

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. PGR2025-00042
U.S. Patent No. 12,037,618

PETITION FOR POST GRANT REVIEW

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I. Introduction

Petitioner Merck Sharp & Dohme LLC (“Merck”) requests post grant review of U.S. Patent No. 12,037,618 (“’618 Patent”).

Claims 1-40 of the ’618 Patent define modified human PH20 polypeptides that (i) *must have* one amino acid substitution at position 309, and (ii) *may have* between 20 and 41 additional substitutions at *any* of 430+ positions, and to *any* of 19 other amino acids. These parameters capture between 10^{60} and 10^{113} distinct PH20 polypeptides, a scale that is unfathomable—the collective weight of one molecule of each polypeptide in the smallest set exceeds the weight of the Earth, and simply making and testing each set per the patent’s methodology would require lifetimes of “making and testing” experiments. Within these massive sets of modified PH20 polypeptide sequences being claimed are undisclosed and unknown numbers of enzymatically active PH20 proteins (“active mutants”).

These immensely broad claims are unpatentable for three independent reasons. The first two are linked to their extreme breadth—measured against the common disclosure of the ’618 Patent and its ultimate parent ’731 Application,¹ each utterly fails the written description and enablement requirements of § 112(a). That also precludes the claims from a valid § 120 benefit claim to the ’731

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

Application, the only non-provisional application filed before March 16, 2013, thus making the '618 Patent PGR eligible.

Regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by all enzymatically active, multiply-modified PH20 polypeptides within each claim's scope—the *only* type of modified PH20 polypeptide within each claims' scope with an established utility. The disclosed examples also are not representative of the “active mutant” subgenus: 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, and even capture combinations the disclosure says to avoid in enzymatically active PH20 mutants.

Regarding enablement, equally fatal problems exist: the disclosure identifies *no* enzymatically active modified PH20 polypeptide with 2 or more substitutions, much less affirmatively guides the selection of *which* of the 10^{60+} combinations of substitutions will yield such enzymes. The only process it discloses for making multiply-substituted active mutants is a prophetic “trial-and-error discovery” experiment that must be repeated innumerable times until between 10^{60} and 10^{113} unique proteins have been made and tested to determine which are active mutants. That is far more than undue experimentation—it is impossible. Indeed, the

Supreme Court found comparable claims non-enabled due to the necessity of performing analogous “trial and error discovery” to discover a much smaller genus of claimed proteins.²

The common disclosure also contemplates “inactive” mutants whose only putative utility is in contraceptive vaccines. But reading the claims as encompassing them only exacerbates their §112 deficiencies. That is because the common disclosure does not describe a representative number of position 309 substituted inactive mutants (it describes none), and a skilled artisan would still have to “make and test” 10^{60+} mutants to discover which (if any) had (implausible) contraceptive utility. That same testing of 10^{60+} mutants is also necessary to weed out which modified PH20 polypeptides within the scope of the claims cannot be made or do not fold—inoperative species that do not have either of the utilities listed in the disclosure.

Finally, claims 1-2, 4-5, 7-22 and 24-40 are unpatentable because each captures one obvious PH20₁₋₄₄₇ mutant that replaces the isoleucine at position 309 with asparagine (I309N PH20₁₋₄₄₇), or its use in compositions or methods. But Patentee’s prior ’429 Patent (EX1005) directs artisans to make single amino acid substitutions in non-essential regions of PH20₁₋₄₄₇ (and expressly claimed them).

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

Skilled artisans implementing that guidance in 2011 would have found Chao (EX1006)—an intervening publication ignored in the common disclosure—would have (i) readily identified position 309 as being in a non-essential region of PH20, (ii) found it obvious to change isoleucine at position 309 to asparagine, and (iii) reasonably expected the mutant to retain enzymatic activity because that is what Patentee said in its '429 Patent (“Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity”).³ Because the claims capture that obvious mutant and obvious compositions and methods that use it, they are unpatentable.

The '618 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 '618 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 '618 Patent.

³ EX1005, 16:17-22.

The '618 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

A patent is PGR eligible if it issued from an application filed after March 16, 2013 “if the patent contains ... at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought.” *See Inguran, LLC v. Premium Genetics (UK) Ltd.*, Case PGR2015-00017, Paper 8 at 16-17 (P.T.A.B. Dec. 22, 2015); *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17 at 8 (P.T.A.B. Jan. 29, 2016); *Collegium Pharm., Inc. v. Purdue Pharma L.P.*, 2021 WL 6340198, at *14-18 (P.T.A.B. Nov. 19, 2021) (same) *aff'd Purdue Pharma L.P. v. Collegium Pharm., Inc.*, 86 F.4th 1338, 1346 (Fed. Cir. 2023); *Intex Recreation Corp. v. Team Worldwide Corp.*, 2020 WL 2071543, at *26 (P.T.A.B. Apr. 29, 2020) (same).

Only one of the applications to which the '618 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 '618 Patent (§§ V.A, V.B). The same is true for the '618 Patent, whose disclosure relative to the claims is generally the same as the '731 Application.⁵ The '618 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the '731 Application filed before March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

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

2. Related Proceedings

PGR2025-00003, PGR2025-00004, PGR2025-00006, PGR2025-00009, PGR2025-00017, PGR2025-00024, PGR2025-00030, PGR2025-00033, and PGR2025-00039 are related proceedings.

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

⁵ “Common disclosure” refers to the shared disclosure of the '618 Patent and the '731 Application (EX1026). Citations are to the '618 Patent; EX1015 correlates citations to the '731 Application. The disclosures are highly similar but not identical. *See* EX1068, ¶ 6.

3. Counsel and Service Information

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Petitioner consents to service via e-mail at the email addresses listed above and at HalozymePGRs@sidley.com.

III. Grounds

The grounds advanced in this Petition are:

- (a) Claims 1-40 are unpatentable under 35 U.S.C. § 112 as lacking adequate written description.
- (b) Claims 1-40 are unpatentable under 35 U.S.C. § 112 as not being enabled.
- (c) Claims 1-2, 4-5, 7-22 and 24-40 are unpatentable as obvious under 35 U.S.C. § 103 based on the '429 Patent (EX1005), Chao (EX1006), and knowledge held by a person of ordinary skill in the art.

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

“PH20” refers to the human PH20 hyaluronidase protein. The full-length PH20 protein (SEQ ID NO: 6) includes a 35 amino acid signal sequence, and mature forms of PH20 differ from SEQ ID NO: 6 by 35 residues.⁶ “PH20_{1-n}” refers to 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.*, “I309N”).

IV. Background on the '618 Patent

A. Field of the Patent

The '618 Patent concerns the human PH20 hyaluronidase enzyme and making structurally altered forms of that protein that retain enzymatic activity.⁷

The information below would have been known to a skilled artisan prior to 2013.

1. Protein Structures

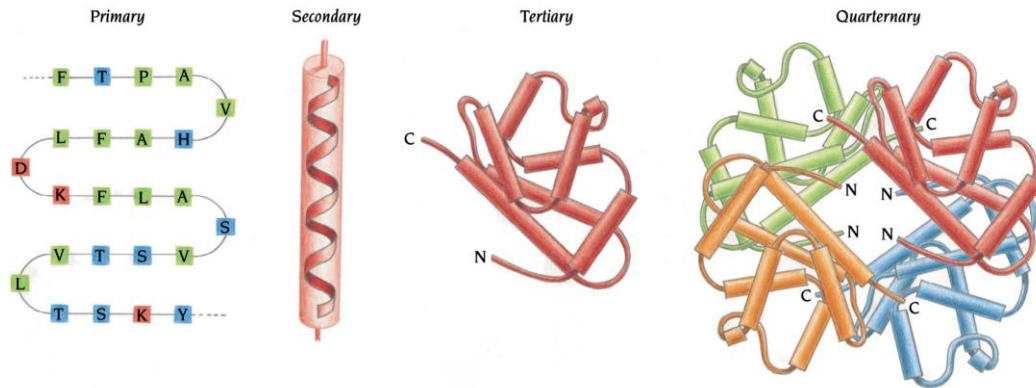
Proteins are comprised of sequences of amino acids. A protein's activity, however, derives from its unique, three-dimensional shape—its structure.⁸ That is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various secondary structures and

⁶ EX1003, ¶ 15.

⁷ EX1001, 2:37-40.

⁸ EX1003, ¶ 36.

structural motifs, which are packed into compact domains that define the protein's overall structure (tertiary structure).⁹



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

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

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

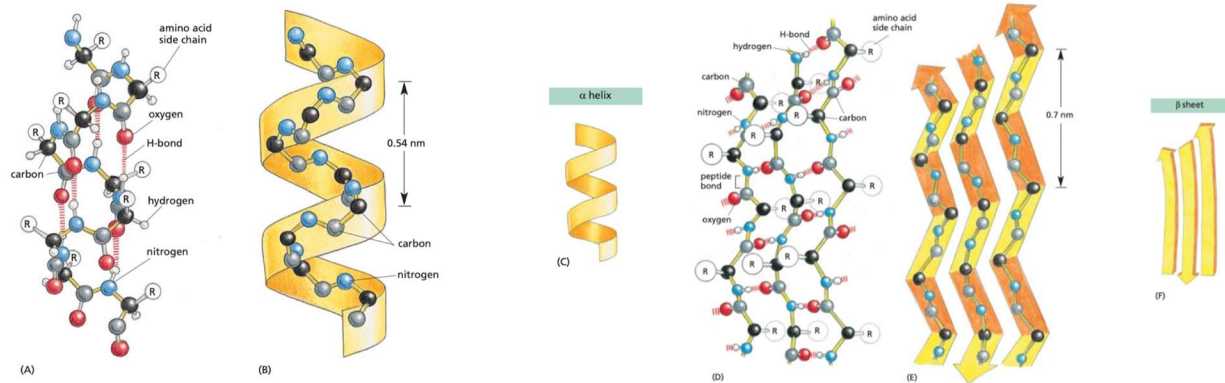


Figure 3-7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT> (A, B, and C) The α helix. The N-H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N-H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

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

¹¹ EX1003, ¶¶ 44-46; EX1014, 21-22.

¹² EX1003, ¶¶ 54, 156; EX1004, ¶¶ 20, 25.

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 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 human hyaluronidases and is homologous—evolutionarily related to—hyaluronidases in many species.¹⁷ PH20

¹³ EX1003, ¶ 165.

¹⁴ EX1003, ¶¶ 55-56, 145; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

¹⁵ EX1003, ¶¶ 57-59.

¹⁶ EX1003, ¶¶ 50, 165, 202, 243; EX1004, ¶¶ 151-153; EX1027 at 8-11.

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

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

Many essential residues in PH20 had been identified before 2011. 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 also essential,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

¹⁸ EX1003, ¶ 77; EX1008, 819.

¹⁹ EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 93, 209; EX1029, 546, Figure 1.

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.

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 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

There are two general approaches used 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

²⁴ EX1006, 6914-18.

²⁵ EX1006, 6912-13, 6916-18; EX1010, 9439-40; EX1003, ¶¶ 84-89; EX1004, ¶¶ 97-99.

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.

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 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 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

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

³⁰ EX1003, ¶¶ 227-28; EX1004, ¶¶ 21-22, 25, 30-31; EX1016, 181-84; EX1017, 224-25; EX1014, 351.

³¹ EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶ 37; *also id.* 33-36; EX1003, ¶¶ 237-40.

³² EX1003, ¶¶ 50, 165; EX1004, ¶¶ 151-153.

“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, 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 ’618 Patent embodies this approach.³⁷

B. Person of Ordinary Skill in the Art

While the ’618 Patent claims priority to provisional applications dating to December 30, 2011 and benefit to the ’731 Application filed December 28, 2012, none of those earlier-filed applications when each was filed supported the claims as required by § 112(a). *See* §§ II.A, V.A, V.B. Conversely, the obviousness

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

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

³⁵ EX1003, ¶ 196.

³⁶ EX1003, ¶¶ 52-53.

³⁷ EX1003, ¶¶ 148, 185, 195, 199.

grounds rely on prior art published before and knowledge/perspectives of a skilled artisan before December 2011.

A person of ordinary skill in the art would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).³⁸

C. Prosecution History

No issues relevant to the present grounds were raised during examination of the '618 Patent. In the sole Office action, indefiniteness rejections were imposed (*e.g.*, unclear references to “modifications”),³⁹ which Patentee overcame with

³⁸ EX1003, ¶ 13.

³⁹ EX1002, 904-05.

claim amendments.⁴⁰ Non-statutory double patenting rejections were also imposed,⁴¹ which Patentee overcame with terminal disclaimers.⁴²

D. The Challenged Claims

The claim terms are either expressly defined in the common disclosure or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition.

A clear understanding of the *breadth* of the claims, however, is important—each captures a subgenus of active mutants from within a massive number of structurally distinct mutant PH20 polypeptides which is neither adequately described in nor enabled by the common disclosure of the '731 Application and the '618 Patent.

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

The claims define an incredibly broad and diverse genus of “modified PH20 polypeptides,” which the common disclosure defines as “a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid

⁴⁰ EX1002, 966-69.

⁴¹ EX1002, 905-10.

⁴² EX1002, 974-76, 987.

replacement ... in its sequence of amino acids compared to a reference unmodified PH20 polypeptide.”⁴³

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

- **must** contain **one** amino acid replacement at position 309; and
- **may** contain **additional** modifications, provided each polypeptide retains **at least 91% sequence identity** to one of 37 unmodified sequences (SEQ ID NOs: 3, 7, or 32-66), ranging in length from 430 (SEQ ID NO: 32) to 474 residues (SEQ ID NO: 7).

Certain dependent claims restrict these parameters:

- (i) claims 2 and 26-27 limit (*inter alia*) sequence identity to 95%,
- (ii) claims 8-16 and 25-27 narrow the comparator sequences (*e.g.*, omitting SEQ ID NO: 7, requiring SEQ ID NOs: 35 or 32, or listing SEQ ID NOs: 576-586),
- (iii) claims 5, 7, 15, 16 and 25 require the position 309 substitution to be to one or more specific amino acids (*e.g.*, N), and
- (iv) claims 3-4 and 6 add functional requirements (*e.g.*, increased “stability,” activity or solubility).

⁴³ EX1001, 46:63-47:1.

Claims 17-24 and 28-40 depend from claim 1 but do not alter its parameters governing the number of PH20 polypeptides. Claims 17-23 and 28 specify additional features of the PH20 polypeptides while claims 24 and 29-40 define pharmaceutical compositions and therapeutic methods using them.

The specification explains that “sequence identity can be determined by standard alignment algorithm programs ...”⁴⁴ and provides an example, explaining a polypeptide that is “‘at least 90% identical to’ refers to percent identities from 90 to 100% relative to the reference polypeptide” where “no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides.”⁴⁵

It further explains that “differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence” and that “[d]ifferences are defined as [] amino acid substitutions, insertions or deletions.”⁴⁶ Also, “amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids” (*e.g.*, 10-18 of the 19

⁴⁴ EX1001, 58:29-31.

⁴⁵ EX1001, 58:64-59:6.

⁴⁶ EX1001, 59:7-15; *see also id.* at 3:22-23, 46:1-5, 14-16.

alternative amino acids).⁴⁷ Except for position 309, no language in the claims restricts *where* substitutions can occur within the modified PH20 sequence, or *which* of 19 other amino acids can be substituted at those positions.

The sequence identity parameters capture immense numbers of modified PH20 polypeptides, each with a unique amino acid sequence (below).⁴⁸

⁴⁷ EX1001, 128:46-53; *see also id.* at 133:63-65.

⁴⁸ EX1003, ¶¶ 131-133; EX1004, ¶¶ 159-163, Appendix F.

Claims	Max Length	Seq. Id. %	Max Changes	Pos. 309 Choices	# of Distinct Polypeptides
1, 3, 17-22, 24, 28-40	474	91	42	19	1.20×10^{113}
2, 4, 6, 23	474	95	23	19	9.85×10^{66}
5	474	91	42	6	3.79×10^{112}
7	474	91	42	1	6.32×10^{111}
8, 22	465	91	41	19	2.68×10^{110}
9	465	95	23	19	6.39×10^{66}
10, 16	465	91	41	1	1.41×10^{109}
11	433	91	41	19	1.35×10^{109}
12	430	91	41	19	1.01×10^{109}
13	433	91	41	1	7.10×10^{107}
14	430	91	41	1	5.30×10^{107}
15	465	91	41	11	1.55×10^{110}
25	447	91	40	1	1.40×10^{106}
26	430	95	21	6	2.64×10^{60}
27	433	95	21	6	3.05×10^{60}

2. The Claims Encompass I309N PH20₁₋₄₄₇

Claims 1-40 capture a modified PH20₁₋₄₄₇ polypeptide that changes only one amino acid: isoleucine at position 309 to asparagine (N) (“I309N”). This single-replacement PH20₁₋₄₄₇ mutant is: (i) 99.7% identical to SEQ ID NO: 3 (1 change /

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

3. The Claims Encompass “Active Mutants”

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

- “*Active mutants*” are modified PH20 polypeptides “whereby the polypeptides exhibit at least 40% of the hyaluronidase activity of the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement).”⁵¹
- “*Inactive mutants*” are modified PH20 polypeptides that “generally exhibit less than 20% ... of the hyaluronidase activity of a wildtype or

⁴⁹ EX1003, ¶ 147.

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

⁵¹ EX1001, 73:61-66; *see also id.* at 77:43-47 (“active mutants” “can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide ...”); *id.* at 77:40-43.

reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7.”⁵²

The common disclosure then classifies mutants into tables of “active” or “inactive” mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).⁵³ There are no examples in the common disclosure of an “active mutant” modified PH20 polypeptide with two or more specific substitutions,⁵⁴ much less one with: (i) a first substitution listed in Tables 3 or 9 *plus* (ii) a second substitution listed in Tables 5 and 10.

The specification portrays “active” and “inactive” mutants as having distinct utilities with mutually exclusive properties. “Active mutants” are portrayed as

⁵² EX1001, 114:24-33. *See also id.* at 249:15-19 (mutants with <20% activity “were rescreened to confirm that the dead mutants are inactive” in Table 10).

⁵³ EX1001, 226:9-11 (“Active mutants were selected whereby *at least one duplicate sample* exhibited greater than 40% of wildtype activity ...”); *id.* at 226:17-21 (Table 9 “...sets forth the *average hyaluronidase activity* of tested duplicates...”); *id.* at 179:7-80:17, 226:10-12, 116:1-24, 249:42-45 (“reconfirmed inactive mutants are set forth in Table 10.”); EX1003 ¶¶ 103, 105-06, 118.

⁵⁴ *E.g.*, EX1003, ¶¶ 150, 184.

having a variety of therapeutic uses *because they possess hyaluronidase activity*.⁵⁵ However, the common disclosure identifies only one for “inactive mutants”—“as antigens in contraception vaccines” (*see* § V.C).⁵⁶

The claim language reinforces that each is limited to—or at a minimum, encompasses—modified PH20 polypeptides that are “active mutants.”

First, dependent claims 5, 7, 15, 16, 25 require modified PH20 polypeptides to have a single substitution at 309 to one or more of the following: I309N, I309L, I309E, I309G, I309H, I309M, I309Q, I309R, I309S, I309T or I309V. The common disclosure describes PH20₁₋₄₄₇ polypeptides with these substitutions as “Active Mutants” with >40% activity.⁵⁷

⁵⁵ EX1001, 172:66-173:5; *see also id.* at 2:54-57, 71:47-61, 172:66-186:26, 149:18-20. EX1003, ¶ 119.

⁵⁶ EX1001, 74:3-5 (“Also provided are modified PH20 polypeptides that are inactive, *and* that can be used, for example, as antigens in contraception vaccines.”); *see also id.* at 186:27-28, 71:7-9, 186:26-45 (for “contraception” “the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.”); EX1003, ¶ 120; EX1001, 149:19-32; EX1060, 1711.

⁵⁷ EX1001, 84 (Table 3), 227 (Table 9), 96:5-17; EX1003, ¶¶ 137-140.

Second, the common disclosure identifies *no examples* of “inactive mutant”

PH20 polypeptides with a substitution at position 309 (Tables 8, 9, 5, below).

TABLE 8-continued

PH20 Variants	
I309D	GAT
I309E	GAG
I309G	GGT
I309H	CAT
I309K	AAG
I309L	CTG
I309M	ATG
I309N	AAT
I309Q	CAG
I309R	CGT
I309S	AGT
I309T	ACT
I309V	GTG
I309W	TGG
I309Y	TAT

EX1001, 209

TABLE 9-continued

ACTIVE MUTANTS		
I309D		0.72
I309E	576	1.99
I309G	577	1.44
I303D		0.34
I309H	578	1.30
I309K		0.98
I309L	579	1.72
I309M	580	1.47
I309N	581	3.11
I309Q	582	1.64
I309R	583	2.27
I309S	584	1.16
I309T	585	2.09
I309V	586	0.60
I309W		0.88

EX1001, 228

TABLE 5-continued

Inactive Mutants					
Corresponding Position	Replacement	Corresponding Position	Replacement	Corresponding Position	Replacement
306	A C H I L V W Y	307	C I P	308	C F L M V W Y
310	C E F K L	311	C E F I L P V W	312	C E M V W
313	C	314	C L W	315	C I V
316	E G I K L M P R S T V W Y	317	G P	318	C P W

EX1001, 83-84

Third, dependent claims 3 and 6 require modified PH20 polypeptides with “increased resistance or stability” or “increased hyaluronidase activity” relative to

an unmodified PH20.⁵⁸ Both require modified PH20s with hyaluronidase activity (*i.e.*, “[a]s used herein, ‘increased stability’ ... means the modified PH20 ... exhibits greater hyaluronidase activity ..., “[a]s used herein, ‘increased activity’ means that, when tested under the same conditions, the modified PH20 hyaluronidase exhibits greater hyaluronidase activity...”).⁵⁹

Fourth, dependent claims 30-40 require use of an “active mutant” PH20. For example, claims specifying administration of a modified PH20 to “increase delivery of a therapeutic agent” (or pharmaceutical compositions of them) require a PH20 that via hyaluronidase activity can degrade HA and thereby cause “spreading” or “diffusion” of the other agent.⁶⁰

Fifth, the specification defines a “modified PH20 polypeptide” as “a PH20 polypeptide that contains at least one amino acid modification,” but explains it can “have up to 150 amino acid replacements, so long as the resulting modified PH20

⁵⁸ EX1001, 50:64-51:3, 125:45-64, 171:56-59, 294:16-295:44.

⁵⁹ EX1001, 50:64-51:12; *also id.* 50:25-33; 50:33-54.

⁶⁰ EX1001, 2:53-3:4, 71:36-61, 172:66-173:5, 173:66-174:-11. EX1003, ¶ 176-77.

polypeptide *exhibits hyaluronidase activity*.”⁶¹ This aligns with the specification’s prophetic methodology for discovering PH20 polypeptides with multiple changes, which selects “active mutants” with one substitution, randomly introduces another, and then screens to find “double mutants” that *retained* hyaluronidase activity.⁶² It also tracks the claims, which require one substitution and permit others.

Patentee may contend the claims encompass both “active” and “inactive” mutants, but that only compounds their § 112 problems. First, every claim (including 1) still encompasses (and must describe and enable) a subgenus of “active mutants” (*e.g.*, claim 1 contains the genus of “active mutants” defined in claim 6).⁶³ Second, analogous § 112 problems exist for “inactive mutants”—those with putative utility as a contraceptive antigen— as they are a distinct subgenus within the 10⁶⁰⁺ claimed PH20 polypeptides and are neither described nor enabled. *See* § V.C.

⁶¹ EX1001, 46:63-47:11; *see also id.* at 46:19-23, 74:19-22, 75:14-21, 79:15-80:17; EX1003, ¶ 141.

⁶² EX1001, 133:30-41; *see also id.* at 41:3-10.

⁶³ EX1003, ¶¶ 141-42.

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

Claims 1-40 are unpatentable because each claims enzymatically active modified PH20 polypeptides that lack written description in and were not enabled by the common disclosure.

Per § IV.D.1, the claim parameters capture between 10^{60} and 10^{113} distinct PH20 polypeptides. To practice the claims' full scope of "active" (or for that matter "inactive") multiply-modified PH20 mutants requires a skilled artisan to make-and-test at least $\sim 10^{60}$ mutants.⁶⁴ Simply producing one molecule of each mutant in the smallest set—required to know if each is active, inactive or exhibits increased stability—would consume an aggregate mass ($\sim 2.36 \times 10^{38}$ kg) that exceeds the mass of the Earth ($\sim 6 \times 10^{24}$ kg).⁶⁵ Testing every polypeptide within the claims' scope in search of "active mutants" is impossible—literally.

Relative to that broad scope, the '618 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 enzymatically active

⁶⁴ EX1003, ¶¶ 196-97.

⁶⁵ EX1003, ¶¶ 134, 202; *see also, e.g.*, EX1039, 136-37 (10^{390} forms of a polypeptide possible from 300 residue sequence).

multiply-modified polypeptides within each claims' scope, nor does it enable a skilled artisan to practice that full-range of active mutants without undue experimentation.

A. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.⁶⁶ “To fulfill the written description requirement, a patent owner must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent.”⁶⁷ If the claims define a genus, the written description must “show that one has truly invented a genus ...,” “[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus.”⁶⁸

⁶⁶ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

⁶⁷ *Idenix Pharm., LLC v. Gilead Scis., Inc.*, 941 F.3d 1149, 1163 (Fed. Cir. 2019) (internal quotation marks omitted).

⁶⁸ *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

“[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.”⁶⁹ “One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent ... [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus.”⁷⁰

A disclosure that fails to “provide sufficient blaze marks to direct a POSA to the specific subset” of a genus with the claimed function or characteristic does not satisfy § 112(a).⁷¹ “[M]erely drawing a fence around the outer limits of a purported genus” is insufficient.⁷² Instead, “the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and

⁶⁹ *Idenix*, 941 F.3d at 1164.

⁷⁰ *AbbVie*, 759 F.3d at 1299-1300.

⁷¹ *Idenix*, 941 F.3d at 1164.

⁷² *Ariad*, 598 F.3d at 1350-54.

do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.”⁷³

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

Although the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.⁷⁴

It also criticized the prophetic description as being “only a research plan, leaving it to others to explore the unknown contours of the claimed genus” and a “trial and error approach.”⁷⁵

Second, *Idenix* addressed method of treatment claims using a broad genera of compounds defined by “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

⁷³ *Id.* at 1349.

⁷⁴ *AbbVie*, 59 F.3d at 1300-1301.

⁷⁵ *Id.*

configurations”).⁷⁶ The court criticized the specification’s failure to indicate which of the thousands of compounds would be effective, and found that “provid[ing] lists or examples of supposedly effective nucleosides,” without “explain[ing] what makes them effective, or why” deprives a skilled artisan “of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result” because they “fail[] to provide sufficient blaze marks to direct a POSA to the specific subset of 2’-methyl-up nucleosides that are effective in treating HCV.”⁷⁷

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) found unpatentable claims employing “90% sequence homology” language that captured “broad genus of amino acid sequence homologues” but which (like claim 1 here) imposed no restrictions where particular replacements could be made, thereby causing the claim “to cover, at minimum, thousands of amino acid sequences.”⁷⁸ Citing dependent claim 12, the Board found fatal to claim 1 the specification’s failure to “explain what, if any, structural features exist (*e.g.*,

⁷⁶ *Idenix*, 941 F.3d at 1158-64.

⁷⁷ *Id.* at 1164.

⁷⁸ *Boehringer*, at 16. The claims included methods of using proteins. *Id.* at 6.

remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification” (*i.e.*, the same property required of “inactive mutant” contraceptive PH20 polypeptides here).⁷⁹ As it observed, the homology limitation “serves to merely draw a fence around the outer limits of a purported genus [which] is not an adequate substitute for describing a variety of materials constituting the genus” for purposes of section 112(a).⁸⁰

The deficiencies of the present claims dwarf those in these three cases. They capture much larger, much less predictable, and much more diverse sub-genera, and the common disclosure is far more limited. Because the common disclosure neither discloses a representative number of species of enzymatically active modified PH20 polypeptides meeting the claim requirements, nor identifies sufficient structural features common to such modified PH20 polypeptides, it fails to demonstrate possession of the full scope of the claims of the ’618 Patent.

1. Claims 1-2, 6-15, and 25-27 Lack Written Description

The claims encompass all enzymatically active PH20 polypeptides meeting the sequence identity parameters of the claims. But the specification does not

⁷⁹ *Boehringer*, at 35; EX1001, 71:7-9.

⁸⁰ *Id.* at 35-36.

identify which of the 10^{60+} are those polypeptides, much less demonstrate possession of all of them.

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

Claims 1-2, 6-15, and 25-27 encompass modified PH20 polypeptides that are not only immense in number but are structurally and functionally diverse. They include mutants with between 2-21 substitutions for the narrowest claims (e.g. claims 24 and 25) to 2-42 for the broadest (claim 1). The optional sets of 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.⁸¹ The claims thus capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with 42 substitutions that mix polar, charged, aliphatic, and aromatic amino acids in any manner.⁸²

Each claim also encompasses substitutions within C-terminally truncated forms of PH20 terminating at positions between 430 to 474, which, via the claims' sequence identity language, capture PH20 polypeptides terminating at positions well before 430. For example, claims referencing SEQ ID NO: 32 allow between

⁸¹ EX1003, ¶ 130; EX1001, 59:7-14, 46:1-5, 46:14-16, 40:25-31.

⁸² EX1003, ¶¶ 130-31.

21 and 42 changes (with any mixture of deletions and substitutions), capturing PH20s terminating at position 416 or below. But removing so many residues from the C-terminus of PH20 can render it inactive, and the disclosure does not describe or suggest that making position 309 substitutions would restore their activity.⁸³

(b) Mutations the Common Disclosure Says to Avoid in Enzymatically Active PH20 Polypeptides

The claims' unconstrained sequence identity language captures not only modified PH20 polypeptides with innumerable combinations of substitutions but those with structural features a skilled artisan would understand the disclosure to be saying to avoid when making "active mutants." Multiply-modified PH20 polypeptides with these different structural features raise questions regarding whether any will possess hyaluronidase activity, but at a minimum would be viewed by a skilled artisan as being structurally distinct types of enzymatically active PH20 polypeptides as compared to singly-substituted PH20₁₋₄₄₇ which do not have those additional structural features. Instead of navigating 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."⁸⁴ The common disclosure thus

⁸³ EX1003, ¶¶ 170-73.

⁸⁴ EX1001, 76:47-52; EX1003, ¶ 206.

does not describe PH20 polypeptides reflecting the structural diversity of the “active mutants” subgenus in the claims’ scope.

(i) No Multiply-Modified “Active Mutant” PH20 Polypeptides with Substitutions that Render PH20₁₋₄₄₇ Inactive

The common disclosure indicates that active mutant modified PH20 polypeptides should not incorporate amino acid substitutions that as single substitutions 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.⁸⁵

It identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10.⁸⁶ It does not limit this observation to single-replacement PH20₁₋₄₄₇ mutants, or suggest that any of these substitutions that render PH20₁₋₄₄₇ inactive should be included in enzymatically active, multiply-modified PH20 polypeptides (much less identify specific combinations of substitutions including them).⁸⁷

⁸⁵ EX1001, 78:27-29 (emphases added).

⁸⁶ EX1001, 78:29-79:2.

⁸⁷ EX1003, ¶¶ 158, 168-69, 175.

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 enzymatically active multiply-modified PH20 polypeptides do not and should not contain these substitutions.⁸⁸ The claim language however captures active mutants that include one or more of the substitutions in Tables 5 and 10.

(ii) No Multiply-Modified “Active Mutant” PH20 Polypeptides with Significant C-terminal Truncations

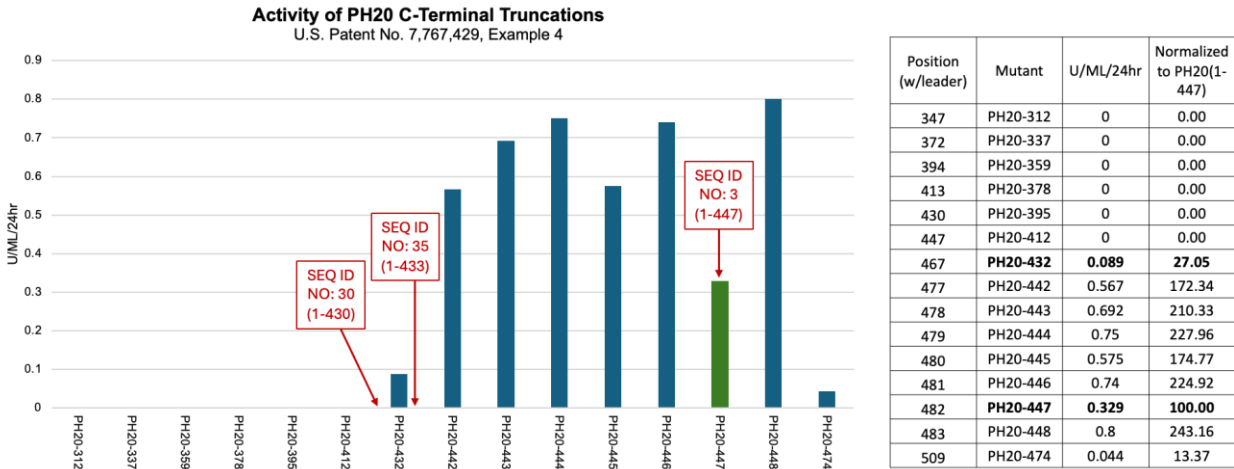
The common disclosure does not describe or provide guidance concerning “active mutant” PH20 polypeptides truncated before position 447, particularly multiply-modified PH20 mutants terminating significantly before that position.⁸⁹

The common disclosure and prior art report that wild-type PH20 polypeptides terminating at or below position 442 have *significantly reduced or no* hyaluronidase activity. For example, Patentee’s ’429 Patent reported that PH20

⁸⁸ EX1003, ¶¶ 155-58, 169; EX1001, 78:27-79:2, 68:60-69:3.

⁸⁹ EX1003, ¶¶ 99, 102, 173-75; EX1001, 72:23-29.

mutants terminating below position 432 lacked hyaluronidase activity, while those terminating between positions 432 and 448 had widely varying activity (below):⁹⁰



Patentee's '429 Patent also reported that “a very narrow range spanning ... [437-447] ... defined the minimally active domain” of human PH20, and observed this “minimally active” human PH20 domain contains at least residues 1-429.⁹¹

⁹⁰ EX1005, 87:52-88:24 (PH20₁₋₄₄₂ activity “decreased to approximately 10%”); EX1013, Figure 2, 430-32 (“[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA”); EX1003, ¶ 95.

⁹¹ EX1005, 6:65-7:7 (“... sHASEGP from amino acids 36 to Cys 464 [429] ... comprise the minimally active human sHASEGP hyaluronidase domain”); EX1003, ¶ 94.

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

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

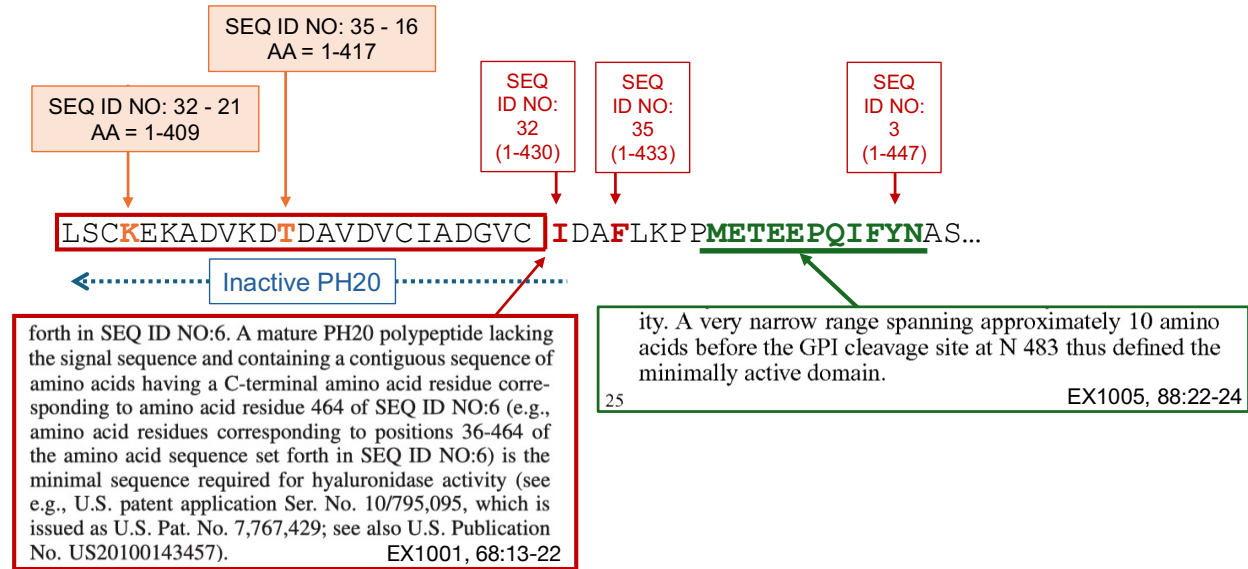
In 2007, Chao reported that the C-terminal region of human hyaluronidases contains a unique domain (“Hyal-EGF”) linked to a characteristic pattern of sequences, which runs from positions 337-409 in PH20.⁹³ In 2009, Zhang showed the Hyal-EGF domain was necessary for hyaluronidase activity.⁹⁴

An illustration of the C-terminus of PH20 (below) shows: (i) positions where SEQ ID NOS: **3** (447), **32** (430) and **35** (433) terminate, (ii) the “minimally active domain” at 437-447, (iii) residues before position 429, and (iv) that PH20 polypeptides with 21 or 16 deletions from SEQ ID NOS: 32 and 35, respectively, terminate before position 429.

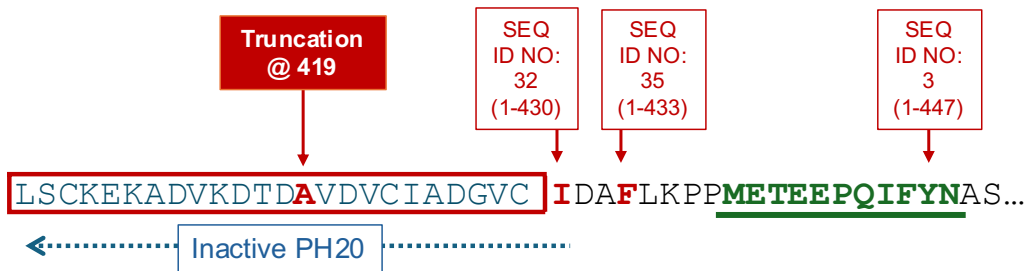
⁹² EX1001, 68:13-22 (emphases added); *also* EX1003, ¶¶ 97, 159.

⁹³ EX1006, 6912-13, 6916-18; EX1004, ¶¶ 97-99; EX1003, ¶ 96.

⁹⁴ EX1010, 9438; EX1003, ¶ 90.



So, for example, a skilled artisan would have believed a PH20 polypeptide terminating at position 419 would be inactive based on the common disclosure and information published before 2011.⁹⁵



The common disclosure provides no examples of (or guidance concerning) enzymatically active multiply-substituted PH20 mutants truncated to positions 419 and 447.⁹⁶ The claims nonetheless capture such mutants.

⁹⁵ EX1003, ¶¶ 96-98, 171-74.

⁹⁶ EX1003, ¶¶ 96-98, 100, 102.

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

The empirical results in the common disclosure do not provide any guidance to a skilled artisan about the structural features of enzymatically active multiply-modified PH20 polypeptides.

(i) Single-Replacement Results Not Probative of Multiple-Replacement Mutants

The common disclosure reports results from testing a portion of a library of ~6,753 single-replacement PH20₁₋₄₄₇ polypeptide sequences.⁹⁷ The mutants were produced using a library of CHO cells transfected with a plasmid encoding mutagenized PH20₁₋₄₄₇ sequences where one of 447 positions in the sequence “was changed to one of about 15 amino acid residues, such that each member contained a single amino change.”⁹⁸ Results for ~5,917 of the mutants are reported.⁹⁹

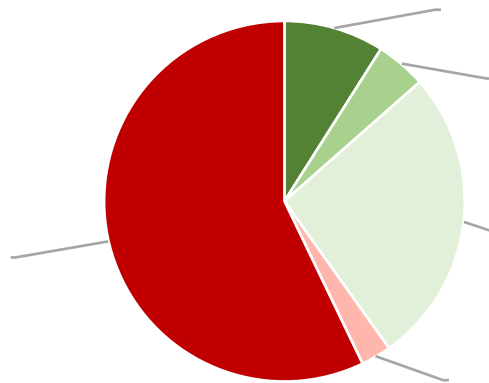
⁹⁷ EX1001, 125:65-126:9, 194:1-3, 192:51-57.

⁹⁸ EX1001, 192:51-60.

⁹⁹ EX1003, ¶¶ 113-14, 116. Inconsistent numbers and classifications of mutants are 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.

The common disclosure classifies more than half (~57%) of the tested mutants as “inactive mutants” and ~30% as having less activity than unmodified PH20₁₋₄₄₇ (20%-100%).¹⁰⁰ In other words, it portrays ~87% of the 5,917 single-replacement PH20₁₋₄₄₇ polypeptides that were made and tested as having *less* activity than unmodified PH20₁₋₄₄₇.

Activity vs. Unmodified	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, ¶ 110, 116-17.

Notably, the data is not analyzed in the common disclosure—it is simply presented. No attempt is made to assess the impact of any single substitution on the protein’s structure, much less extrapolate these results to PH20 polypeptides with multiple substitutions.

The data’s quality is also questionable: no control values or statistical assessments are provided for these activity results. The common disclosure also does not report the hyaluronidase activity measured for 3,380 inactive mutants, and provides no information on 836 other single substitution PH20₁₋₄₄₇ mutants that were made and tested, or classify them as “active” or “inactive” mutants. *See* § V.C.

The data reveal no trends or correlations even for single-replacement PH20₁₋₄₄₇ polypeptides. For example, different substitutions at the same position in PH20₁₋₄₄₇ yielded active and inactive mutants, with >800 unclassified mutants.¹⁰¹

Position	Active	Inactive	Unclassified
45	I, K	A, D, F, G, P, W	H, M, Q, S, T, V, Y
110	V	F, K, L, M, P, W	A, C, D, G, H, N, R, S
124	H, L, R	C, D, E, F, N	A, G, I, P, S, T, V, W
290	I, M	D, Q, Y	A, C, G, H, K, L, R, S, T, V
343	T, V	C, D, F, I, P, W	E, G, L, M, R, S, Y

¹⁰¹ EX1001, Table 8, 9, 10.

Changing multiple residues in PH20 polypeptides can cause unpredictable interactions within the protein's structure and resulting function that do not occur in single-substitution mutants.¹⁰² The empirical test results for single substitution mutants do not identify to a skilled artisan which of the 10⁶⁰⁺ PH20 mutants with a 309 substitution and 1-41 additional substitutions are enzymatically active (or for that matter, are inactive or cannot be made and are useless).¹⁰³ Instead, all it shows is that *most* single-substitutions impaired or eliminated hyaluronidase activity.

(ii) Purported Stability Data Is Not Reliable or Probative

The common disclosure reports results testing ~409 single-replacement PH20₁₋₄₄₇ polypeptides in “stability” assays.¹⁰⁴ Table 11 reports hyaluronidase activities of the mutants at 4° C and 37° C, and with a “phenolic preservative” (m-cresol).¹⁰⁵ Table 12 reports relative hyaluronidase activities of those mutants.¹⁰⁶

¹⁰² EX1003, ¶¶ 54-58, 243.

¹⁰³ EX1003, ¶¶ 149, 151, 206.

¹⁰⁴ EX1001, Tables 11-12.

¹⁰⁵ EX1001, 258:9-267:67 (Table 11).

¹⁰⁶ EX1001, 269:1-281:13 (Table 12).

The “stability” data provides no meaningful insights.¹⁰⁷ Unsurprisingly, many single-replacement PH20₁₋₄₄₇ polypeptides showed more activity at 37° C than at 4° C.¹⁰⁸ And testing with m-cresol showed only a few mutants resisted denaturation.¹⁰⁹ With one exception, the measured activity data cannot be attributed to improved stability of PH20.¹¹⁰ The data are also largely meaningless—many measured activity values are within the activity ranges reported for the positive control.¹¹¹

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

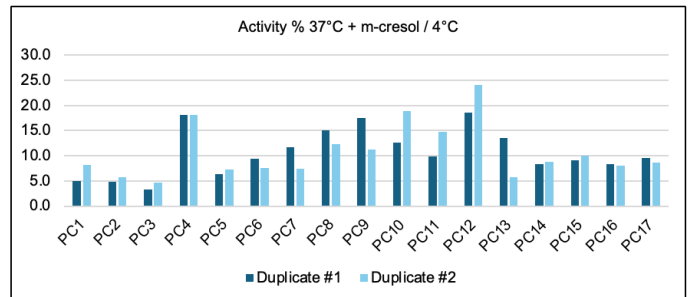
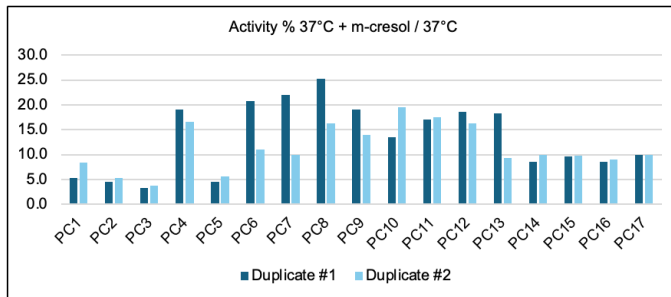
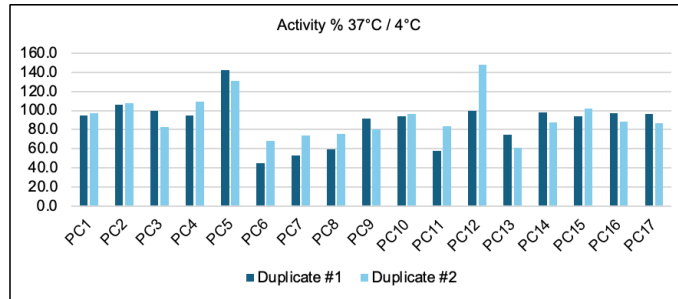
¹⁰⁷ EX1003, ¶ 76.

¹⁰⁸ EX1003, ¶ 73; EX1001, 169:46-55.

¹⁰⁹ EX1003, ¶ 69.

¹¹⁰ EX1003, ¶ 69.

¹¹¹ EX1003, ¶ 71, Appendix A-7, A-8; EX1001, 279-281:14 (Table 12).



	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.”¹¹²

Importantly, the common disclosure does not identify any—let alone *which*—combinations of substitutions in a multiply-modified PH20 improve

¹¹² EX1003, ¶¶ 70-72; see also EX1001, 281:20-30 (positive control also varied).

stability.¹¹³ The common disclosure thus does not describe or provide meaningful guidance concerning which of the 10^{60+} multiply-modified PH20 polypeptides that may have increased stability.

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

The common disclosure does not describe any multiply-modified PH20 polypeptides that are “active mutants.” Instead, it simply presents *the idea* of multiply-modified PH20 polypeptides.

First, it observes that “[a] modified PH20 polypeptide can have up to 150 amino acid replacements,” “[t]ypically” contains between 1 and 50 amino acid replacements and “can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.”¹¹⁴ It also contends a modified PH20 polypeptide with “a sequence of amino acids that exhibits” between 68% and 99% sequence identity with any of unmodified SEQ ID NOS: 74-855 “*can* exhibit altered, such as improved or increased, properties or activities

¹¹³ EX1003, ¶¶ 69, 76.

¹¹⁴ EX1001, 47:1-11.

compared to the corresponding PH20 polypeptide not containing the amino acid modification (*e.g.*, amino acid replacement).”¹¹⁵

None of these statements *identify* any actual multiply-modified PH20 polypeptides (*i.e.*, PH20 polypeptides with specific sets of 2 or more amino acid substitutions). They simply draw boundaries around immense numbers of PH20 polypeptides that may be enzymatically active.

The common disclosure also describes no multiply-modified, enzymatically active PH20 polypeptides that were made and tested. Instead, it provides only a prophetic research plan requiring “iterative” make-and-test experiments that *might discover* such PH20 polypeptides, stating they “*can be* modified or further modified” and “*can be* identified.”¹¹⁶ This research plan does not identify *which* multiply-modified PH20 polypeptides can be made or *are* active mutants.¹¹⁷

Alternatively, it proposes mutations that *can be* “targeted near” “critical residues” which supposedly “*can be* identified because, when mutated, a normal

¹¹⁵ EX1001, 95:24-38 (emphasis added).

¹¹⁶ EX1001, 133:29-41 (emphases added); *see also id.* at 41:3-10, 126:44-49; EX1003, ¶¶ 185-89.

¹¹⁷ EX1003, ¶¶ 185, 196-97, 200; EX1001, 42:23-25; *see generally id.*, 125:65-126:43, 126:52-128:28, 128:55-133:28.

activity of the protein is ablated or reduced.”¹¹⁸ But Tables 5 and 10 report at least one substitution at each of 405 positions between positions 1 and 444 of PH20₁₋₄₄₇ resulted in an inactive mutant.¹¹⁹ This guidance to target locations “near” ~90% of the amino acids in PH20₁₋₄₄₇ is no different than targeting *every residue*.¹²⁰

These prophetic research plans, based entirely on unfocused, iterative “make-and-test” experiments, do not identify to a skilled artisan which of the 10⁶⁰⁺ multiply-modified PH20 polypeptides within the claims’ scope *are* enzymatically active.¹²¹ Instead, they require a skilled artisan to perform repeated cycles of mutagenesis, screening and selecting until 10⁶⁰ to 10¹¹³ modified PH20 polypeptides are made and screened.¹²² That in no way demonstrates possession of all active mutants within each claims’ scope.

¹¹⁸ EX1001, 133:42-67; EX1003, ¶¶ 190-91.

¹¹⁹ EX1003, ¶ 192, Appendix A-3.

¹²⁰ EX1003, ¶ 192.

¹²¹ EX1003, ¶ 203.

¹²² EX1003, ¶¶ 187-89, 200-01; EX1001, 128:36-41, 128:29-53, 131:47-51, 131:62-67, 132:17-31.

The specification also incorrectly equates hyaluronidase activity with “stability.”¹²³ As Dr. Hecht explains, to assess a protein’s stability requires experiments that measure the energy associated with the protein’s transition between its folded and unfolded states.¹²⁴ Activity may or may not be influenced by stability but is not itself a measure of stability.¹²⁵

(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 or ~830 mutants that were uncharacterized). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured

¹²³ EX1003, ¶¶ 67, 69, 191.

¹²⁴ EX1003, ¶¶ 63-66.

¹²⁵ EX1003, ¶ 67.

change in hyaluronidase activity.¹²⁶ Instead, it simply lists single replacements to random amino acids that yielded “active mutants.”¹²⁷

The common disclosure also does not identify any *sets* of specific amino acid replacements that correlate to changes in structural domains or motifs that positively or negatively influence hyaluronidase activity, much less *predictably* increase activity to defined thresholds.¹²⁸

The common disclosure’s empirically identified examples of “active mutant” single-replacement PH20₁₋₄₄₇ mutants do not *by themselves* identify any “structure-function” relationship between “active mutants” and the set of single-replacement modified PH20₁₋₄₄₇ polypeptides.¹²⁹ Nor do they do so for the unknown number of multiply-modified active mutant PH20 polypeptides of varying lengths with between 2 and 42 substitutions.¹³⁰

The common disclosure *does not even contend* that a particular amino acid replacement at a particular position (*e.g.*, 309) that makes PH20₁₋₄₄₇ an “active

¹²⁶ EX1003, ¶¶ 148-49, 158.

¹²⁷ EX1001, 226:10-37; EX1003, ¶¶ 148-49.

¹²⁸ EX1003, ¶¶ 55, 151-152.

¹²⁹ EX1003, ¶¶ 61, 152, 164, 166.

¹³⁰ EX1003, ¶ 164.

mutant” will make any other modified PH20 polypeptide with that replacement plus 1-41 additional substitutions an “active mutant.”¹³¹ 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.¹³² Thus, even the inventors did not view their compilation of empirical test results as identifying a structure-function relationship for 10^{60+} multiply-modified “active mutants.”

The common disclosure, thus, does not identify to a skilled artisan *any structural features* shared by all “active mutant” modified PH20 polypeptides within the scope of the claims.

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

The ~2,500 active mutant single-replacement PH20₁₋₄₄₇ polypeptides in the disclosure are not representative of the sub-genus of “active mutant” PH20 polypeptides encompassed by the claims.¹³³

¹³¹ EX1003, ¶¶ 174, 204-05.

¹³² EX1003, ¶¶ 56-57.

¹³³ EX1003, ¶¶ 61,152, 162, 166.

Single-replacement PH20₁₋₄₄₇ examples are not representative of the 10⁶⁰⁺ PH20₁₋₄₄₇ polypeptides having **2 to 42 additional substitutions** to any of 19 other amino acids at any of hundreds of positions within the protein.¹³⁴ The latter group includes a massive number of structurally distinct proteins (*e.g.*, distinct sequences, distinct secondary structures, distinct structural motifs, etc.) that form when PH20 sequences with multiple amino acid substitutions successfully fold.¹³⁵ None of them are described in the common disclosure.

Multiple substitutions made to a protein can cause different interactions between neighboring residues relative to those caused by single substitutions.¹³⁶ For example, a first amino acid substitution can affect the neighbors of the replaced amino acid by (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, and/or (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).¹³⁷ A second substitution in that region may reverse those interactions (or not), and a third substitution may do the

¹³⁴ See § IV.D.1; EX1003, ¶¶ 61, 152, 166.

¹³⁵ EX1003, ¶¶ 58-63.

¹³⁶ EX1003, ¶¶ 55-56, 58, 60, 163, 166.

¹³⁷ EX1003, ¶¶ 56-58.

same, and so on up to 21 rounds permitted by the narrowest claims, each potentially causing different interactions.¹³⁸

The common disclosure, however, does not identify effects of any single substitution on the various domains, secondary structures and structural motifs within any PH20 polypeptides within the scope of the claims.¹³⁹ And the activity of a protein with multiple substitutions is rarely dictated by only one of the substitutions—it is dictated by the unique structure that reflects *the totality* of effects of those many substitutions.¹⁴⁰ The common disclosure provides no information on structural effects of multiple substitutions.

The single-replacement active mutant PH20 polypeptides in the disclosure thus are not representative of the unidentified number of undisclosed enzymatically active multiply-substituted PH20 mutants within the claims' scope, which comprise myriad combinations of substitutions that each can uniquely impact the structures and properties of the mutated protein.¹⁴¹

¹³⁸ EX1003, ¶¶ 58-60, 151.

¹³⁹ EX1003, ¶¶ 164-65, 243.

¹⁴⁰ EX1003, ¶¶ 61, 150.

¹⁴¹ EX1003, ¶¶ 152, 166.

Enzymatically active single-replacement PH20₁₋₄₄₇ polypeptides also are not representative of multiply modified PH20 polypeptides that incorporate changes that render wild-type PH20 inactive (*e.g.*, truncations terminating below position 429, or single substitutions that rendered PH20₁₋₄₄₇ inactive).¹⁴² Such single-replacement active mutants do not contain the additional and distinct structural features that rendered the latter PH20 polypeptides enzymatically *inactive*. For example, the I309N PH20₁₋₄₄₇ polypeptide would not be considered representative of a PH20 terminating at position 419 with that I309N substitution, as the former omits the structural feature (the C-terminal truncation) that rendered the latter inactive.¹⁴³ The common disclosure does not teach—and a skilled artisan could not have predicted from the examples of single-replacement PH20₁₋₄₄₇ mutants—which single substitutions would restore enzymatic activity to a truncated PH20 mutant that was inactive, much less identifies the precise combinations that do.¹⁴⁴

The common disclosure thus provides a very narrow set of working examples relative to the diversity of enzymatically active modified PH20

¹⁴² EX1003, ¶¶ 168-170.

¹⁴³ EX1003, ¶¶ 173-75.

¹⁴⁴ EX1003, ¶ 174.

polypeptides being claimed.¹⁴⁵ The examples are restricted to *one type of change* (a single amino acid replacement) in *one type of PH20 polypeptide* (SEQ ID NO: 3).¹⁴⁶ By contrast, the claims encompass changes in 37 different unmodified PH20 sequences, and include, in addition to a replacement at position 309, up to 41 (1, 3, 5, 7, 17-22), 39 (25), 22 (2, 4, 6, 9, 23) or 20 (claims 26-27) additional changes.¹⁴⁷ The simple figure below illustrates how *non-representative* the single-replacement PH20₁₋₄₄₇ mutants are for claim 2.

SEQ	Number of Changes																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3	■																						
7																							
32																							
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¹⁴⁵ EX1003, ¶ 162.

¹⁴⁶ EX1003, ¶¶ 102, 104, 108, 113-14.

¹⁴⁷ EX1003, ¶¶ 127-131.

Consequently, a skilled artisan would not have viewed the examples of single amino acid replacements in PH20₁₋₄₄₇ in the common disclosure to be *representative* of the diversity of “active mutant” modified PH20 polypeptides encompassed by the claims.¹⁴⁸

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

The claims, read literally or in context, concern enzymatically active PH20 polypeptides. For example, some explicitly require activity (3 and 6), require a 309 substitution that yielded an active mutant PH20₁₋₄₄₇ (5, 7, 15-16, 25-27), or specify compositions/methods requiring use mutants with hyaluronidase activity (30-40). Others depend from claim 1, which, given that no disclosed 309 substitution created an inactive mutant, is properly read as being limited to active mutants.

The common disclosure instructs that certain changes are to be avoided in active mutant PH20 polypeptides (*i.e.*, substitutions listed in Tables 5/10 or C-terminal truncations before position 429). It provides no guidance for incorporating substitutions that restore enzymatic activity to such mutants. Yet the claims capture such enzymatically active multiply modified PH20 polypeptides with these changes the disclosure says to omit from active mutants.

¹⁴⁸ EX1003, ¶ 152.

The claims thus independently violate the written description requirement pursuant to *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 3-4, 6, 17-24, and 28-40 Lack Written Description

(a) Claims 3, 6, 23

Claims 3, 6, and 23 specify the modified PH20 polypeptides in the genus defined by claim 1 exhibits (i) increased stability (claim 3) or (ii) increased hyaluronidase activity (claims 6, 23) 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 these claims.

In addition, the recitation in claims 3, 6, and 23 of a *desired* level of stability or hyaluronidase activity does not identify *which* of the 10⁶⁰⁺ PH20 polypeptides with 91% or 95% sequence identity to SEQ ID NOS: 3, 7, or 32-66 and any replacement at position 309 will exhibit those functional properties.¹⁴⁹

First, the singly-substituted position 309 PH20₁₋₄₄₇ polypeptides in the common disclosure that exhibited increased activity are not representative of each

¹⁴⁹ EX1003, ¶¶ 197, 204-06.

claim's genus, which includes PH20 polypeptides with 1 to 41 additional substitutions and/or truncations.¹⁵⁰ Likewise, while some position 309 PH20₁₋₄₄₇ single replacements were tested, most exhibited activity within the range of the control (unmodified) PH20₁₋₄₄₇, and none were in multiply-modified PH20 polypeptides.¹⁵¹

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides (if any) exhibiting increased activity or stability.¹⁵² The presence of a single position 309 substitution does not demonstrate possession of all multiply-modified PH20 polypeptides with that substitution and exhibit increased activity or stability, and the common disclosure does not contend otherwise.¹⁵³

Claims 3, 6, and 23 lack written description in the common disclosure.

(b) Claim 4

Claim 4 requires the modified PH20 polypeptide to be “soluble.”

¹⁵⁰ EX1001, 227 (Table 9); EX1003, ¶¶ 204-06.

¹⁵¹ EX1003, ¶ 71; *see* § V.A.1.c.ii.

¹⁵² EX1003, ¶¶ 164, 197, 203.

¹⁵³ EX1003, ¶¶ 153, 174, 197.

Claim 4 lacks written description support for the same reasons identified for claim 1.

In addition, claim 4 lacks written description because it encompasses modified PH20 polypeptides that the common disclosure suggests will be insoluble. It explains that “a soluble PH20 lacks all or a portion of a glycosylphosphatidy anchor (GPI) attachment sequence,” which was known to be hydrophobic,¹⁵⁴ and identifies position 456 as the first residue of the GPI sequence in PH20 (position 491 in SEQ ID NO: 6).¹⁵⁵ 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).¹⁵⁶ The common disclosure thus suggests that human PH20 sequences that terminate below position 448 are soluble while those terminating above position 456 are insoluble.¹⁵⁷

Claim 4 encompasses PH20 polypeptides based on SEQ ID NOS:59-66, which terminate between positions at 457 to 464 respectively (*i.e.*, beyond position

¹⁵⁴ EX1001, 44:52-54, 70:22-23, 46-58, 72:40-52; EX1005, 86:18-22; EX1003, ¶¶ 93-95.

¹⁵⁵ EX1001, 70:46-58.

¹⁵⁶ EX1001, 73:30-32; EX1005, 3:57-62.

¹⁵⁷ EX1003, ¶¶ 93-94.

456). It also requires a replacement at position 309. Consequently, claim 4 captures modified PH20 polypeptides that are C-terminally truncated but, per the common disclosure, **are not** “soluble modified PH20 polypeptide[s]” because each contains “all or a portion of” the GPI attachment sequence.¹⁵⁸

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.”¹⁵⁹ But the common disclosure does not identify **which** modified PH20 polypeptides terminating above position 448 (particularly 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.

Claim 4 is unpatentable for this additional, independent reason.

(c) Claims 17-24, 28-36

Dependent claims 17-24 and 28-36 do not alter the structure of PH20 polypeptides in the genus of claim 1. They instead specify additional features (claims 17-23, 28), pharmaceutical compositions (24, 29-33), or methods of

¹⁵⁸ EX1001, 45:12-18.

¹⁵⁹ EX1001, 72:33-39.

treatment (34-36) that reference the genus of claim 1. They lack written description for the same reasons explained in § V.A.1.¹⁶⁰

(d) *Claims 37-40*

Claims 37-40 concern methods for “increasing delivery of a therapeutic agent to a subject” (e.g., an antibody (claim 40)) by administering any of the PH20 polypeptides within claim 1’s scope with the other agent (together or separately), and subcutaneously (claim 39).

The common disclosure attributes PH20’s “increasing delivery” capability to its ability to cause “spreading” or “diffusion,” and indicates that requires the PH20 to *at least* have hyaluronidase activity.¹⁶¹ It also describes testing modified PH20 polypeptides in a live mouse assay to determine if they increase delivery (even if they have hyaluronidase activity).¹⁶² But the common disclosure does not identify which of the 10⁶⁰⁺ PH20 polypeptides within the scope of the claims possess (i) hyaluronidase activity and (ii) cause “spreading”/“diffusion” activity per its mouse

¹⁶⁰ *Idenix*, 941 F.3d at 1155, 1165; *Boehringer*, PGR2020-00076, Paper 42, at 40-41.

¹⁶¹ EX1001, 172:63-173:5, 173:65-174:10, 71:36-61; EX1003, ¶¶ 176-77.

¹⁶² EX1001, 171:16-36; EX1003, ¶ 180.

assay.¹⁶³ Indeed, it tested only *one* (F204P PH20₁₋₄₄₇) that falls *outside* the claims.¹⁶⁴

The modified PH20 polypeptides within claim 1's genus also include those with multiple substitutions in the Hyal-EGF region of PH20 (positions 337-409).¹⁶⁵ By 2011, it was believed the Hyal-EGF domain mediated protein-protein interactions, and mutations to it substantially eliminated hyaluronidase activity in otherwise unaltered PH20 polypeptides.¹⁶⁶ A skilled artisan would have thus believed that making multiple substitutions to the Hyal-EGF domain could alter its structure and disrupt not only PH20's hyaluronidase activity but any protein-protein interactions that might be involved in PH20's spreading activity *in vivo*.¹⁶⁷

Claims 37-40 thus lack written description because the common disclosure does not identify which of the 10⁶⁰⁺ modified PH20 polypeptides within the scope

¹⁶³ EX1003, ¶ 176.

¹⁶⁴ EX1001, 295:47-298:10.

¹⁶⁵ EX1004, ¶ 98; EX1006, 6912.

¹⁶⁶ EX1003, ¶¶ 85-86, 90-91, 100; EX1006, 6912, 6913, 6916-17; EX1010, 9439; EX1005, 87:52-88:24; EX1079, 84.

¹⁶⁷ EX1003, ¶¶ 100-102, 176-180.

of claim 1 can be used in the claimed methods of increasing delivery of another therapeutic agent.¹⁶⁸

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

“If a patent claims an entire class of ... compositions of matter, the patent’s specification must enable a person skilled in the art to make and use the *entire* class,” *i.e.*, “the *full scope* of the invention,” and so the “more one claims, the more one must enable.”¹⁶⁹ “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.”¹⁷⁰ “Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation.”¹⁷¹

Although not required, enablement may be assessed using the *Wands* factors, which consider: “(1) the quantity of experimentation necessary; (2) how

¹⁶⁸ EX1003, ¶ 181.

¹⁶⁹ *Amgen*, 598 U.S. at 610 (emphases added).

¹⁷⁰ *Idenix*, 941 F.3d at 1159.

¹⁷¹ *Wyeth & Cordis Corp. v. Abbott. Labs*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention.”¹⁷²

Where the scope of the claims is large, few working examples are disclosed, and the only guidance to practice “the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims’ functional limitations—the asserted claims are not enabled.”¹⁷³

“It is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101.”¹⁷⁴ A claimed invention must be *presently useful*—stating a hypothesis and proposing testing to determine its accuracy is insufficient.¹⁷⁵ Further, if a claim encompasses significant numbers of inoperative

¹⁷² *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

¹⁷³ *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, T., sitting by designation) *aff’d* 81 F.4th 1362 (Fed. Cir. 2023).

¹⁷⁴ *In re Fisher*, 421 F.3d 1365, 1379 (Fed. Cir. 2005).

¹⁷⁵ *In re ’318 Patent Infringement Litigation*, 583 F.3d 1317, 1327 (Fed. Cir. 2009); *In re Kirk*, 376 F.2d, 936, 942 (C.C.P.A. 1967) (emphasis added).

embodiments, and a skilled artisan must engage in undue experimentation to identify the operative ones, that renders the claims non-enabled.¹⁷⁶

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using the disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the $10^{60}+$ PH20 polypeptides having multiple amino acid replacements and/or truncations within the scope of the claims that are useful because they are “active mutants,” those “inactive mutants” that the disclosure contends are useful as a contraceptive antigen, and those which have no utility.¹⁷⁷

1. Claims 1-2, 5, 7-16, and 25-27 Are Not Enabled

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

¹⁷⁶ *Crown Operations Intern. Ltd v. Solutia Inc.*, 389 F.3d 1367, 1380, FN8 (Fed. Cir. 2002); *Atlas Powder Co. v. E.I. Dupont De Nemours*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

¹⁷⁷ EX1003, ¶¶ 182-84, 203.

(a) *Extreme Scope of the Claims*

As explained in § IV.D.1, claims 1-2, 5, 7-16, and 25-27 capture between 10^{60} and 10^{113} modified PH20 polypeptides that have (i) any or particular substitution(s) at position 309, and (ii) 1 to 41 additional substitutions to any other amino acid anywhere in a PH20 polypeptide sequence ranging from 430 to 474 residues. Within these immense sets of PH20 polypeptides is subgenus having an unknown and undisclosed number of “active mutant” PH20 polypeptides.

Practicing the full scope of just this “active mutant” subgenus within the claims requires navigating substantial scientific questions left unanswered by the common disclosure. Other than by making and testing $\sim 10^{60}$ to 10^{113} multiply modified PH20 polypeptides, the common disclosure does not explain how to determine *which* combinations of substitutions (in addition to position 309) will yield enzymatically active mutants.

There are also many types of PH20 mutants that the common disclosure would lead a skilled artisan to believe will *not* be enzymatically active, but which are nonetheless captured by the claim language, including those that:

- (i) have substitutions the disclosure instructs to not include in an enzymatically active modified PH20 polypeptide because they rendered PH20₁₋₄₄₇ an inactive mutant;¹⁷⁸
- (ii) terminate before position 429, which the disclosure reports will eliminate activity in unmodified PH20 proteins;¹⁷⁹ and
- (iii) include substitutions at positions that the common disclosure instructs “are less tolerant to change or required for hyaluronidase activity.”¹⁸⁰

Whether there are any (or how many) such “active mutant” PH20 polypeptides within the scope of the claims is unknown, but the common disclosure identifies none.¹⁸¹

The common disclosure also does not provide any guidance that a skilled artisan could use to identify which of the 10⁶⁰-10¹¹³ modified PH20 polypeptides with a position 309 substitution and 1-41 additional substitutions *are* inactive and useful as a contraceptive antigen, or cannot be produced and thus have no utility at all.

¹⁷⁸ EX1001, 78:27-29.

¹⁷⁹ EX1001, 68:13-22; EX1003, ¶¶ 97-98, 159-161, 170-72.

¹⁸⁰ EX1001, 75:59-76:4.

¹⁸¹ EX1003, ¶ 173.

In short, the claims capture a massive number of multiply-modified PH20 polypeptides that have *unknowable* properties absent the skilled artisan producing and testing 10^{60} and 10^{113} distinct mutants pursuant to the common disclosure's prophetic "make and test" methodology.¹⁸²

Claims that capture a massive and diverse sets of proteins such as those here have routinely been found non-enabled. For example, the claims in *Amgen* covered "millions" of different, untested antibodies,¹⁸³ while in *Idenix*, the court found that a skilled artisan would "understand that 'billions and billions' of compounds literally meet the structural limitations of the claim."¹⁸⁴ In both cases (as here), the enormous claim scope was contrasted to limited working examples in the patent, the field of technology was unpredictable, and an immense quantity of experimentation was required to practice the claims' full scope (*Wands* Factors 1, 3, 4, and 7). Importantly, as the *Idenix* court also observed, it is improper to 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

¹⁸² EX1003, ¶¶ 163-65, 175.

¹⁸³ 598 U.S. at 603.

¹⁸⁴ 941 F.3d at 1157.

compounds should be selected for screening, and which in this case is impossible.¹⁸⁵

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

The common disclosure provides an extremely narrow set of working examples: ~5,917 randomly generated single-replacement PH20₁₋₄₄₇ polypeptides, of which ~2500 were “active mutants,” ~3380 were “inactive mutants” and ~830 mutants that are only characterized by their desired sequence—they are not classified as either “active” or “inactive” mutants.¹⁸⁶ Combined, those examples are a tiny fraction of the 10⁶⁰ to 10¹¹³ modified PH20 polypeptides covered by the claims. They also provide no guidance that would help a skilled artisan bypass the “trial-and-error” methodology the common disclosure describes using to make multiply-modified PH20 polypeptides; indeed, none incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.¹⁸⁷

The common disclosure provides no credible guidance on practicing the full scope of the claims.¹⁸⁸ Instead, it describes an explicitly prophetic and “iterative”

¹⁸⁵ *Id.* at 1159.

¹⁸⁶ EX1003, ¶¶ 113-114.

¹⁸⁷ EX1003, ¶¶ 162-66, 173.

¹⁸⁸ EX1003, ¶¶ 143, 149.

“make and test” process for *discovering* active mutant PH20 polypeptides. *See* § V.A.1.d. And its research plan requires a skilled artisan to engage in undue experimentation to practice the full scope of the claims.

First, the common disclosure describes a process requiring manually performing iterative rounds of *randomized* mutations (up to 41 rounds per starting molecule under the broadest claims) to *discover* which of the $10^{60}+$ possible modified PH20 polypeptides the claims encompass might possess hyaluronidase activity.¹⁸⁹

Second, the common disclosure provides no meaningful guidance or information that a skilled artisan could use to implement the prophetic procedure it discloses for making and discovering “active mutant” modified PH20 polypeptides:

¹⁸⁹ EX1003, ¶¶ 191-93; *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 credited a “ground-breaking” predictive molecular modeling technique that was later shown to be false. EX1018, 384, 382; EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

- (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 the regions or residues in PH20 polypeptides that are “associated with activity and/or stability of the molecule” or “critical residues that are involved in the structural folding or other activities of the molecule” particularly when two or more replacements have been made.¹⁹⁰

Instead, the common disclosure requires the skilled artisan to iteratively repeat its prophetic research plan to make and test 10^{60+} multiply-modified PH20 polypeptides to discover which are enzymatically active.¹⁹¹

Regardless whether individual rounds of “iterative” production and testing of PH20 mutants might be considered “routine,” the aggregate scale of experimentation required to practice the full scope of the claims goes far beyond undue—it is impossible. Simply put, the common disclosure’s prophetic, iterative

¹⁹⁰ EX1001, 133:43-55; EX1003, ¶¶ 153, 165, 184, 196-97.

¹⁹¹ EX1003, ¶¶ 184, 198-99.

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.¹⁹² The “*iterative, trial-and-error process[es]*” the common disclosure specifies here are thus indistinguishable from those consistently found to not enable broad genus claims to modified proteins or other useful compounds.¹⁹³

(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.¹⁹⁴ 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.¹⁹⁵

As explained in § VI below, by 2011, skilled artisans could have assessed whether certain *single* amino acid substitutions at certain positions would be

¹⁹² EX1003, ¶¶ 178, 195-97, 202.

¹⁹³ *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.

¹⁹⁴ EX1003, ¶ 61.

¹⁹⁵ EX1003, ¶¶ 61, 204-05.

tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.¹⁹⁶ By contrast, skilled artisans around this time period could *not* have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide.¹⁹⁷

More generally, 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.¹⁹⁸ Replacing multiple amino acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.¹⁹⁹

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.²⁰⁰ For example, the further away the modeled amino acid sequence gets

¹⁹⁶ EX1003, ¶ 207.

¹⁹⁷ EX1003, ¶¶ 165, 243.

¹⁹⁸ EX1003, ¶¶ 59-60, 197.

¹⁹⁹ EX1003, ¶¶ 55, 58, 61.

²⁰⁰ EX1003, ¶ 165.

from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model became.²⁰¹ 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.²⁰² And the time required to carry out rational design techniques to “practice” the full scope of the claimed genus would be unimaginable.²⁰³

Consequently, a skilled artisan could not have used conventional rational design techniques to identify multiply-modified PH20 polypeptide sequences having more than a few substitutions, and certainly not 20 or 42 substitutions.²⁰⁴ Moreover, using such techniques to identify even a handful of active mutant PH20 polypeptides with more than 1 substitution would have taken an extreme amount of time and effort.²⁰⁵

²⁰¹ EX1003, ¶¶ 165, 203, 243; EX1004, ¶¶ 152-153.

²⁰² EX1003, ¶¶ 165, 243; EX1004, ¶¶ 142-144; EX1012, 4, 8.

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

²⁰⁴ EX1003, ¶¶ 50, 201.

²⁰⁵ EX1003, ¶¶ 165, 203.

(d) *Other Wands Factors and Conclusion*

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

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of the range of multiply-changed PH20 polypeptides being claimed.²⁰⁶ Likewise, while there was significant public knowledge about hyaluronidases, there was no solved structure of the PH20 protein. Also, the public literature generally reported on *loss of activity* from mutations in hyaluronidases, and did not predictably teach how to introduce changes that preserved or *enhanced* stability or activity of such proteins.²⁰⁷

Practicing the full scope of claims 1-2, 5, 7-16, and 25-27 thus would have required a skilled artisan to engage in undue experimentation, which renders those claims non-enabled.

²⁰⁶ EX1003, ¶¶ 165, 243.

²⁰⁷ EX1011, 812-814; EX1010, 9437-9439.

2. Dependent Claims 3-4, 6, 17-24, and 28-40 Are Not Enabled

(a) Claims 3, 6, 23

Claims 3, 6, and 23 require the modified PH20 polypeptides to have increased activity (*i.e.*, >100% of unmodified PH20) or increased resistance to or stability in denaturing conditions.

These claims are not enabled for the same reasons that claims 1-2, 5, 7-16, and 25-27 are not enabled (*see* § V.B.1). Specifically, a skilled artisan could not have predicted which of the 10^{60+} PH20 polypeptides having up to 41 changes beyond a required change at position 309 would exhibit increased activity or stability relative to unmodified PH20.²⁰⁸ Instead, a skilled artisan would need to make-and-test each molecule in order to practice the “full scope” of the claims.²⁰⁹

(b) Claim 4

Claim 4 requires “soluble” forms of PH20. Because claim 4 encompasses a substantial portion of the genus of 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 extending past position 456 are “insoluble.” A skilled artisan would have expected the presence of the hydrophobic GPI sequence in a

²⁰⁸ EX1003, ¶¶ 197, 203.

²⁰⁹ *Id.*

PH20 protein to cause aggregation, loss of activity, and/or reduced expression.²¹⁰

The common disclosure recognizes these problems, but provides no examples of modified PH20 polypeptides extending past position 456 that are soluble, much less a broader solution.

(c) Claims 17-24, 28-36

Claims 17-24 and 28-36 employ the genus definition used in claim 1 and recite either further modifications to the modified polypeptides (17-23, 28), pharmaceutical compositions (24, 29-33), or methods of treatment (34-36) using the claimed genus. These claims do not add requirements that limit the structure of polypeptides in the claim 1 genus, and are not enabled for the same reasons.²¹¹

(d) Claims 37-40

Claims 37-40 encompass methods of increasing delivery of a therapeutic agent using any of the modified PH20 polypeptides within claim 1's genus.

The common disclosure indicates that a modified PH20 must possess hyaluronidase activity to be capable of increasing delivery of a therapeutic agent.²¹² Because the common specification does not enable claim 1's genus of

²¹⁰ EX1003, ¶¶ 93-94, 209, 236.

²¹¹ See, e.g., *Idenix*, 941 F.3d at 1155, 1165.

²¹² EX1001, 172:63-173:5, 173:65-174:10, 71:36-61.

“active mutant” modified PH20 polypeptides (*see* § V.B.1), it cannot enable methods dependent on using any “active mutant” modified PH20 polypeptides within claim 1’s genus.

Claims 37-40 are not enabled for another reason. The common disclosure attributes the PH20’s “increased delivery” capability to its ability to cause “spreading” / “diffusion.”²¹³ The common disclosure then explains that one can determine if any modified PH20 polypeptide can cause “spreading” by testing it in an *in vivo* assay: “[t]he ability of a PH20 polypeptide ... to act as a spreading or diffusing agent can be assessed” using a specified *in vivo* experiment using a mouse.²¹⁴ Notably, this is a different test than the *in vitro* assay used to detect hyaluronidase activity.²¹⁵ And, the common disclosure identifies only one mutant with this “spreading” capability determined using its mouse test.²¹⁶

In other words, to determine which of the 10^{60+} modified PH20 polypeptides within claims 1’s genus can be used in the claimed method of increasing delivery of another agent of claims 37-40, a skilled artisan must make and test each of the

²¹³ See § V.A.2.d; EX1001, 172:63-173:5, 173:65-174:10, 71:36-61.

²¹⁴ EX1001, 171:16-36, 285:45-286:24; EX1003, ¶¶ 177-78, 180.

²¹⁵ EX1001, 187:46-62, 223:24-225:20; EX1003, ¶ 195.

²¹⁶ EX1001, 295:47-298:9.

mutants in a mouse experiment.²¹⁷ Practicing the full scope of claims 37-40, thus, would require a skilled artisan to engage in an impossible amount of “make and test” experiments, rendering each of those claims not enabled.

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

Patentee may contend certain claims do not require the modified PH20 polypeptides to be “active mutants,” but that would only compound the written description and enablement problems of those claims.

First, the claims *encompass* all enzymatically active PH20 polypeptides meeting the parameters of the claims. *See* § V.B.2.a. Claims 6 and 23, for example, define a portion of this sub-genus of “active mutants” within claim 1’s scope (*i.e.*, those with >100% hyaluronidase activity). The failure of the common disclosure to describe or enable the full scope of this subgenus of “active mutants” within each claim’s scope renders each claim unpatentable. *See* §§ V.A and V.B.²¹⁸

²¹⁷ EX1003, ¶ 198.

²¹⁸ *ABS Glob., Inc. v. Inguran*, 914 F.3d 1054, 1070, 1074 (7th Cir. 2019) (citing *Alcon Research, Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1367-68 (Fed. Cir. 2012)).

Second, the common disclosure describes *no* examples of a modified PH20 with a substitution at position 309 that rendered it an “inactive mutant”²¹⁹ Of the 15 single-substitution I309 PH20₁₋₄₄₇ mutants listed in Table 8, fourteen had activity above 40% and no data is reported for I309Y, while Table 5 lists *no* I309 “inactive mutants” (*see* § IV.D.3).

The lack of *even one* example of an I309 “inactive mutant” forecloses finding the common disclosure to demonstrate possession of 10⁶⁰⁺ others. There also is no guidance in the common disclosure specific to position 309, or which explains how to *intentionally* produce inactive multiply-mutated PH20 polypeptides. Instead, the common disclosure describes processes that screen mutants *for activity*.²²⁰

The common disclosure also identifies no correlation between the 10⁶⁰⁺ multiply-modified PH20 polypeptides within the claims’ scope and either of the mutually exclusive sub-genera of active and inactive mutants.²²¹ To determine which are one or the other (or neither), the skilled artisan must perform trial-and-

²¹⁹ EX1001, 209 (Table 8), 227 (Table 9).

²²⁰ EX1003, ¶¶ 186, 188, 195; EX1001, 126:44-49, 131:47-51.

²²¹ EX1003, ¶ 153.

error testing of those 10^{60+} modified PH20 polypeptides.²²² Claims read to encompass inactive mutant I309-substituted PH20 polypeptides thus lack written description in, and are not enabled by, the common disclosure.

Finally, the only putative utility identified for “inactive mutants” is as “antigens in contraception vaccines,”²²³ which is not scientifically credible. The disclosure cites two studies involving guinea pig PH20,²²⁴ but ignores other evidence—subsequent peer reviewed journal articles—that demonstrated that immunizing *other mammals* with their species’ PH20 did *not* cause contraception.²²⁵ And Halozyme’s own published clinical studies of unmodified human PH20₁₋₄₄₇ (what the claims concern) showed that “[a]lthough some antisperm antibodies are associated with decreased fertility [], no evidence of

²²² EX1003, ¶ 197-98.

²²³ EX1001, 74:3-5, 186:26-45.

²²⁴ EX1001, 186:26-45; EX1022, 1142-43; EX1023, 1133-34.

²²⁵ 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 ...”).

negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex.”²²⁶

Settled law holds that a claimed invention “must have ‘substantial utility’ and ‘specific benefit exist[ing] in currently available form’”—a theoretical or unproven utility is insufficient.²²⁷ Where an asserted utility is implausible (as here), credible evidence is required to support it.²²⁸ There is none in the common disclosure:

- it identifies **no** “inactive mutants” that were tested, much less proven to have contraceptive effect;
- it provides **no** guidance on selecting “inactive mutants” with contraceptive utility;
- it identifies **no** epitopes or structures on PH20 that induce antibody production that confers contraceptive effects, and

²²⁶ EX1024, 87-88; *see also* EX1061, 1154; EX1003, ¶¶ 121-22.

²²⁷ *In re '318 Patent Infringement Litigation*, 583 F.3d. 1317, 1324 (Fed. Cir. 2009), citing *Brenner v. Manson*, 383 U.S. 519, 86 S.Ct. 1033 (1966) at 86 S.Ct. 1033.

²²⁸ EX1003, ¶¶ 123-25.

- it provides *no* evidence that any such epitopes/structures are preserved in every multiply-modified I309 PH20 “inactive mutant.”²²⁹

Given this absence of information, a skilled artisan could not have reasonably predicted from the common disclosure whether *any* “inactive mutant” PH20 polypeptide within the scope of the claims would cause contraceptive effects, much less that up to 10^{60+} I309 mutants would.²³⁰

There also is no basis for assuming that every PH20 polypeptide that is not an “active mutant” is an “inactive mutant” useful for contraception. A skilled artisan would have considered it highly likely that some number of modified PH20 polypeptides within the 10^{60+} mutants being claimed cannot be produced and/or recovered.²³¹ For example, instability caused by amino acid substitutions can induce cells to break down rather than secrete proteins, prevent proper folding, expose hydrophobic residues leading to aggregation, and cause other problems.²³² Modified PH20 polypeptides that cannot be produced or are not properly folded

²²⁹ EX1003, ¶¶ 121, 124.

²³⁰ EX1003, ¶ 124.

²³¹ EX1003, ¶ 115.

²³² *Id.*; EX1081, 895-897.

will not retain the native protein structure of PH20 and cannot be “useful” “inactive mutants”—they have no utility.²³³

The common disclosure also did not demonstrate that ~3,380 properly folded “inactive mutant” PH20 polypeptides were produced. The experimental protocol instead equated the *absence* of hyaluronidase activity in the supernatant from each transfected cell with proof of production of an “inactive mutant.”²³⁴ But an absence of hyaluronidase activity in the supernatant would also be observed if the cell did not secrete the mutant or if the secreted mutant did not fold.²³⁵

The common disclosure does not report the measured hyaluronidase activity values of the 3,380 mutants labeled “inactive mutants” or ~830 (12%) unclassified mutants, even though it did so for the thousands of “active mutants” in Table 9.²³⁶ It is thus impossible to determine from the common disclosure which of the ~4,180 mutants were (i) actually expressed, properly folded and enzymatically

²³³ EX1003, ¶¶ 124-25; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

²³⁴ EX1003, ¶¶ 109, 112.

²³⁵ EX1003, ¶¶ 110-112.

²³⁶ EX1003, ¶¶ 112-14, 116-17; EX1001, 226:36-249:12 (Table 9), 249:47-255:28 (Table 10).

inactive, (ii) were not successfully produced by or secreted from the transfected cells, or (iii) were secreted but did not fold.²³⁷

And even if a fraction of a percent of the 10^{60+} multiply-modified PH20 polypeptides within the scope of the claims cannot be produced or did not properly fold, they represent a massive absolute number of inoperative embodiments that must be identified by making and testing 10^{60+} polypeptides. Performing the scale of testing necessary to identify such inoperative species within the scope of the claims independently demonstrates a lack of enablement.²³⁸

The common disclosure thus presents only a “research proposal” to discover “inactive mutants” with contraceptive utility, which is insufficient.²³⁹ It does not demonstrate possession of or teach “how to make and use” all inactive PH20 polypeptides with contraceptive utility (if any exist) within the claims. Thus,

²³⁷ EX1003, ¶¶ 111, 114.

²³⁸ EX1003, ¶¶ 124-25; *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).

²³⁹ *See Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009).

regardless of whether the claims are appropriately limited to “active mutants” or also include “inactive mutants,” they are unpatentable under § 112(a).

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

The original claims of the ’731 Application provide no additional guidance demonstrating written description or enablement of the claimed genera of multiply-modified PH20 polypeptides. Those original claims claimed equivalently broad genera via sequence identity language (*e.g.*, 85% to SEQ ID NOS: 3, 7, or 32-66) (claims 1-3) or having up to “75 or more amino acid replacements” (claim 4). Dependent claims listed single positions (claim 12) or replacements (claims 13-16) in those polypeptides. And, while certain claims contemplated 2-3 particular combinations of amino acid replacements (from dozens listed), others encompassed substitutions at unspecified locations.²⁴⁰ The original claims do not provide § 112 support for the challenged claims.²⁴¹

²⁴⁰ EX1026, 335.

²⁴¹ *See, e.g., Ariad Pharms.*, 598 F.3d at 1349; *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993).

VI. Challenged Claims 1-2, 4-5, 7-22 and 24-40 Are Unpatentable Under § 103

Claims 1, 2, 5, 7-16 and 25-27 define genera of modified PH20 polypeptides that encompass one specific modified PH20 polypeptide: I309N PH20₁₋₄₄₇. *See* § IV.D.2. Because this mutant would have been obvious from the '429 Patent in view of Chao and the knowledge of a skilled artisan, each of those claims is unpatentable. Claims 4, 17-22, 24 and 28-40 are also obvious, as each recites attributes met by I309N PH20₁₋₄₄₇, or are suggested by the '429 Patent alone or with Chao and knowledge in the art.

A. The Prior Art

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

Chao (EX1006) was published in "Biochemistry" in 2007. Chao is not discussed in the common disclosure of the '618 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 I309N PH20₁₋₄₄₇ Is Obvious, Claims 1-2, 5, 7-16, and 25-27 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 within non-essential regions of PH20₁₋₄₄₇ that would have been tolerated (*i.e.*, a PH20₁₋₄₄₇ with that single substitution would retain enzymatic activity). I309N PH20₁₋₄₄₇ is one such example. Because claims 1-2, 5, 7-16 and 25-27 encompass at least this obvious variant of PH20₁₋₄₄₇, each is unpatentable.

1. Patentee's '429 Patent Motivates a Skilled Artisan to Make Single Amino Acid Substitutions in Non-Essential Regions of 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.²⁴² It exemplifies and claims one such "sHASEGP" that terminates at position 447 (positions 36-482 of SEQ ID NO: 1).²⁴³

The '429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, to increase delivery of other therapeutic agents (*e.g.*,

²⁴² EX1005, 6:4-10, 10:30-59.

²⁴³ EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

antibodies, chemotherapeutics), treating cancer and hyaluronidase disorders.²⁴⁴

PH20₁₋₄₄₇ was approved by the FDA as Hylenex[®] in 2005.²⁴⁵ The '429 Patent's teachings combined with knowledge of PH20₁₋₄₄₇ as an approved human therapeutic before 2011 would have induced a skilled artisan to focus on this particular PH20 polypeptide.²⁴⁶

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.²⁴⁷ As it states:

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 ...²⁴⁸

²⁴⁴ 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.

²⁴⁵ EX1049, 1.

²⁴⁶ EX1003, ¶ 208.

²⁴⁷ EX1005, 9:65-10:13, 18:64-19:6.

²⁴⁸ EX1005, 16:14-22.

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.”²⁴⁹

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 that do not substantially alter the activity or function of PH20₁₋₄₄₇.²⁵⁰ The '429 Patent also motivates skilled artisans to undertake this effort to make single-amino acid substituted PH20₁₋₄₄₇ proteins by assuring them their efforts will be successful.²⁵¹ A skilled artisan would have reasonably 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 PH20₁₋₄₄₇.²⁵²

²⁴⁹ EX1005, 16:24-36.

²⁵⁰ EX1003, ¶¶ 219-220; EX1004, ¶ 32.

²⁵¹ EX1003, ¶ 221.

²⁵² EX1003, ¶¶ 212-15, 221, 236.

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 would have used rational design to do so, which would require determining (i) which regions are non-essential in PH20, and (ii) which single amino acids are appropriate to substitute into positions in those non-essential regions.²⁵³

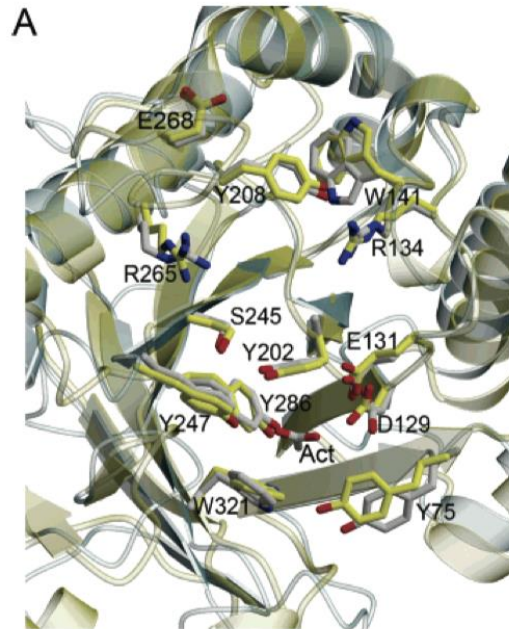
The '429 Patent was written eight years before 2011. Given that, a skilled artisan would have reviewed literature providing insights into the structure of human hyaluronidase enzymes such as PH20.²⁵⁴ That would have led to Chao (EX1006), which reported an experimentally determined structure for human HYAL1 and provided new insights into the shared characteristics of human hyaluronidase enzymes.²⁵⁵

²⁵³ EX1003, ¶¶ 226-28.

²⁵⁴ EX1003, ¶¶ 100, 221-22.

²⁵⁵ EX1003, ¶¶ 81-89; EX1004, ¶ 88; EX1006, 6912-17.

Chao showed that human and non-human hyaluronidases share a highly conserved active site and identified residues that interact with HA, *inter alia*, by superimposing HYAL1 and bee venom hyaluronidase structures.²⁵⁶



The '429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20,²⁵⁷ and taught that hyaluronidase domains share similarity among species, including residues necessary for enzymatic activity.²⁵⁸

²⁵⁶ EX1006, 6917 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1004, ¶¶ 89-91; EX1003, ¶¶ 81-82.

²⁵⁷ EX1005, 4:12-22, 86:49-53, 88:14-24.

²⁵⁸ EX1005, 2:6-67, 4:11-22.

Second, using an alignment of five human hyaluronidases, Chao identified predicted secondary structures (*e.g.*, β -sheets, α -helices) (Figure 3, below), as well as invariant conserved positions (blue), residues involved in catalysis (red), conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).²⁵⁹

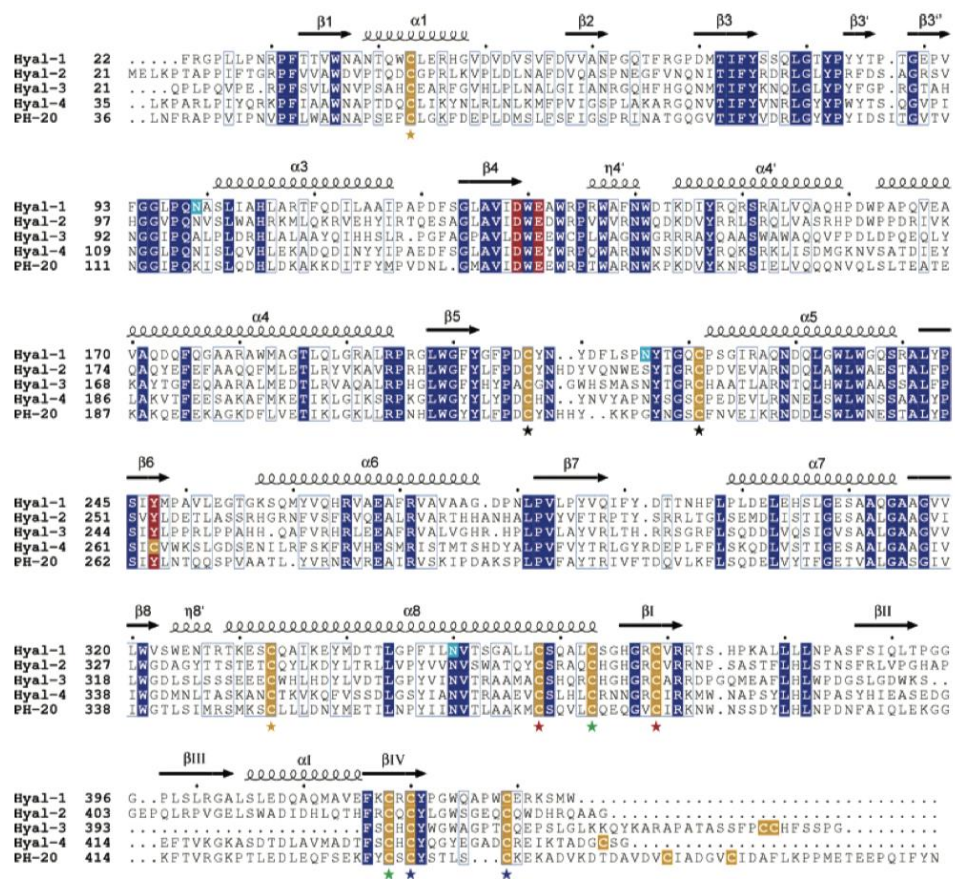


FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative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

²⁵⁹ EX1006, 6916; EX1003, ¶¶ 83, 225; EX1004, ¶ 92.

Third, Chao reported the presence of “a novel, EGF-like domain” in the C-terminal region of human hyaluronidases that was “closely associated” with the catalytic domain (discussed above, § V.A.1.b.iii). It identified a characteristic pattern for the Hyal-EGF domain, which in PH20 is at positions 337-409.²⁶⁰

3. A Skilled Artisan Would Have Identified Position 309 as Being in a Non-Essential Region of PH20₁₋₄₄₇ in 2011

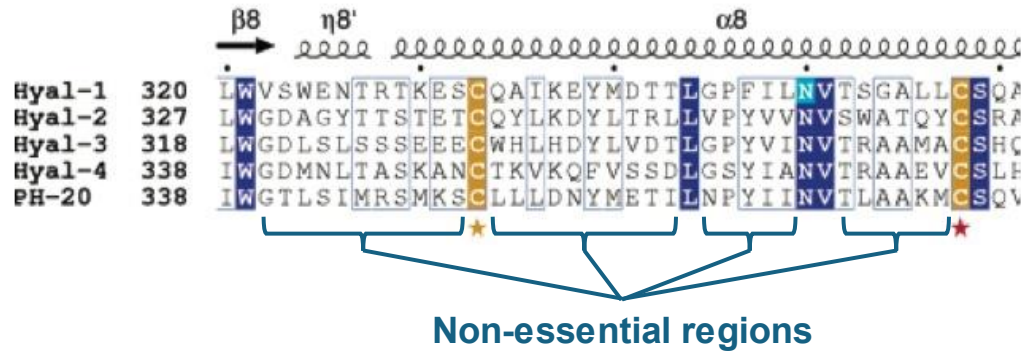
To implement the '429 Patent's suggestion to produce modified PH20₁₋₄₄₇ polypeptides with single amino acid substitutions in non-essential regions that retain hyaluronidase activity, a skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011.²⁶¹ The artisan would have done that using conventional sequence alignment tools in conjunction with the information in the '429 Patent and Chao, all publicly available in 2011.²⁶² In particular, a skilled artisan would have prepared a multiple-sequence alignment to identify essential residues in PH20—which thereby identifies the non-essential regions of PH20 (*i.e.*, the sequences between essential residues) (illustrated below).²⁶³

²⁶⁰ EX1006, 6911; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84, 88.

²⁶¹ EX1003, ¶¶ 226-28; EX1004, ¶¶ 22, 25-30, Appendix D-3.

²⁶² EX1003, ¶¶ 20-21, 227-29; EX1004, ¶¶ 22-24; EX1017, 224-26.

²⁶³ EX1004, ¶¶ 31-32, Appendix D-2; EX1003, ¶¶ 227-28; EX1006, 6916.



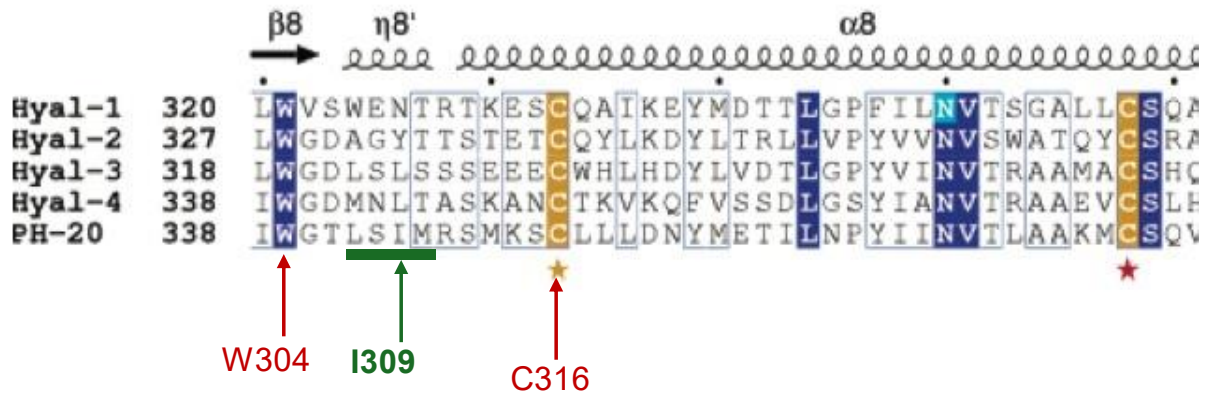
Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps. He identified 88 homologous hyaluronidase protein sequences published by December 29, 2011.²⁶⁴ Then he prepared a multiple-sequence alignment of these sequences, as Chao did with the five human hyaluronidases, and from that alignment identified essential (Appendix D-3) and non-essential (Appendix D-2) residues.²⁶⁵

Position 309 is within a non-essential region of PH20₁₋₄₄₇—Dr. Park’s analysis and Chao’s Figure 3 both report the same bounding essential residues (*i.e.*, W304 and C316) (below).²⁶⁶

²⁶⁴ EX1004, ¶¶ 27, 134-137; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

²⁶⁵ EX1004, ¶¶ 28-32, 138-139, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

²⁶⁶ EX1003, ¶ 231; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.



Thus, a skilled person in December 2011 using conventional sequence analysis tool would have readily identified position 309 as being a position within a non-essential region of PH20₁₋₄₄₇.²⁶⁷

4. A Skilled Artisan Would Have Viewed Asparagine as an Obvious Single Amino Acid Substitution for Isoleucine at Position 309 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.²⁶⁸ This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms

²⁶⁷ EX1003, ¶ 234; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

²⁶⁸ EX1003, ¶ 228; EX1004, ¶¶ 21-22.

those variations in the sequences of a protein that do not yield stable and active forms of the protein.²⁶⁹

Using a multiple-sequence alignment, a skilled artisan can readily compile a list of amino acids tolerated at positions within non-essential regions of PH20.²⁷⁰ Dr. Park did this: using his multiple-sequence alignment of the 88 hyaluronidase proteins known by December 2011, he identified the identity and frequency of different amino acids that occur at positions corresponding to position 309 in PH20 in homologous hyaluronidases (below).²⁷¹

AA at position 344/309 in PH20 ₁₋₄₄₇	Count	Most frequent AA at position in set of proteins	% of occurrence of AA in set of proteins
wt 344: I	4.54	L	32.95
res383: L	29		32.95
res383: Y	26		29.54
res383: F	8		9.09
res383: N	8		9.09
res383: D	4		4.54
res383: I	4		4.54
res383: K	2		2.27
res383: M	2		2.27
res383: -	2		2.27
res383: S	1		1.13
res383: C	1		1.13
res383: V	1		1.13

²⁶⁹ EX1003, ¶ 228; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 (evolutionarily conserved sequences useful for determining protein structure and function); EX1014, 351.

²⁷⁰ EX1003, ¶¶ 228-29; EX1004, ¶¶ 21-22.

²⁷¹ EX1004, ¶¶ 30-32, 41-43, 106, 114, Appendix D-1; EX1003, ¶¶ 229, 231-32.

The wild-type residue at position 309 in PH20 is isoleucine (I), which occurs at positions corresponding to position 309 in ~4.5% of homologous proteins, while leucine is the most prevalent amino acid found at those positions (~33%) (*i.e.*, leucine occurs in 29 different hyaluronidase proteins), and asparagine occurs at that position in ~9% of the proteins.²⁷²

As explained in §VI.B.3, a skilled artisan would have recognized that I309 is within a non-essential region of PH20₁₋₄₄₇ at which a single amino acid substitution could be made pursuant to the guidance in the '429 Patent.²⁷³

The skilled artisan would have selected asparagine (N) as one of the obvious choices for a single substitution at position 309 in PH20₁₋₄₄₇.²⁷⁴ Asparagine occurs at positions corresponding to 309 in 9% of homologous, naturally occurring hyaluronidase sequences known by 2011, including in human HYAL1 (as shown in Chao Figure 3, above).²⁷⁵ This high frequency of occurrence suggests to a skilled artisan that asparagine will be tolerated in PH20 at position 309, and makes it an obvious amino acid to substitute into position 309 of PH20₁₋₄₄₇ under the

²⁷² EX1004, ¶ 114; EX1003, ¶ 232.

²⁷³ EX1003, ¶¶ 231, 234.

²⁷⁴ EX1003, ¶¶ 234, 235; EX1004, ¶¶ 41-42, 106, 114.

²⁷⁵ EX1004, ¶¶ 43, 106, 114; EX1003, ¶¶ 232, 234.

rationale of the '429 Patent.²⁷⁶ Consequently, a skilled artisan would have found asparagine to be an obvious substitution for isoleucine at position 309 in PH20₁₋₄₄₇ pursuant to the guidance in the '429 Patent, Chao, and publicly available information.²⁷⁷

5. A Skilled Artisan Would Have Reasonably Expected the I309N PH20₁₋₄₄₇ to Be Enzymatically Active

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

Replacing the isoleucine at position 309 with asparagine yields a PH20₁₋₄₄₇ with a single amino acid substitution in a non-essential region of the polypeptide.²⁷⁸ 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.²⁷⁹

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

²⁷⁶ EX1003, ¶ 235; EX1004, ¶ 114.

²⁷⁷ EX1003, ¶¶ 232-35.

²⁷⁸ See § VI.B.3; EX1003, ¶ 231; EX1004, ¶ 32.

²⁷⁹ EX1005, 16:17-20.

on its statements that a skilled artisan would have expected *any* single amino acid substitution in *any* non-essential position of PH20₁₋₄₄₇ to not substantially affect the activity of the enzyme. Patentee should not be permitted to now contend a skilled artisan would not have reasonably expected that the I309N substitution in PH20₁₋₄₄₇ would yield an enzyme with substantially the same activity as unmodified PH20₁₋₄₄₇.

(b) Skilled Artisans Would Reasonably Expect the I309N Substitution to be Tolerated in PH20₁₋₄₄₇

Independently, a skilled artisan would have reasonably expected the I309N substitution to not substantially alter the biological activity (hyaluronidase activity) of PH20₁₋₄₄₇.

First, both experts noted that many naturally occurring homologous hyaluronidase proteins contain asparagine at positions corresponding to position 309 in PH20 (including asparagine in human HYAL1 (Chao)), which would have led a skilled artisan to believe that asparagine would be tolerated at position 309 in PH20.²⁸⁰

Second, Dr. Park's sequence alignment shows that many (10) other amino acids occur in homologous proteins at positions corresponding to position 309 in

²⁸⁰ EX1003, ¶¶ 232-34; EX1004, ¶¶ 106, 114.

PH20.²⁸¹ The amino acids that occur at that position have diverse characteristics (e.g., polar and non-polar, have high and low helix propensities, and have large or small side chains), which suggests that many different amino acids can be tolerated at position 309 in PH20.²⁸²

In view of these factors, a skilled artisan would have reasonably expected the I309N substitution to be tolerated in PH20₁₋₄₄₇.²⁸³

(c) A PH20 Structural Model Confirms that PH20₁₋₄₄₇ Would Tolerate Asparagine at Position 309

Dr. Park also assessed whether single amino acid substitutions in PH20₁₋₄₄₇ would be tolerated, including I309N, 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.²⁸⁴

²⁸¹ EX1004, ¶ 106.

²⁸² EX1003, ¶ 233; EX1004, ¶ 106.

²⁸³ EX1003, ¶¶ 234-35; EX1004, ¶ 106.

²⁸⁴ EX1004, ¶¶ 39-40, 140-141; EX1003, ¶¶ 237-42; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

Dr. Park explains that his PH20 model was reliable in the region of position 309 of PH20 based on QMEAN values,²⁸⁵ 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).²⁸⁶

Dr. Park also devised a consistent, objective methodology for assessing substitutions using the PH20₁₋₄₄₇ model.²⁸⁷ Factors he considered included, *inter alia*, the number of neighboring residues at position 309 (*i.e.*, those within 5 Å), the various possible interactions between neighbors (*e.g.*, hydrophobic, charged, van der Waals, steric, etc.), and solvent accessibility.²⁸⁸ Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*, hydrophobic-hydrophilic,

²⁸⁵ EX1004, ¶¶ 142-144 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

²⁸⁶ EX1004, ¶¶ 145-146, 150; EX1038, 3382-4; EX1017, 229-230; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

²⁸⁷ EX1004, ¶¶ 102-103; *see generally id.* at § IV.C (description of Dr. Park's methodology); EX1003, ¶¶ 229-230.

²⁸⁸ EX1004, ¶¶ 44-47, 53-60, 65-85, Appendix D-5; EX1035, 1408, Table 2; EX1043, 2, Table 1.

effects on secondary structures, size related issues such as steric clashes, or creation/filling of “holes” in the structure).²⁸⁹

Dr. Park assessed the environment of position 309 visually by comparing the wild-type with the version incorporating substituted amino acids at position 309 using functionality within the viewer (PyMol) and as a modeled sequence generated from the PH20₁₋₄₄₇ sequence incorporating the single substitution in SWISS-MODEL.²⁹⁰ These technologies were all available in 2011.²⁹¹ He used his methodology to assess substitutions representing diverse interactions, and confirmed it provided a consistent, objective and unbiased evaluation of substitutions.²⁹²

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed (below).²⁹³

²⁸⁹ EX1004, ¶¶ 62-63, 85.

²⁹⁰ EX1004, ¶¶ 61, 107, 113, 115, 118, 156-167; EX1003, ¶¶ 239-241.

²⁹¹ EX1004, ¶¶ 140, 145-146, 153-154, 157-158; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4; EX1003, ¶¶ 20-22.

²⁹² EX1004, ¶¶ 102-103; EX1003, ¶¶ 229-230.

²⁹³ EX1004, ¶¶ 85-87.

<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 I309N substitution in PH20₁₋₄₄₇, indicating it would be a neutral change that would be tolerated.²⁹⁴ He observed that in the wild-type PH20 environment, isoleucine is in a short helix that is not a strictly conserved secondary structure, consistent with position 309 tolerating many different kinds of amino acids.²⁹⁵ He observed that I309 is a buried residue shielded from solvent,²⁹⁶ and supports the short helix (including L307) which appears to interact with ligand (below).²⁹⁷ In addition, he observed a significant amount of space around position 309 that would accommodate larger amino acids.²⁹⁸

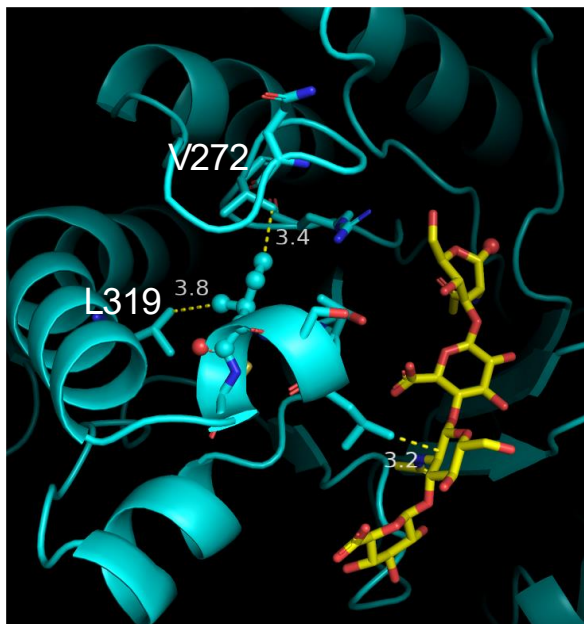
²⁹⁴ EX1004, ¶ 119, Appendix C.

²⁹⁵ EX1004, ¶ 108; EX1006, 6916, 6913 (describing as the η8₃₁₀ sequence in HYAL1).

²⁹⁶ EX1004, ¶ 109.

²⁹⁷ EX1004, ¶ 110.

²⁹⁸ EX1004, ¶ 111.

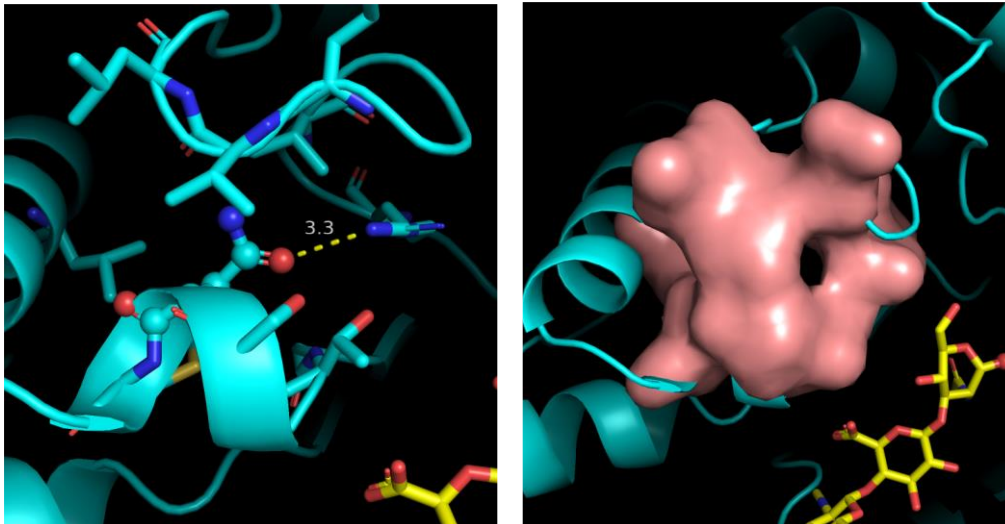


Dr. Park analyzed the I309N substitution within the PH20 model. He observed that asparagine's amide bond forms a strong hydrogen bond with R270 (below).²⁹⁹ He also found I309N to support the short helix in PH20 between 306 and 310.³⁰⁰ From his analysis, Dr. Park concluded asparagine would likely be tolerated at position 309, which he also confirmed by energy minimization.³⁰¹

²⁹⁹ EX1004, ¶ 116.

³⁰⁰ EX1004, ¶¶ 116-117.

³⁰¹ EX1004, ¶¶ 118-19.



Dr. Park's visualization-based assessment was a prevalent technique used in 2011.³⁰² Similarly, his technique of assessing interactions between neighbors and assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications.³⁰³

³⁰² EX1017, 228 (“... a structural biologist’s intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this.”); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 240-42.

³⁰³ EX1004, ¶¶ 48-52; EX1031, 459, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 242.

Dr. Hecht reviewed Dr. Park's analysis and conclusions concerning the I309N single substitution and agreed with them.³⁰⁴ He concluded that asparagine would likely have been tolerated at position 309 as a single substitution in PH20₁₋₄₄₇ because it frequently occurs in homologous hyaluronidase proteins, and because Dr. Park's model showed that it would be tolerated at position 309.³⁰⁵

6. I309N PH20₁₋₄₄₇ Would Have Reasonably Been Expected to Be an Active Mutant

The common disclosure defines an "active mutant" as a modified PH20 polypeptide with at least ~40% of the activity of unmodified PH20₁₋₄₄₇.³⁰⁶ Drs. Hecht and Park each independently concluded that the I309N substitution would have been tolerated by PH20₁₋₄₄₇.³⁰⁷ A skilled artisan thus would have reasonably expected that the I309N PH20₁₋₄₄₇ polypeptide would exhibit at least 40% of the activity of unmodified PH20₁₋₄₄₇.³⁰⁸

Based on the '429 Patent, Chao, and information available in 2011, the I309N PH20₁₋₄₄₇ polypeptide would have been obvious to a skilled artisan in 2011.

³⁰⁴ EX1003, ¶¶ 241, 244.

³⁰⁵ EX1003, ¶¶ 242, 244.

³⁰⁶ EX1001, 73:61-66; *also id.* at 77:43-47.

³⁰⁷ EX1003, ¶¶ 244-46, 250; EX1004, ¶¶ 17, 119.

³⁰⁸ EX1003, ¶ 248.

And because claims 1-2, 5, 7-16, and 25-27 each encompass this single-substitution mutant, each claim is unpatentable.

C. Dependent Claims 4, 17-22, 24, and 28-40 Are Obvious

Each of claims 4-5, 17-22, 24, and 28-40 defines subject matter that would have been obvious to a skilled artisan from the '429 Patent alone or with Chao and knowledge in the art.

1. Claim 4

Claim 4 requires the modified PH20 polypeptide of claim 1 to be “soluble.”

The '429 Patent indicates that PH20₁₋₄₄₇ omits the C-terminal residues containing the GPI anchor sequence and is thus soluble.³⁰⁹ A skilled artisan would have expected that a single substitution in a non-essential region of PH20₁₋₄₄₇ that was tolerated, such as I309N, would remain soluble as it would not meaningfully alter the overall structure of PH20₁₋₄₄₇.³¹⁰

2. Claims 17-19

Claims 17-19 specify post-translational modifications of PH20 including that they: (i) “comprise one or more post-translational modifications” including glycosylation (17), is “glycosylated” (18), and “comprise an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues” (19).

³⁰⁹ EX1005, 3:57-62, 87:52-88:24.

³¹⁰ EX1003, ¶¶ 209, 216, 236.

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 yields active glycosylated forms of PH20₁₋₄₄₇.³¹¹ 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.³¹² Frost confirmed that 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.”³¹³

Based on the '429 Patent and knowledge in the art, a skilled artisan would have found it obvious to produce I309N PH20₁₋₄₄₇ in a CHO cell, and that doing so causes its six N-linked glycosylation sites to be glycosylated as claims 17-19 specify.³¹⁴

³¹¹ EX1005, 95:13-30, 40:41-51, 89:53-91:67, 88:5-9.

³¹² EX1005, 3:27-35, claims 1, 6.

³¹³ EX1013, 432.

³¹⁴ EX1003, ¶¶ 210-11, 216-17.

3. Claims 20-22, 28

Claims 20-22 and 28 specify modified PH20 polypeptides: (i) that are conjugated to a polymer (*e.g.*, polyethylene glycol) (20-21) or (ii) comprise a heterologous signal sequence (22, 28).

A skilled artisan would have found the '429 Patent to suggest each of these requirements.³¹⁵ First, it teaches (as claims 20-21 specify) that PH20₁₋₄₄₇ proteins with mutations (“sHASEPGs”) can be “modif[ied]” “with polymers such as polyethylene glycol.”³¹⁶ Second, it describes expression of modified PH20 polypeptides that incorporate heterologous signal sequences (as claims 22 and 28 specify).³¹⁷ Claims 20-22 and 28 thus would have been obvious.

4. Claims 24, 29-40

Claims 24 and 29-33 specify pharmaceutical compositions comprising (24) or consisting of (29) any modified PH20 polypeptide in the genus of claim 1, or which include a “therapeutically active agent formulated in the same composition or in a separate composition” (30). Claims 31-33 specify a variety of additional

³¹⁵ EX1003, ¶¶ 217, 218.

³¹⁶ EX1005, 3:64-4:1, 4:45-53, 26:20-28:4.

³¹⁷ EX1005, 34:33-37; 88:28-90:15.

classes or types of therapeutic agents (31), including “chemotherapeutic agents” (32) and “an antibody” (33).

Claims 34-36 specify methods “for treating a hyaluronan-associated disease or condition” (34) such as cancer (35) or a solid tumor (36) by administering modified PH20 polypeptides of claim 1.

Claims 37-40 specify methods of “increasing delivery of a therapeutic agent” that comprises administering it with a modified PH20 polypeptide of claim 1 (37), administering the two agents subcutaneously (38), administering the PH20 before the therapeutic agent (39), and where the other agent is an antibody (40).

The '429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*, PH20₁₋₄₄₇) (24), alone (29) or with other therapeutic agents used in treating cancer, tumors, and hyaluronan-associated disease (30, 34-36), including an “antibody” which is a “protein” (31, 33) or a “chemotherapeutic agent” (32).³¹⁸ It similarly describes and claims methods of subcutaneously administering formulations that combine an enzymatically active “sHASEPGs” (*e.g.*, PH20₁₋₄₄₇ with one substitution) with another therapeutic agent, which together enable increased

³¹⁸ EX1005, 54:40-57:21, 73:4-74:29, 58:67-59:12, 61:14-57, claims 14, 29, 33.

delivery of the therapeutic agent.³¹⁹ It likewise explains that the therapeutic agent and the PH20 can be subcutaneously administered together or sequentially.³²⁰ The '429 Patent also teaches administering enzymatically active "sHASEPGs" (*e.g.*, PH20₁₋₄₄₇ with one substitution) to treat hyaluronan-related diseases, including solid tumors.³²¹

Because the I309N PH20₁₋₄₄₇ polypeptide would be expected to have a comparable structure and activity as unmodified PH20₁₋₄₄₇, a skilled artisan would have believed it would share the utilities of the unmodified PH20₁₋₄₄₇ in the pharmaceutical compositions, methods of administration, and methods of treatment described in the '429 Patent.³²² Indeed, in the '429 Patent, Patentee secured claims encompassing pharmaceutical compositions containing PH20 polypeptides with 1+ substitutions and chemotherapeutic agents despite the absence of any

³¹⁹ *Id.*; also EX1005, 8:25-38, 63:40-64:4, 76:18-77:37, claim 27; EX1003, ¶ 210.

³²⁰ *Id.*; EX1005, 75:25-50; EX1003, ¶¶ 213-15.

³²¹ *Id.*; also EX1005, 73:4-8, 40-58, 54:40-45, 10:6-13; EX1003, ¶¶ 212-15.

³²² EX1003, ¶¶ 207-210, 216-18, 231.

exemplification.³²³ Claims 24 and 29-33 also impose no restrictions on the makeup of the pharmaceutical composition.

The '429 Patent also teaches that enzymatically active “sHASEPGs” (*e.g.*, PH20₁₋₄₄₇ with one substitution) can be used to enhance delivery of another therapeutic agent, and illustrates doing that with antibodies.³²⁴ A skilled artisan would have expected the I309N PH20₁₋₄₄₇ polypeptide to cause spreading comparably to unmodified PH20₁₋₄₄₇ as it would be expected to retain much of its hyaluronidase activity and the overall structure of unmodified PH20₁₋₄₄₇, including the Hyal-EGF domain, given that the 309 substitution is not within that sequence (*i.e.*, 337-409).³²⁵ A skilled artisan thus would have found the claimed methods to have been obvious from the '429 Patent.³²⁶

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

³²³ EX1005, claims 29, 30, 50.

³²⁴ EX1005, 8:25-37, 54:40-45, 56:36-57:21, 73:4-20, 97:36-98:18, 98:49-99:24, 100:7-47; EX1003, ¶¶ 213-14.

³²⁵ EX1003, ¶¶ 215, 236.

³²⁶ EX1003, ¶¶ 212-15, 221, 236.

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 I309N PH20₁₋₄₄₇ substitution is obvious. For example, Patentee may contend that the variant has unexpectedly high hyaluronidase activity as a single substitution mutant. Demonstrating that result for one mutant out of the $\sim 10^{60}$ to 10^{113} modified PH20 polypeptides encompassed by the claims utterly fails to establish a nexus between that evidence and the claims. As explained in § V.A.1, the single-substitution I309N PH20₁₋₄₄₇ mutant is not representative of the numerous, structurally different proteins encompassed by the claims, particularly those expected to be inactive. No evidence or explanation is provided in the common disclosure that resolves this confusion.

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

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

No litigation involving the '618 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). Since November 2024, Merck has diligently filed 10 PGRs against this family of Halozyme patents.

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.³²⁷ The present obviousness grounds also rely on Chao (EX1006), which was not cited or considered during examination, and are supported by evidence not available to the Examiner (*e.g.*, expert testimony of Drs. Hecht and Park).

Also, while certain indefiniteness rejections were imposed and overcome by claim amendments,³²⁸ 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: April 15, 2025

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³²⁷ EX1002, 903-11.

³²⁸ EX1002, 966-69, 988.

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,037,618
1002	File History of U.S. Patent No. 12,037,618
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	Branden & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '618 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	2024 Chemistry Nobel Prize Background
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 '618 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 I309N Mutation
1071	Swiss Model Printout of PH20 Model with I309L Mutation
1072	Swiss Model Printout of PH20 Model with I309M Mutation
1073	[Reserved]
1074	[Reserved]
1075	[Reserved]
1076	[Reserved]
1077	[Reserved]
1078	[Reserved]
1079	Hunnicutt et al., "Sperm Surface Protein PH-20 Is Bifunctional: One Activity Is a Hyaluronidase and a Second, Distinct Activity Is Required in Secondary Sperm-Zona Binding," Biol. Reprod., 55(1):80-86 (1996)

No.	Exhibit Description
1080	Bookbinder et al., "A Recombinant Human Enzyme for Enhanced Interstitial Transport of Therapeutics," J. Controlled Release, 114:230-241 (2006)
1081	Goldberg, "Protein degradation and protection of against misfolded or damaged proteins," Nature, 426:895-899 (2003)

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 18,688 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 15th day of April, 2025, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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