published by December 29, 2011.²⁵⁴ Dr. Park then prepared a multiple-sequence alignment of the 88 homologous proteins, similar to what Chao did with the five human hyaluronidases, and from that alignment identified essential (Appendix D-3) and non-essential (Appendix D-2) residues.²⁵⁵

²⁵⁴ EX1004, ¶¶ 27, 125-128; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

²⁵⁵ EX1004, ¶¶ 28-32, 129-130, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

Position 312 is within a non-essential region of PH20₁₋₄₄₇, which is shown by Dr. Park's analysis, and also by Chao's Figure 3; both report the same bounding essential residues (*i.e.*, W304 and C316) (below).²⁵⁶



Following the guidance and information in the '429 Patent and Chao, and assessing information publicly available in December 2011 using conventional sequence analysis tools, a skilled artisan would have readily identified position 312 as a position within a non-essential region PH20₁₋₄₄₇.²⁵⁷

²⁵⁶ EX1003, ¶ 217; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.

²⁵⁷ EX1003, ¶ 220; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

4. A Skilled Artisan Would Have Found Threonine or Asparagine to Be Suggested as an Obvious Single Amino Acid Substitution for Serine at Position 312 of PH20₁₋₄₄₇

The multiple-sequence alignment reveals a second powerful insight: it identifies *which* amino acids have been tolerated at specific positions in the amino acid sequence of homologous, stable and active naturally occurring hyaluronidase enzymes.²⁵⁸ This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms those variations in the sequences of a protein that do not yield stable and active forms of the protein.²⁵⁹ A skilled artisan can readily compile a list of amino acids that have been tolerated at positions within non-essential regions of PH20 using a multiple-sequence alignment of homologous hyaluronidase enzymes.²⁶⁰

²⁵⁸ EX1003, ¶¶ 20, 49, 214, 218, 220; EX1004, ¶¶ 21-22.

²⁵⁹ EX1003, ¶¶ 20, 214; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 (“Evolution provides a tremendously useful model for protein design. ... By considering the common features of the sequences of these proteins, it is possible to deduce the key elements that determine protein structure and function—even in absence of any explicit structural information.”); EX1014, 351.

²⁶⁰ EX1003, ¶¶ 218, 220; EX1004, ¶¶ 21-22.

Using his multiple-sequence alignment of the 88 hyaluronidase proteins known by December 2011, Dr. Park identified and calculated the frequency of each amino acid that occurs at positions corresponding to position 312 in PH20 (shown below).²⁶¹ The wild-type residue at position 312 in PH20 is serine (S), which occurs in ~65% of the proteins (including PH20). The second-most prevalent amino acid at position 312 is threonine (T) (~25%), which is present in 22 different hyaluronidase proteins. Asparagine (N) appears third-most frequently (~6%, 5 proteins).

AA at position 347/312 in PH20₁₋₄₄₇ Most frequent AA at position in set of proteins

wt 347:	S	64.77	S	64.77
res386:	S	57	64.77	
res386:	T	22	25	
res386:	N	5	5.68	
res386:	R	2	2.27	
res386:	D	1	1.13	
res386:	-	1	1.13	

% of occurrence of AA in set of proteins

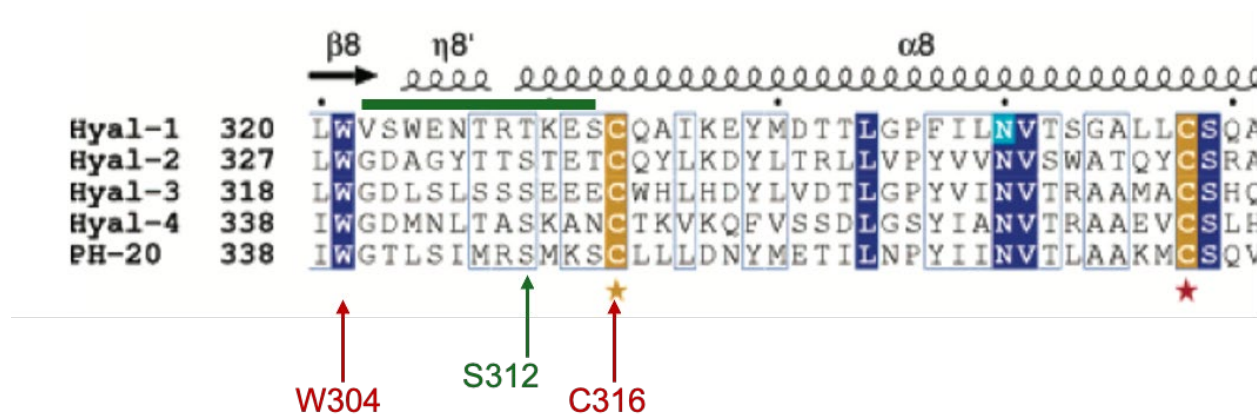
A skilled artisan would have found it obvious to substitute threonine (T) or asparagine (N) for serine (S) at position 312 as a single amino acid substitution in a non-essential region of PH20₁₋₄₄₇.²⁶²

²⁶¹ EX1004, ¶¶ 30-32, 41-43, 106, 111, 121, Appendix D-1; EX1003, ¶ 218;

²⁶² EX1003, ¶¶ 214, 218-22; EX1004, ¶¶ 41-42, 106.

First, threonine and asparagine are the second and third-most prevalent amino acids found at positions corresponding to 312 in PH20, respectively.²⁶³

These amino acids would have been the obvious candidates to substitute for serine at position 312 of PH20, as they are each tolerated at that position in many naturally occurring homologous hyaluronidase enzymes.²⁶⁴ Threonine also occurs at the position corresponding to 312 in another human hyaluronidase, HYAL1.²⁶⁵



Second, Chao identifies residue S312 as being the first residue of the α8 α-helix in PH20, which is termed the “N-cap” residue (above).²⁶⁶ Asparagine was known to be the most preferred residue for an N-cap residue at the start of an α-

²⁶³ EX1004, ¶¶ 43, 106, 111, 121; EX1003, ¶ 218.

²⁶⁴ EX1003, ¶¶ 218-21; EX1004, ¶¶ 106, 111, 121.

²⁶⁵ EX1006, 6916, Fig. 3.

²⁶⁶ EX1003, ¶ 219; EX1004, ¶¶ 108-109.

helix, in proteins, and threonine was known to be highly favored at that position.²⁶⁷

A skilled artisan thus would have found both asparagine and threonine to be obvious substitutes for the serine in the N-cap residue at position 312 for the $\alpha 8$ helix in PH20.²⁶⁸

Third, the serine at position 312 is solvent-exposed.²⁶⁹ A skilled artisan would recognize that other hydrophilic amino acids, such as asparagine and threonine, would be favored in this hydrophilic position, and would be obvious choices for this reason.²⁷⁰

Fourth, the '429 Patent identifies threonine as a conservative amino acid substitution for serine in its Table 1.²⁷¹ A skilled artisan would understand the '429 Patent to be suggesting replacing a serine residue in a non-essential position in PH20 (such as at position 312) with a threonine residue.²⁷²

²⁶⁷ EX1003, ¶ 220; EX1004, ¶ 120; EX1077, 1325; EX1076, 1650-52; EX1078, 2-3.

²⁶⁸ EX1003, ¶ 220; EX1004, ¶¶ 120-121.

²⁶⁹ EX1003, ¶ 219; EX1004, ¶¶ 32, 108.

²⁷⁰ EX1003, ¶ 220; EX1004, ¶¶ 32, 108-10, 115, 119.

²⁷¹ EX1005, 16:7-36.

²⁷² EX1003, ¶¶ 208, 220.

For all these reasons, a skilled person would have found it obvious to change the serine (S) at position 312 to either threonine (T) or asparagine (N) in PH20₁₋₄₄₇.

²⁷³

5. A Skilled Artisan Would Have Reasonably Expected the S312T and S312N Substitutions in PH20₁₋₄₄₇ to Yield Enzymatically Active PH20 Proteins

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

Replacing the serine (S) at position 312 with threonine (T) or asparagine (N) yields a PH20₁₋₄₄₇ with a single amino acid substitution in a non-essential region of the polypeptide.²⁷⁴ In its '429 Patent, Patentee stated:

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

Patentee also secured claims in the '429 patent to modified PH20₁₋₄₄₇ proteins with at least one substitution (*e.g.*, claim 1), despite not providing examples of PH20 proteins with any substitutions. Patentee, thus, made and relied on its statements that a skilled artisan would have expected *any* single amino acid

²⁷³ EX1003, ¶¶ 217-220.

²⁷⁴ See § VI.B.3; EX1003, ¶¶ 217-218; EX1004, ¶ 32.

²⁷⁵ EX1005, 16:17-20.

substitution in *any* non-essential position of PH20₁₋₄₄₇ to not substantially affect the activity of the enzyme, and particularly ones in Table 1. Patentee should not be permitted to now contend a skilled artisan would not have reasonably expected that the S312T or S312N substitutions in PH20₁₋₄₄₇ would yield an enzyme with substantially the same activity as unmodified PH20₁₋₄₄₇.

b) Skilled Artisans Would Reasonably Expect S312T and S312N to be Tolerated in PH20₁₋₄₄₇

Independently, a skilled artisan would have reasonably expected the S312T and S312N substitutions to not substantially alter the biological activity (hyaluronidase activity) of PH20₁₋₄₄₇. Both experts noted that many naturally occurring homologous hyaluronidase proteins contain either threonine or asparagine at the position corresponding to position 312 in PH20 (including for threonine in human HYAL1 (Chao)), which suggests both would be tolerated at position 312 in PH20.²⁷⁶ Asparagine and threonine are both commonly n-cap positions of an α -helix, and both have hydrophilic characteristics compatible with the solvent-exposed environment of position 312.²⁷⁷ A skilled artisan thus would

²⁷⁶ EX1003, ¶ 214; EX1004, ¶¶ 111, 121.

²⁷⁷ EX1003, ¶ 220; EX1004, ¶ 120; EX1077, 1325; EX1076, 1650-52; EX1078, 2-3.

have reasonably expected the S312T and S312N substitutions to be tolerated in PH20₁₋₄₄₇.²⁷⁸

c) A PH20 Structural Model Confirms that PH20₁₋₄₄₇ Would Tolerate Threonine and Asparagine at 312

Dr. Park further assessed whether single amino acid substitutions in PH20₁₋₄₄₇ would be tolerated, including S312T and S312N, using a PH20 protein structural model generated by SWISS-MODEL using Chao's HYAL1 structure as the template, as would have been done in 2011 by a skilled artisan.²⁷⁹

Dr. Park explains that his PH20 model was reliable in the region of position 312 of PH20 based on QMEAN values,²⁸⁰ and would be very similar to a PH20 model generated by SWISS-MODEL in 2011 (*e.g.*, it used 165 conserved positions in the backbone of the two proteins).²⁸¹

²⁷⁸ EX1003, ¶¶ 221-222.

²⁷⁹ EX1004, ¶¶ 39-40, 131-32; EX1003, ¶¶ 225, 227; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

²⁸⁰ EX1004, ¶¶ 133-35 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

²⁸¹ EX1004, ¶¶ 136-37, 141; EX1038, 3382-4; EX1017, 229-230; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

Dr. Park also devised a consistent, objective methodology for assessing substitutions using the PH20₁₋₄₄₇ model.²⁸² Factors he considered included, *inter alia*, the number of neighboring residues at position 312 (*i.e.*, those within 5 Å), the various possible interactions between neighbors (*e.g.*, hydrophobic, charged, van der Waals, steric, etc.), and solvent accessibility.²⁸³ Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*, hydrophobic-hydrophilic, effects on secondary structures, size related issues such as steric clashes or creation/filling of “holes” in the structure).²⁸⁴

Dr. Park assessed the environment of position 312 visually by comparing the wild-type with the version incorporating substituted amino acids at position 312 using functionality within the viewer (PyMol) and as a modeled sequence generated from the PH20₁₋₄₄₇ sequence incorporating the single substitution in

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

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

²⁸⁴ EX1004, ¶¶ 62-63, 85.

SWISS-MODEL.²⁸⁵ These technologies were available in 2011.²⁸⁶ He used his methodology to assess substitutions representing diverse interactions, and confirmed it provided a consistent, objective and unbiased evaluation of substitutions.²⁸⁷

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

<i>Score</i>	<i>Expected Impact</i>	<i>Expected Toleration</i>
1	Significantly Destabilized	Likely Not Tolerated
2	Neutral or Minor Impacts	Tolerated
3	Improved Stability	Tolerated

Dr. Park assigned a score of 2 for the S312T and S312N substitutions in PH20₁₋₄₄₇, indicating that each would not be expected to significantly impact stability.²⁸⁹ He observed that in the wild-type environment, position 312 is a

²⁸⁵ EX1004, ¶¶ 61, 107, 110, 116, 122, 146-48; EX1003, ¶¶ 22, 49, 225, 227.

²⁸⁶ EX1004, ¶¶ 131, 136-37, 145, 147-49; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4.

²⁸⁷ EX1004, ¶¶ 102-103.

²⁸⁸ EX1004, ¶¶ 85-87.

²⁸⁹ EX1004, ¶¶ 117, 123, Appendix C.

solvent exposed position, and that several amino acids (including T and N) occur at this position in homologous proteins.²⁹⁰

Dr. Park identified several reasons why threonine would be tolerated at position 312 of PH20. One is that threonine is a hydrophilic residue, making it compatible with the solvent-exposed environment at position 312.²⁹¹ Also, like the S312 in PH20, the oxygen of threonine's hydroxyl group plays a stabilizing role by acting as a hydrogen bond acceptor for the hydrogen on the amide bond between positions 314 and 315 (image below, 3.1 line).²⁹² This interaction occurs in the HYAL1 and bee venom structures, which both have threonine at the position corresponding to 312.²⁹³ Threonine in position 312 also will have van der Waals interactions with another nearby residue (M313) (4.0 line below), further enhancing stability around this position.²⁹⁴ Overall, Dr. Park found that the S312T substitution would have a neutral effect on the protein's stability.²⁹⁵

²⁹⁰ EX1004, ¶¶ 108, 106.

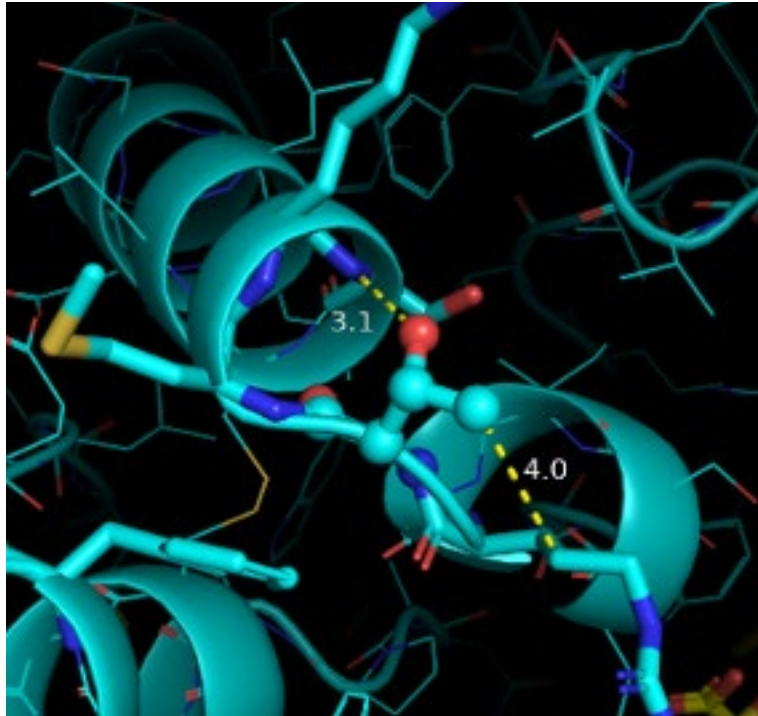
²⁹¹ EX1004, ¶ 112.

²⁹² EX1004, ¶ 114.

²⁹³ EX1004, ¶ 115.

²⁹⁴ EX1004, ¶ 114.

²⁹⁵ EX1004, ¶ 117.



Dr. Park also identified several reasons why asparagine would be tolerated at position 312 of PH20. Like threonine and serine, it is a hydrophilic residue and compatible with the solvent-exposed environment at position 312.²⁹⁶ He also observed that the carbonyl oxygen in asparagine can dynamically form hydrogen bonds with the hydrogen on the amide bond between positions 314 and 315.²⁹⁷ Further, Dr. Park identified asparagine as the most common n-cap residue for α -

²⁹⁶ EX1004, ¶ 120.

²⁹⁷ *Id.*

helices.²⁹⁸ Overall, Dr. Park found that the S312N substitution would have a neutral effect on the stability of the protein.²⁹⁹

Dr. Park's visualization-based assessment is a technique that was prevalent in 2011.³⁰⁰ Similarly, his technique of assessing interactions between neighbors and assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications.³⁰¹

Dr. Hecht reviewed Dr. Park's analysis and conclusions and agreed with both.³⁰² Through his own assessment, he observed that threonine and asparagine would be likely tolerated at position 312. For example, he explained that each

²⁹⁸ EX1004, ¶ 120.

²⁹⁹ EX1004, ¶ 123.

³⁰⁰ EX1017, 228 (“... a structural biologist's intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this.”); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 22, 49, 225, 227.

³⁰¹ EX1004, ¶¶ 48-52; EX1031, 459, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 227.

³⁰² EX1003, ¶ 229.

amino acid's hydrophilic character would be compatible with the high solvent accessibility of position 312.³⁰³ He also pointed out that asparagine was known to be the most common N-cap residue in α -helix structures in proteins, while threonine was known to have a high prevalence at N-cap positions; both points suggest they will be tolerated at position 312.³⁰⁴

The common disclosure defines an "active mutant" as a modified PH20 polypeptide with at least ~40% of the activity of unmodified PH20₁₋₄₄₇.³⁰⁵ Drs. Hecht and Park each independently concluded that the S312T and S312N substitutions would have been tolerated by PH20₁₋₄₄₇, meaning it would exhibit comparable hyaluronidase activity to unmodified PH20₁₋₄₄₇ (*i.e.*, activity well above 40%).³⁰⁶ A skilled artisan considering the S312T and S312N substitutions in PH20₁₋₄₄₇ would have reasonably expected that both would exhibit at least 40% of the activity of unmodified PH20₁₋₄₄₇.³⁰⁷

³⁰³ EX1003, ¶ 230.

³⁰⁴ EX1003, ¶¶ 220, 231-32; EX1076, 1648, 1650-52; EX1077, 1325, 1331, 1334; EX1078, 2-3.

³⁰⁵ EX1001, 75:47-52; *also id.* at 79:29-33.

³⁰⁶ EX1003, ¶¶ 229-232, 234; EX1004, ¶¶ 117, 123.

³⁰⁷ EX1003, ¶ 234.

Based on the '429 Patent, Chao, and information available in 2011, the S312T and S312N PH20₁₋₄₄₇ mutant polypeptides would have been obvious to a skilled artisan in 2011. And because claims 1-2, 6-14, and 24-25 each encompass one or both of the single-replacement modified S312T and S312N PH20₁₋₄₄₇ polypeptides, each claim is unpatentable.

C. Dependent Claims 5, 15-23, and 26-34 Are Obvious

None of the dependent claims define subject matter that is independently patentable from claims 1-2, 6-14, and 24-25. For the reasons below, each would have been obvious to a skilled artisan.

1. Claims 5 and 15

Claims 5 and 15 require the modified PH20 polypeptide to be “a soluble PH20 polypeptide” and, in the case of claim 15, “C-terminally truncated.”

The '429 Patent indicates that PH20₁₋₄₄₇ exists as a soluble form of the PH20 protein because it omits the C-terminal residues above position 448 (483) containing the GPI anchor sequence.³⁰⁸ A skilled artisan would have expected that changing serine to threonine or asparagine at position 312 would not change the

³⁰⁸ EX1005, 3:57-62; 87:52-88:24.

solubility of the PH20₁₋₄₄₇ as it would not meaningfully alter the structure of the protein.³⁰⁹

2. Claims 16-18

Claims 16-18 require the modified PH20 polypeptide to “comprise[] one or more post-translational modifications” including glycosylation (claims 16-17) and be a “glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues” (18).

The '429 Patent teaches (i) that human PH20 must be glycosylated to exhibit activity, and (ii) expression of PH20₁₋₄₄₇ in mammalian (CHO) host cells that yield active forms of PH20₁₋₄₄₇.³¹⁰ It further teaches that “N- and O-linked glycans are attached to polypeptides through asparagine-N-acetyl-D-glucosamine ... linkages,” and claims PH20 polypeptides (including PH20₁₋₄₄₇) having asparagine-linked sugar moieties.³¹¹ Frost reports that the recombinant production of PH20₁₋₄₄₇ in CHO cells “resulted in a 447 amino acid 61 kDA glycoprotein with a properly processed amino terminus and 6 N-linked glycosylation sites.”³¹²

³⁰⁹ EX1003, ¶¶ 196, 203, 222.

³¹⁰ EX1005, 95:13-30; 40:41-51, 89:53-91:67; 88:5-9.

³¹¹ EX1005, 3:27-35, claims 1, 6.

³¹² EX1013, 432.

Based on the '429 Patent and knowledge in the art, a skilled artisan would have found it obvious to produce S312T PH20₁₋₄₄₇ in a CHO cell, and that doing so causes six N-linked glycosylation sites to be glycosylated.³¹³

3. Claims 23, 26-32

Claim 23 specifies a pharmaceutical composition comprising any modified PH20 polypeptide in the genus of claim 1. Claims 26-29 add a “therapeutically active agent formulated in the same composition or in a separate composition” (26), and that the active agent may be a “drug” (27) or “chemotherapeutic agent” (28) or “antibody” (29).

Claims 30-32 concern methods of treating “hyaluronan-associated disease” (29) such as cancer (30) or a “solid tumor” by administering any of the modified PH20 polypeptides captured by claim 1.

The '429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*, PH20₁₋₄₄₇), alone or in combination with other therapeutic agents including antibodies, small molecule drugs, chemotherapeutics, and agents used in treating

³¹³ EX1003, ¶¶ 197-98, 203-04.

cancer and hyaluronan-associated disease.³¹⁴ It similarly describes and claims methods of administering them subcutaneously via formulations that combine an enzymatically active hyaluronidase protein with another therapeutic agent, which together enable “spreading” of the therapeutic agent after injection.³¹⁵

A skilled artisan would have appreciated that a single-replacement PH20₁₋₄₄₇ polypeptide with comparable hyaluronidase activity to PH20₁₋₄₄₇ (such as the S312T mutant) would be equivalently useful in the therapeutic compositions, methods of administration, and methods of treatment described in the '429 Patent for PH20₁₋₄₄₇.³¹⁶ Indeed, in the '429 Patent, Patentee secured claims encompassing pharmaceutical compositions containing certain modified PH20 polypeptides and chemotherapeutic agents despite the absence of any exemplification.³¹⁷ Claims 23 and 26-32 also impose no restrictions on the makeup of the pharmaceutical

³¹⁴ EX1005, 8:60-9:4, 54:40-55:35, 56:28-57:21, 55:61-56:9, 56:66-57:21, 63:41-44, 73:4-74:29, claims 14, 29, 33.

³¹⁵ EX1005, 8:25-38, 56:28-56, 57:22-36, 58:59-59:12, 63:40-64:4, 76:18-77:37, claim 27.

³¹⁶ EX1003, ¶¶ 199-202, 207, 221-22, 234.

³¹⁷ EX1005, claims 29, 30, 50.

composition. A skilled artisan would have found such compositions and methods of administration/treatment to have been obvious from the '429 Patent.³¹⁸

4. Claims 19-22, 33-34

Claims 19-20 and 33-34 concern conjugation of a modified PH20 polypeptide to (i) a polymer (claim 19) that may be polyethylene glycol (claim 20), (ii) a moiety such as a toxin, drug, label or multimerization domain (claim 33) or (iii) to an Fc domain (claim 34). Claim 21 specifies that the modified PH20 polypeptide further comprises a heterologous signal sequence, while Claim 22 specifies a chimeric peptide comprising the modified PH20 polypeptides of claim 1.

A skilled artisan would have found these further modifications to the S312T or S312N PH20₁₋₄₄₇ mutants obvious from the '429 Patent.³¹⁹ The '429 Patent teaches PH20₁₋₄₄₇ proteins with mutations (“sHASEPGs”) can be (i) “modif[ied]” “with polymers such as polyethylene glycol”;³²⁰ (ii) conjugated to “one or more targeting agents” (*e.g.*, any moiety that specifically binds to a receptor);³²¹ (iii)

³¹⁸ EX1003, ¶¶ 199-202, 207.

³¹⁹ EX1003, ¶¶ 203, 205.

³²⁰ EX1005, 3:64-4:1, 4:45-53, 26:20-28:4.

³²¹ EX1005, 18:33-52.

attached to a label;³²² and (iv) incorporated into fusion (*i.e.*, “chimeric”) proteins.³²³ It also teaches expression of modified PH20 polypeptides that incorporate a heterologous signal sequence.³²⁴

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

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

Patentee is likely to dispute that the S312T and S312N PH20₁₋₄₄₇ are obvious, for example, because the S312N variant is reported to have unexpectedly high hyaluronidase activity as a single substitution mutant. Demonstrating that result for one mutant out of the $\sim 10^{59}$ and 10^{112} modified PH20 polypeptides encompassed by the claims, however, utterly fails to establish a nexus between that evidence and the claims. The argument is inapplicable to the S312T mutant, which

³²² EX1005, 38:40-49, 40:15-21.

³²³ EX1005, 18:33-52, 47:10-22, 51:25-30.

³²⁴ EX1005, 34:33-37; 88:28-90:15 (“Kappa leader sequence” used in expression of PH20 polypeptides).

exhibits reduced activity.³²⁵ As explained in § V.A.1, the single-substitution S312T and S312N PH20₁₋₄₄₇ mutants are not representative of the numerous, structurally different proteins encompassed by the claims, particularly those expected to be inactive. No evidence or explanation is provided in the common disclosure that resolves this confusion.

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

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

No litigation involving the '035 Patent is pending, making discretionary denial unwarranted under the factors in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020).

The examination record also does not warrant the Board exercising its discretion to not institute. As explained in § IV.C, no obviousness rejections were raised during prosecution.³²⁶ The present obviousness grounds also are based in part on Chao (EX1006), which was not cited or considered during examination,

³²⁵ EX1001, Table 9, column 248.

³²⁶ EX1002, 465-67.

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

Also, while certain indefiniteness rejections were imposed and overcome by claim amendments,³²⁷ the Examiner erred by not rejecting the claims for lack of written description and non-enablement. *See* §§ V.A and V.B.

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

VIII. CONCLUSION

For the foregoing reasons, the challenged claims are unpatentable.

Dated: December 27, 2024

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³²⁷ EX1002, 465-67, 538-41.

EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,123,035
1002	File History of U.S. Patent No. 12,123,035
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," <i>Biochemistry</i> , 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," <i>Chem. Rev.</i> 106:818-839 (2006)
1009	Jedzrejas et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," <i>Proteins: Structure, Function and Bioinformatics</i> , 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," <i>J. Biol. Chem.</i> , 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," <i>Eur. J. Biochem.</i> , 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," <i>Nature Protocols</i> , 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," <i>Expert Opinion on Drug Delivery</i> , 4(4):427-440 (2007)
1014	Brandon & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '035 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, "Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes," <i>Methods in Enzymology</i> , 388:176-186 (2004)
1017	Green, "Computer Graphics, Homology Modeling, and Bioinformatics," <i>Protein Eng'g & Design</i> , 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," <i>Curr. Opin. Biotechnol.</i> , (4):378-384 (2005)
1019	Hardy et al., "Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20," <i>Reprod.</i> , 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," <i>Am. J. Reprod. Immunol.</i> , (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," <i>J. Biol. Chem.</i> , 277(33):30310-4 (2002)
1022	Primakoff et al., "Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs," <i>Biol Reprod.</i> , 56(5):1142-6 (1997)
1023	Tung et al., "Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20," <i>Biol. Reprod.</i> , 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," <i>BioDrugs</i> , 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	[Reserved]
1028	[Reserved]
1029	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," <i>FEBS Letters</i> , 3:545-548 (1993)

No.	Exhibit Description
1030	Sills, "Retraction," <i>Science</i> , 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," <i>J. Mol. Biol.</i> , 353:459-473 (2005)
1032	Wang & Moulton, "SNPs, Protein Structure, and Disease," <i>Hum. Mutation</i> , 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," <i>Structure</i> , 8:1025-1035 (2000)
1034	"Negative Results," <i>Nature: Editorials</i> , 453:258 (2008)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," <i>Protein Sci.</i> , 12:1406-1417 (2003)
1036	Hayden, "Chemistry: Designer Debacle," <i>Nature</i> , 453:275-278 (2008)
1037	Benkert et al., "Toward the Estimation of the Absolute Quality of Individual Protein Structure Models," <i>Bioinformatics</i> , 27:343-350 (2010)
1038	Schwede et al., "SWISS-MODEL: An Automated Protein Homology-Modeling Server," <i>Nucleic Acids Res.</i> , 31:3381-3385 (2003)
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007).
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," <i>PNAS</i> , 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," <i>PNAS</i> , 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," <i>Nature Comm.</i> , 14 (2023)
1043	Sievers et al., "Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega," <i>Molecular Sys. Biology</i> , 7.1 (2011)
1044	Mihel, "PSAIA – Protein Structure and Interaction Analyzer," <i>BMC Structural Biology</i> , 8:21 (2008)

No.	Exhibit Description
1045	Redline Comparison of the '731 and '035 Specifications
1046	Beasley & Hecht, "Protein Design: The Choice of <i>de Novo</i> Sequences," J. Biological Chemistry, 272:2031-2034 (1997)
1047	Xiong et al., "Periodicity of Polar and Nonpolar Amino Acids is the Major Determinant of Secondary Structure in Self-Assembling Oligomeric Peptides," PNAS, 92: 6349-6353 (1995)
1048	Hayden, "Key Protein-Design Papers Challenged," Nature, 461:859 (2009)
1049	KEGG, DRUG: Hyaluronidase (<i>human recombinant</i>), available at: https://www.genome.jp/entry/D06604
1050	Pace & Scholtz, "A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins," Biophysical J. 75:422-427 (1998)
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
1057	Ph20_pre2011.aln-clustal_num
1058	Ph20_pre2011 Alignment html
1059	Leisola & Turunen, "Protein Engineering: Opportunities and Challenges," Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	Hecht et al., "De Novo Proteins from Designed Combinatorial Libraries," Protein Sci., 13:1711-1723 (2004)
1061	Rosengren et al., "Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration," AAPS J., 17:1144-1156 (2015)
1062	[Reserved]
1063	[Reserved]

No.	Exhibit Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with S312T Mutation
1071	Swiss Model Printout of PH20 Model with S312N Mutation
1072	[Reserved]
1073	[Reserved]
1074	[Reserved]
1075	[Reserved]
1076	Richardson & Richardson, "Amino Acid Preferences for Specific Locations at the Ends of α Helices," <i>Science</i> , 240, 1648-1652 (1988)
1077	Doig & Baldwin, "N- and C-capping Preferences for All 20 Amino Acids in α -helical Peptides," <i>Protein Science</i> , 4:1325-1336 (1995)
1078	Keedy et al., "The Role of Local Backrub Motions in Evolved and Designed Mutations," <i>PLoS Computational Biology</i> , 8(8):1-10 (August 2012)

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,644 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 27th day of December, 2024, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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