

Paper No. 1

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00004
U.S. Patent No. 12,018,298

PETITION FOR POST GRANT REVIEW

Halozyme EX2023
Merck v. Halozyme
PGR2025-00017

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I. Introduction

Petitioner Merck Sharp & Dohme LLC (“Merck”) requests post grant review of claims 1-22 of U.S. Patent No. 12,018,298 (“’298 Patent”).

The ’298 Patent claims are unpatentable for three independent reasons.

The first two are linked to the extreme breadth of the claims, which encompass between 10^{49} and 10^{66} different mutated forms of an enzymatically active human hyaluronidase protein called PH20. That breadth results from the unconstrained language in claims 1 to 4, which each define a genus of PH20 polypeptides that *requires one* amino acid substitution at position 313, but then *permits* (via sequence identity language) up to 16, 20, 21, or 22 additional substitutions at *any* of between 430 and 465 positions of PH20, and to *any* of 19 other amino acids. The scale of this genus is unfathomable. The weight of a set of one molecule of each polypeptide in one genus exceeds that of the Earth, and practicing the claims’ full scope using the patent’s iterative methodology would require many lifetimes of “making-and-testing” by a skilled artisan.

These immensely broad claims, measured against the common disclosure of the ’298 Patent and its ultimate parent ’731 Application,¹ utterly fail to satisfy the written description and enablement requirements of § 112(a). That deficiency

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

renders every claim of the '298 Patent unpatentable. It also precludes those claims from a valid § 120 benefit claim to the '731 Application, the only non-provisional application filed before March 16, 2013, thus making the '298 Patent PGR eligible.

First, regarding written description, the common disclosure makes no effort to identify (and never contends there is) a common structure shared by enzymatically active, multiply-modified PH20 polypeptides within each claimed genus. The disclosed examples also are plainly not representative of that gargantuan and structurally diverse genus: every disclosed mutant has only *one* amino acid substitution in *one* PH20 sequence (1-447), while the claims encompass myriad structural variants of PH20, resulting from incorporation of innumerable, *undescribed* combinations of 5, 10, 15 or 20+ substitutions anywhere in the PH20 sequence. The claims even capture mutated PH20 polypeptides the disclosure says to exclude, such as those which rendered PH20 inactive with a single mutation, or truncated forms the disclosure and prior art describe as inactive. The disclosure is nothing more than a research plan, lacking any blaze marks, while the claims improperly seek to capture any enzymatically active, multiply-mutated PH20 polypeptides that might be discovered now or in the future.

Second, regarding enablement, the common disclosure has equally fatal problems. It neither describes nor characterizes *any* modified PH20 with 2 or more substitutions that is enzymatically active, much less affirmatively guides the

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selection of *which* combinations of substitutions yield such proteins. And the only disclosed process for making PH20 mutants with multiple substitutions is a prophetic, “iterative” research plan that explicitly requires the same type of 2011-era “trial-and-error” experiments the Supreme Court recently found incapable of enabling a large genus of diverse polypeptides.² Indeed, to practice the full scope of the claims would require scientists to repeat this “make-and-test” methodology innumerable times until they had made and tested between 10^{49} and 10^{66} unique proteins. That is far more than undue experimentation—it is impossible.

Finally, claims 1-4 and 7-22 are also independently unpatentable because each captures a *single* PH20 mutant with a *single* amino acid substitution at position 313 (from methionine (M) to lysine (K)) (“M313K PH20₁₋₄₄₇”). But Patentee’s earlier ’429 Patent (EX1005)³ makes that mutant obvious, along with methods of making and using it. In particular, it directs artisans to make single amino acid substitutions in non-essential regions of the PH20₁₋₄₄₇ sequence, and then explicitly claimed them. Implementing that guidance in 2011 would have led the skilled artisan to an intervening publication—Chao (EX1006)—that is ignored in Patentee’s 2011-era disclosure and was never cited to the Office during

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

³ U.S. Patent No. 7,767,429.

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examination. The collective guidance of the '429 Patent and Chao (i) readily identifies position 313 as being in a non-essential region of PH20, and (ii) motivates the skilled artisan to substitute lysine at that position—the most commonly occurring amino acid in that position in known, homologous hyaluronidases. And the skilled artisan would have reasonably expected M313K PH20₁₋₄₄₇ to retain the enzymatic activity of its parent because that is precisely what the '429 Patent says (“Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity”).⁴ A skilled artisan, in 2011, would have considered M313K PH20₁₋₄₄₇ to be *one* obvious PH20 mutant in the claimed genus.

The evidence demonstrates the '298 Patent claims are unpatentable. The Board should institute post grant review.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition is filed within 9 months of the '298 Patent's issuance. Petitioner certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '298 Patent.

⁴ EX1005, 16:17-22.

The '298 Patent is eligible for post-grant review because at least one of its claims is not entitled to an effective filing date prior to March 16, 2013.

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

The '298 Patent claims benefit under 35 U.S.C. § 120 and/or § 121 to seventeen earlier-filed non-provisional applications. Only one—U.S. Application No. 13/694,731 (the '731 Application)—was filed before March 16, 2013. That application, issued as U.S. Patent No. 9,447,401 (EX1025), claims priority to and incorporates by reference the disclosures of two provisional applications (61/631,313, filed November 1, 2012 and 61/796,208, filed December 30, 2011),

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as well as WO 01/3087 (“WO087”). The ’731 application alters several passages of the provisional disclosures, adds new examples and tested mutants and makes other changes.⁵

The disclosure of the ’731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the ’298 Patent (§§ V.A, V.B). The same is true for the ’298 Patent, whose disclosure is substantively identical to the ’731 Application.⁶ The ’298 Patent is PGR eligible as at least one of its claims does not comply with § 112(a) based on the ’731 Application filed before March 16, 2013.

B. Mandatory Notices**1. Real Party-in-Interest**

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

2. Related Proceedings

PGR2025-00003 is a related proceeding.

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

⁶ References to the “common disclosure” are to the shared disclosure of the ’298 Patent and the ’731 Application (EX1026). Citations are to the ’298 Patent, and EX1015 correlates citations to the ’731 Application.

3. Counsel and Service Information

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

III. Grounds

The grounds advanced in this Petition are:

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

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

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

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signal sequence, while mature forms of PH20 omit those 35 residues and have positions that differ from SEQ ID NO: 6 by 35 residues.⁷ The annotation “PH20_{1-n}” is used to refer to a sequence of 1-n residues in PH20 (*e.g.*, PH20₁₋₄₄₇ is SEQ ID NO: 3), and “AxxxB” is used to identify the position of a substitution (“M313K”).

IV. Background on the '298 Patent

A. Field of the Patent

The '298 Patent concerns the human PH20 hyaluronidase enzyme, and structurally altered forms of that protein that retain enzymatic activity.⁸

1. Protein Structures

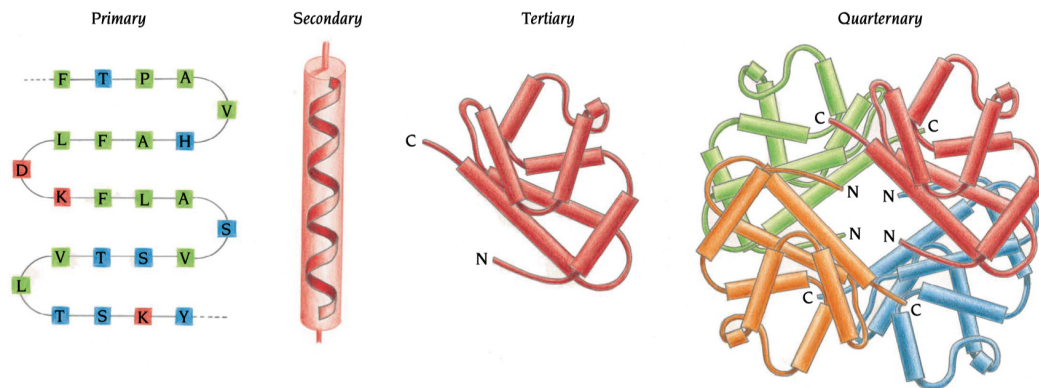
Proteins are comprised of sequences of amino acids. The activity of a protein, however, derives from its unique, three-dimensional shape—its structure.⁹ That, in turn, is dictated by specific and often characteristic patterns of amino acids in its sequence, which induce formation and maintenance of various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

⁷ EX1003, ¶ 15.

⁸ EX1001, 2:50-54.

⁹ EX1003, ¶ 36.

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



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

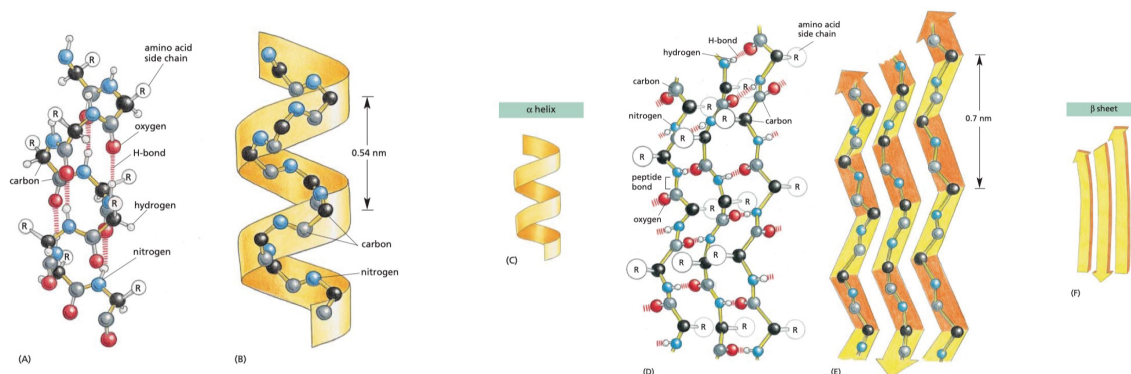


Figure 3-7 The regular conformation of the polypeptide backbone in the α helix and the β sheet. <GTAG> <TGCT>
(A, B, and C) The α helix. The N-H of every peptide bond is hydrogen-bonded to the C=O of a neighboring peptide bond located four peptide bonds away in the same chain. Note that all of the N-H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

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

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

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

In 2011, making many concurrent changes to a protein's sequence was highly unpredictable, which can cause myriad effects on the protein's structure, especially when they are in or affect the same region(s) of the protein.¹⁴ For example, introducing numerous changes in a protein's sequence can disrupt the characteristic patterns, spacing and/or types of amino acids required to induce formation and stability of secondary structures, while changes to intervening sequences can disrupt folding and positioning of the secondary structures and

¹² EX1003, ¶¶ 44-46; EX1014, 21-22.

¹³ EX1003, ¶¶ 54, 150; EX1004, ¶¶ 20, 25.

¹⁴ EX1003, ¶ 158.

structural motifs into the protein's tertiary structure.¹⁵ Multiple changes introduced at different regions of the amino acid sequence also can cause unfavorable spatial interactions that destabilize or impair folding.¹⁶ In 2011, predicting the possible effects of the myriad interactions that may be disrupted by multiple concurrent substitutions was beyond the capacity of skilled artisans and the computational tools available at that time.¹⁷

2. Hyaluronidase Enzymes

PH20 is one of five structurally similar hyaluronidase proteins in humans and is homologous—evolutionarily related to—hyaluronidases in many species.¹⁸ It breaks down hyaluronan (“HA”) by selectively hydrolyzing glycosidic linkages in it.¹⁹ The human PH20 protein exists naturally as a GPI anchored protein, but a

¹⁵ EX1003, ¶¶ 55-56, 142; EX1047, 6349; EX1046, 2034; *see also* EX1040, 14412-13; EX1041, 21149-50; EX1042, 1-3.

¹⁶ EX1003, ¶¶ 57-59.

¹⁷ EX1003, ¶¶ 50, 158, 190, 224; EX1004, ¶¶ 166-68.

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

¹⁹ EX1003, ¶ 77; EX1008, 819.

truncation at the C-terminal region of PH20 yields a soluble, neutral active form of the enzyme.²⁰

Various groups before 2011 had identified various essential residues in PH20. These included several in the catalytic site of the protein, a conserved structure shared by many species.²¹ Mutating certain residues in or near the catalytic site can abolish the enzymatic activity of hyaluronidases.²² Conserved cysteine residues that stabilize the protein structure are another example,²³ as are conserved asparagine residues involved in glycosylation, which was known to be important for PH20 activity.²⁴

In 2007, Chao reported an experimentally determined structure of the human HYAL1 hyaluronidase, and used an alignment of the five human hyaluronidases to

²⁰ EX1005, 2:40-61, 87:52-88:24; EX1013, 430-32, Figure 2; EX1003, ¶¶ 89, 196; EX1029, 546, Figure 1.

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

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

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

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

illustrate shared secondary structures and conserved residues in these proteins.²⁵

Among its findings was that human hyaluronidases contain a unique structure—the Hyal-EGF domain.²⁶ Using its sequence analysis, an earlier structure of bee venom hyaluronidase and a computer model of the protein structures, it analyzed the catalytic site of HYAL1 and identified residues in it that interact with HA.²⁷

3. Engineering Proteins in 2011

In 2011, skilled artisans used two general approaches to engineer changes into proteins.²⁸ “Rational design” employed computational tools like sequence alignments and protein structure models to study the protein sequence and structure. Using known sequence-structure relationships for the protein, artisans then selected where and what changes to introduce into the protein sequence.²⁹ For example, sequences of naturally occurring proteins homologous to the one being studied would be compiled and compared in a “multiple-sequence alignment”

²⁵ EX1006, 6914-18.

²⁶ EX1006, 6916-18; EX1010, 9439-40; EX1003, ¶¶ 84-86; EX1004, ¶¶ 97-99.

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

²⁸ EX1003, ¶ 47.

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

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(“MSA”).³⁰ The MSA identifies conserved (“essential”) positions with no or little amino acid variation and positions where different amino acids occur (“non-essential” residues).³¹ A structural model of the protein using its sequence but based on a suitable known structure of a homologous protein was then used to visualize locations within the protein’s structure to identify and assess interactions of the amino acids at that position.³² In 2011, skilled artisans could assess, with varying amounts of effort, the effects of changing one or a few amino acids, but predicting the effects of many concurrent changes was not possible, given the escalating complexity of predicting numerous, interrelated interactions (which exponentially increase with the number of changes) and the limits of protein modeling tools.³³

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

³¹ EX1003, ¶¶ 209-210; EX1004, ¶¶ 21-22, 25, 30-31; EX1016, 181-84; EX1017, 224-25; EX1014, 351.

³² EX1017, 228-30; EX1031, 461, 463, 469-71; EX1014, 351-52; EX1032, 265-66; EX1004, ¶¶ 37, *also id.* 33-36; EX1003, ¶¶ 219, 221.

³³ EX1003, ¶¶ 50, 158; EX1004, ¶¶ 167-168.

“Directed evolution” techniques arose due to the limits of rational design.³⁴ It uses “trial-and-error” experiments to find mutants with randomly distributed changes that exhibit desired properties, but requires creation and screening of large libraries of mutants, each with one amino acid randomly changed at one position in its sequence.³⁵ Importantly, until a desired mutant is made, tested and found, whether it exists and its sequence are unknown.³⁶ Sophisticated assays that rapidly and precisely identify mutants with desired properties are critical, given the scale of experimentation this approach requires.³⁷ The ’298 Patent embodies this approach.³⁸

B. Person of Ordinary Skill in the Art

The ’298 Patent claims priority to two provisional applications filed in 2011. § II.A. Its claims, however, are not entitled to those dates or the filing date of the ’731 Application (December 28, 2012), as they are not supported as § 112(a) requires by those earlier-filed applications. *See* §§ V.A, V.B. The prior art of the

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

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

³⁶ EX1003, ¶ 184.

³⁷ EX1003, ¶¶ 52-53.

³⁸ EX1003, ¶¶ 138, 173, 186.

grounds, however, was published by December 2011, and the obviousness grounds thus use that date to assess the knowledge and perspectives of the skilled artisan.

In 2011, a person of ordinary skill in the art would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function (*e.g.*, chemistry, biochemistry, biology, biophysics). From training and experience, the person would have been familiar with factors influencing protein structure, folding and activity, production of modified proteins using recombinant DNA techniques, and use of biological assays to characterize protein function, as well with techniques used to analyze protein structure (*i.e.*, sequence searching and alignments, protein modeling software, etc.).³⁹

C. Prosecution History

In the sole Office action issued during examination of the '298 Patent, three rejections were imposed, none of which is relevant to the grounds. First, a dependent claim to soluble PH20 polypeptides was rejected for failing to further limit an independent claim.⁴⁰ Patentee mooted the rejection by cancelling the

³⁹ EX1003, ¶ 13.

⁴⁰ EX1002, 436-39.

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claim.⁴¹ Second, claims to pharmaceutical compositions were rejected as indefinite,⁴² which Patentee overcame by amendments specifying the composition is “formulated in the same composition or ... in a separate composition.”⁴³ Third, non-statutory double patenting rejections were imposed over U.S. Patent 10,865,400 in view of US 20100143457 A1 (“Wei”),⁴⁴ which Patentee overcame with terminal disclaimers.⁴⁵

The claims were allowed without further rejections.⁴⁶

D. The Challenged Claims

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

⁴¹ EX1002, 555-57.

⁴² EX1002, 440.

⁴³ EX1002, 531, 555-57.

⁴⁴ EX1002, 440-48.

⁴⁵ EX1002, 557.

⁴⁶ EX1002, 551-60.

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genus of structurally distinct mutant PH20 polypeptides that is neither adequately described in nor enabled by the common disclosure of the '731 Application and the '298 Patent.

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

Claim 1 defines an incredibly broad and diverse genus of “modified PH20 polypeptides,” which are defined as “a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement ... in its sequence of amino acids compared to a reference unmodified PH20 polypeptide.”⁴⁷

Claim 1 specifies the modified PH20 polypeptides in its genus:

- **must** contain **one** amino acid replacement at position 313 (*i.e.*, from M to any of K, A, H, L, P, R, or Y); and
- **may** contain **additional** modifications, provided each polypeptide retains **at least 95% sequence identity** to one of the 35 unmodified sequences (SEQ ID NOs: 3 or 32-66), ranging in length from 430 (SEQ ID NO: 32) to 465 residues (SEQ ID NO: 35).

Claim 2 requires position 313 to be to K. Claims 3 and 4 restrict claim 1's genus by specifying each polypeptide has: (i) 96% sequence identity to SEQ ID NO: 35 (PH20₁₋₄₃₃), or (ii) 95% sequence identity to SEQ ID NO: 32 (PH20₁₋₄₃₀).

⁴⁷ EX1001, 47:15-20.

The specification explains that “sequence identity can be determined by standard alignment programs ...”⁴⁸ It then provides an example, explaining a polypeptide that is “‘at least 90% identical’ refers to percent identities from 90 to 100% relative to the reference polypeptide” where “no more than 10% (*i.e.*, 10 out of 100) of amino acids [] in the test polypeptide [] differs from that of the reference polypeptides.”⁴⁹ Per claim 1, “terminal gaps” are “treated as non-identical” residues.

The specification further explains that “differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence” and that “[d]ifferences are defined as [] amino acid substitutions, insertions or deletions.”⁵⁰ Also, “amino acids selected to replace the target positions on the particular protein being optimized can be either all of the remaining 19 amino acids, or a more restricted group containing only selected amino acids” (*e.g.*, 10-18 of the 19 alternative amino acids).⁵¹ Consistent with these passages, no language in the claims restricts *where* substitutions can occur

⁴⁸ EX1001, 58:45-47.

⁴⁹ EX1001, 59:13-22.

⁵⁰ EX1001, 59:23-31; *see also id.* at 3:36-37; 46:20-24, 33-35.

⁵¹ EX1001, 135:52-59; *see also id.* at 141:2-4.

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within the sequence of the modified PH20 polypeptides, or *which* of 19 other amino acids can be substituted at those positions.

The parameters in claims 1-4 cause them to encompass an immense number of distinct polypeptides, each with a unique amino acid sequence.⁵² In particular, it permits the modified PH20 polypeptides to contain between 17 and 23 total changes but requires only one change: a substitution at position 313, with either 7 alternatives (claim 1) or one alternative (“K”) (claims 2, 3, 4). Based on Dr. Park’s calculations, each claim’s parameters capture an immense number of distinct polypeptides (below).⁵³

Claim	SEQ ID / % Identity	PH20 length	# Changes	Pos. 313 Choices	Add'l Changes	# Distinct Polypeptides
1	3 / 95%	447	22	7	21	2.35×10^{63}
	66 / 95%	465	23	7	22	2.63×10^{66}
2	3 / 95%	447	22	1	21	3.76×10^{62}
3	35 / 96%	433	17	7	16	1.53×10^{49}
4	32 / 95%	430	21	7	20	4.40×10^{59}

2. The Claims Encompass One Particular PH20 Mutant: M313K PH20₁₋₄₄₇

The structural parameters used in claims 1-4 also cause them to capture a *single* modified PH20 polypeptide with *one* replacement. That is the PH20₁₋₄₄₇

⁵² EX1003, ¶¶ 120, 122.

⁵³ EX1004, ¶¶ 174-177, Appendix F.

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protein (SEQ ID NO: 3), in which the methionine (M) at position 313 is changed to lysine (K) (“M313K PH20₁₋₄₄₇”). This single-replacement M313K 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).⁵⁴

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

When a specification discloses alternative embodiments, the language used in the claims may cause them to be limited to only one.⁵⁵ That is the case here: the specification describes two mutually exclusive categories of “modified PH20 polypeptides” (*i.e.*, “active mutants” vs. “inactive mutants”) but the claims are limited to one of them: “active mutants.”

According to the specification:

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

⁵⁴ EX1003, ¶ 136.

⁵⁵ *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008).

polypeptide not containing the amino acid modification (e.g., amino acid replacement).”⁵⁶

- “*Inactive mutants*” are modified PH20 polypeptides that “generally exhibit less than 20% ... of the hyaluronidase activity of a wildtype or reference PH20 polypeptide, such as the polypeptide set forth in SEQ ID NO: 3 or 7.”⁵⁷

It then classifies mutants into tables of “active” and “inactive” mutants using the >40% threshold (Tables 3 and 9) or <20% threshold (Tables 5 and 10).⁵⁸

⁵⁶ EX1001, 74:11-16; *see also id.* at 77:61-65 (“active mutants” “can exhibit 40% to 5000% of the hyaluronidase activity of a wildtype or reference PH20 polypeptide ...”).

⁵⁷ EX1001, 117:44-53. *See also id.* at 255:26-30 (mutants exhibiting <20% hyaluronidase activity “were rescreened to confirm that the dead mutants are inactive” in Table 10).

⁵⁸ EX1001, 79:25-80:26 (Table 3 “Active Mutants”); 232:40-42 (Table 9 “Active Mutants”); 118:44-67 (Table 5 “Inactive Mutants”), 255:53-56 (“reconfirmed inactive mutants are set forth in Table 10.”); EX1003 ¶¶ 98, 104-105, 107, 126-28.

The common disclosure reports no examples of a modified PH20 with two replacements.⁵⁹ More directly, it reports no examples of a PH20₁₋₄₄₇ that was made and tested and which incorporated: (i) a mutation listed in Tables 3 and 9 (“active mutants”), and (ii) a mutation listed in Tables 5 and 10 that yielded an “inactive mutant” (Tables 5 and 10).

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

- “Active mutants” are portrayed as being therapeutically useful *because they possess hyaluronidase activity*. For example, the specification explains that *due to* having hyaluronidase activity, “the modified PH20 polypeptides can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents.”⁶⁰
- “Inactive mutants” are portrayed as being therapeutically useful *because they lack hyaluronidase activity*. Their only identified utility

⁵⁹ E.g., EX1003, ¶¶ 141, 172.

⁶⁰ EX1001, 179:53-59; *see also id.* at 2:67-3:3, 71:64-72:11, 179:53-193:14.

is “as antigens in contraception vaccines,” which is implausible (*see* § V.C) but ostensibly requires them to lack activity.⁶¹

Notably, the specification does not portray “active mutants” as having contraceptive utility even though they may differ by only one amino acid from an inactive mutant, and instead proposes using them *in combination* with contraceptive agents.⁶²

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

First, every claim requires each modified PH20 polypeptide in its scope to have one of seven replacements at position 313 that yielded an “active mutant” as a single-replacement PH20₁₋₄₄₇ polypeptide (*i.e.*, M313K, M313A, M313H, M313L,

⁶¹ EX1001, 71:24-26; *see also id.* at 193:15-16, 74:20-22, 193:14-33 (for “contraception” “the modified PH20 polypeptides can be inactive enzymes, such as any described in Sections C.2.”).

⁶² EX1001, 156:1-14 (“co-formulations containing a modified PH20 polypeptide and a therapeutic agent that is ... a contraceptive agent ...”); EX1003, ¶ 113; EX1060, 1711.

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M313P, M313R, or M313Y). These mutants are listed in Table 3 and reported as having >40% activity in Table 9.⁶³

Second, claims 5 and 6 restrict the genus of active mutants in claim 1 (*i.e.*, those with at least 40% activity) to active mutant modified PH20 polypeptides that have at least 100% or 120% of the activity of unmodified PH20, respectively.

Third, the specification defines a “modified PH20 polypeptide” as “a PH20 polypeptide that contains at least one modification,” but can also “have up to 150 changes, so long as the resulting modified PH20 polypeptide *exhibits hyaluronidase activity*.”⁶⁴ This aligns with the specification’s prophetic methodology for discovering PH20 polypeptides with multiple changes, which starts with one substitution that yields an “active mutant,” randomly introduces another, and then screens to find “double mutants” that *retained* hyaluronidase activity.⁶⁵ This tracks the claims, which require one substitution and permit others.

Patentee may contend the claims should be read as encompassing both alternative embodiments (*i.e.*, “active” and “inactive” mutants). Reading the claims in that manner is incorrect. It also exacerbates the § 112 problems, as every

⁶³ EX1001, 85 (Table 3), 235 (Table 9).

⁶⁴ EX1001, 47:15-30; *see also id.* at 46:38-42, 74:36-39, 75:32-39.

⁶⁵ EX1001, 140:36-47; *see also id.* at 41:17-24.

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claim still necessarily includes (and thus must describe and enable) the full sub-genus of “active mutants” defined by claims 5 and 6.⁶⁶

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

Claims 1-22 are unpatentable because each lacks written description in and was not enabled by the common disclosure of the '298 Patent and the '731 Application in 2011.

As explained in § IV.D.1, the claim language defines enormous genera: between 10^{49} and 10^{66} distinct polypeptides. To illustrate the real-world absurdity of those claims, consider what practicing claim 1's full scope requires. Excluding single-replacement PH20₁₋₄₄₇ mutants, and only focusing on mutants with multiple substitutions in PH20₁₋₄₄₇, a skilled artisan would need to make-and-test $\sim 10^{63}$ mutants having between 2 and 22 substitutions. Producing only one molecule of each—each must be made and tested to see if it is active or inactive—would require consuming an aggregate mass ($\sim 1.37 \times 10^{27}$ kg) that exceeds the mass of the Earth ($\sim 6 \times 10^{24}$ kg).⁶⁷ Testing every polypeptide within the claims' scope in search of “active mutants” is impossible—literally.

⁶⁶ EX1003, ¶ 135.

⁶⁷ EX1003, ¶¶ 123, 189; *see also, e.g.*, EX1039, 136-37 (cell theoretically can make 10^{390} forms of a polypeptide with 300 amino acids).

In support of that broad scope, the '298 Patent and the '731 Application provide only a meager disclosure: *singly*-modified PH20 polypeptides and a prophetic, make-and-test research plan to discover multiply-modified ones. The patent provides *nothing* that demonstrates possession of the vast remainder of multiply-modified polypeptides in the claims' scope or which enables a skilled artisan to practice that full-range of structurally diverse mutant polypeptides without undue experimentation.

A. Claims 1 to 4 Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.⁶⁸ “To fulfill the written description requirement, a patent owner ‘must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent.’”⁶⁹ If the claims define a genus, the written description must “show that one has truly invented a genus ...,”

⁶⁸ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*).

⁶⁹ *Idenix Pharm., LLC v. Gilead Scis., Inc.*, 941 F.3d 1149, 1163 (Fed. Cir. 2019).

“[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus.”⁷⁰

“[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.”⁷¹ “One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent ... [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus.”⁷²

A disclosure that fails to “provide sufficient blaze marks to direct a POSA to the specific subset” of a genus with the claimed function or characteristic does not satisfy § 112(a).⁷³ And “merely drawing a fence around the outer limits of a

⁷⁰ *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

⁷¹ *Idenix*, 941 F.3d at 1164.

⁷² *AbbVie*, 759 F.3d at 1299-1300.

⁷³ *Idenix*, 941 F.3d at 1164.

purported genus” is insufficient.⁷⁴ Instead, “the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.”⁷⁵

Three cases applying these principles are particularly relevant here. First, in *AbbVie*, the Federal Circuit affirmed a finding that the disclosure of 300 examples of IL-12 antibodies was not representative of the functionally defined genus of antibodies, explaining:

Although the number of the described species appears high quantitatively, the described species are all of the similar type and do not qualitatively represent other types of antibodies encompassed by the genus.⁷⁶

The court also criticized what that patentee cited to support the non-exemplified portion of the claim scope, portraying it as “only a research plan, leaving it to others to explore the unknown contours of the claimed genus” and being a “trial and error approach.”⁷⁷ Both criticisms are particularly relevant to the present

⁷⁴ *Ariad*, 598 F.3d at 1350-54.

⁷⁵ *Ariad*, 598 F.3d at 1349.

⁷⁶ *AbbVie*, 59 F.3d at 1300-1301.

⁷⁷ *Id.*

disclosure, which exemplifies only single-substitution PH20 mutants and otherwise provides only a research plan, yet claims all multiply-modified PH20 mutants with 2 to 22 additional substitutions.

Second, in *Idenix*, the court considered claims to methods of treatment using a broad genera of compounds defined by formulas analogous to the challenged claims here: “eighteen position-by-position formulas describing ‘principal embodiments’ of compounds that may treat HCV,” each with “more than a dozen options” at each position (totaling “more than 7,000 unique configurations”).⁷⁸ The court criticized the specification’s failure to indicate which of the thousands of compounds would be effective, and found that “providing lists or examples of supposedly effective nucleosides,” without “explain[ing] what makes them effective, or why” deprives a skilled artisan “of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result” because they “fail to provide sufficient blaze marks to direct a POSA to the specific subset of 2’-methyl-up nucleosides that are effective in treating HCV.” Again, that logic resonates strongly with the deficiencies of the common disclosure here.

⁷⁸ *Idenix*, 941 F.3d at 1158-64.

Finally, the Board in *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Research Found.*, PGR2020-00076, Paper 42, 6 (P.T.A.B. Jan. 31, 2022) considered sequence homology claims. Specifically, the claims used “90% sequence homology” language to capture “a broad genus of amino acid sequence homologues” but (like here) imposed no restrictions on where particular amino acids replacements could be made, thus causing the claim “to cover, at minimum, thousands of amino acid sequences.”⁷⁹ The Board found the specification’s failure to “explain what, if any, structural features exist (e.g., remain) in sequences that vary by as much as 10% that allow them to retain the antigenic characteristics referenced in the Specification” fatal, and that the homology limitation “serves to merely draw a fence around the outer limits of a purported genus [which] is not an adequate substitute for describing a variety of materials constituting the genus” for purposes of section 112(a).⁸⁰

The deficiencies of claims 1 to 4 dwarf those identified in these three cases. The present claims define much larger, much less predictable and much more diverse genera of modified PH20 polypeptides, and the common disclosure is far

⁷⁹ *Boehringer*, at 16. The claims at issue encompassed both compositions containing the protein, and methods of using the protein. *Id.* at 6.

⁸⁰ *Id.* at 35-36.

more limited. As explained below, the common disclosure neither discloses a representative number of species within each immense claimed genus, nor identifies sufficient structural features common to the members of each claimed genus. It thus falls woefully short of demonstrating possession of the genera of modified PH20 polypeptides defined by claims 1 to 4 of the '298 Patent.

1. The Claims Define a Massive and Diverse Genus of Enzymatically Active PH20 Polypeptides

The incredible breadth of the genus defined by claims 1 to 4 has been described above. *See* § IV.D.1. The genera of each claim are also incredibly diverse in their structures and functions.

Most significantly, the use of a *maximum* sequence identity boundary with no condition or restrictions other than one required substitution means the claims capture mutants with 2 substitutions, 3 substitutions and so on up to a number set by the boundary (*i.e.*, 17 for claim 3, 21 for claim 4, and 23 for claim 1). The substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, and arranged in any manner. They capture a mutant with 5 substituted hydrophobic residues clustered in a small region, as well as one with 22

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substitutions mixing polar, charged, aliphatic and aromatic residues together in any manner.⁸¹

There is more. Each claim also encompasses substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 35 alternative sequences ranging from 430 to 465 residues. They also encompass varying lengths due to the sequence identity language, as the claims encompass both “additions” and “deletions.” To illustrate, if one makes the M313K substitution and makes 5 more substitutions to SEQ ID NO: 32, claim 4’s parameters would capture that mutant as well as one that also deletes 14 more residues from the C terminus. But, as explained in § V.A.2.c, removing that many residues from the C-terminus of the wild-type PH20 makes it inactive, and nothing in the common disclosure shows (much less suggests) that adding the M313K mutant (plus up to 5 other substitutions) will restore activity to that C-terminally truncated mutant. Patentee nonetheless claims all these polypeptides too.⁸²

2. The Claims Capture Modified PH20 Polypeptides the Common Disclosure Says to Avoid or Not Make

The claims’ unconstrained sequence identity language causes them to capture three categories of PH20 mutants a skilled artisan would understand the

⁸¹ EX1003, ¶¶ 119-20.

⁸² EX1003, ¶¶ 164-67.

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disclosure to be saying to avoid or not make. Each category raises unique questions relative to the remainder of the genus, and are thus “sub-genera” of PH20 mutants that are not representative of other “sub-genera” within the claimed genera. But instead of providing guidance that navigates this confusing landscape, the patent simply instructs the skilled artisan “to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein.”⁸³ In other words, it directs the skilled artisan to blindly make-and-test all such candidate mutants using trial-and-error experimentation.⁸⁴

a) Multiply-Modified PH20 Mutants to Not Make

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

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

⁸³ EX1001, 76:65-77:3.

⁸⁴ EX1003, ¶ 193.

contains only three amino acid replacements, the amino acid replacements are *not* N47A/N131A/N219A.⁸⁵

Notably, the common disclosure provides *no explanation* why these particular combinations of replacements should be avoided, and provides no data testing their activity or other characteristics.⁸⁶ Further, none (P13A, N47A, N131A, N219A, N333A, N358A, L464W) are included in Tables 5 and 10, which are single-replacements that rendered PH20₁₋₄₄₇ an “inactive mutant.” Indeed, one (N219A) yielded a PH20₁₋₄₄₇ with increased activity (129%) as a single replacement.⁸⁷ Instead, the skilled artisan is left to discover this information themselves. And nothing in the claim language excludes these combinations.

b) Substitutions to Avoid in Active Mutants

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

⁸⁵ EX1001, 76:10-22 (emphases added).

⁸⁶ EX1003, ¶¶ 146-47.

⁸⁷ EX1001, 245 (Table 9).

To retain hyaluronidase activity, modifications typically *are not made* at those positions that are less tolerant to change or required for hyaluronidase activity.⁸⁸

It identifies these changes as: (i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10 that are made at other positions.⁸⁹

Notably, the common disclosure does not condition this observation on single-replacement PH20₁₋₄₄₇ mutants, and as such, it clearly conveys to a skilled artisan that modified PH20 polypeptides with “hyaluronidase activity” do not include, and should not be modified to contain, the amino acid replacements listed in Tables 5 and 10, and that is true regardless of the length or the number of additional amino acid substitutions in the PH20 polypeptide.⁹⁰

The skilled artisan also would find no description of, much less guidance concerning, *which* of these identified substitutions that did render PH20₁₋₄₄₇ inactive should be incorporated into enzymatically active multiply-modified PH20

⁸⁸ EX1001, 78:45-47 (emphases added).

⁸⁹ EX1001, 78:47-79:20 (“For example, generally modifications are not made at a position corresponding to position ...”).

⁹⁰ EX1003, ¶¶ 148-51.

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polypeptides (and what other substitutions should be combined with them).⁹¹

Instead, by stating that the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides, it clearly conveys to the skilled artisan that the ***claimed*** enzymatically active multiply-modified PH20 polypeptides do not contain them. And again, nothing in the claim language operates to exclude such combinations.

c) PH20 with Significant C-terminal Truncations Can Lose Activity

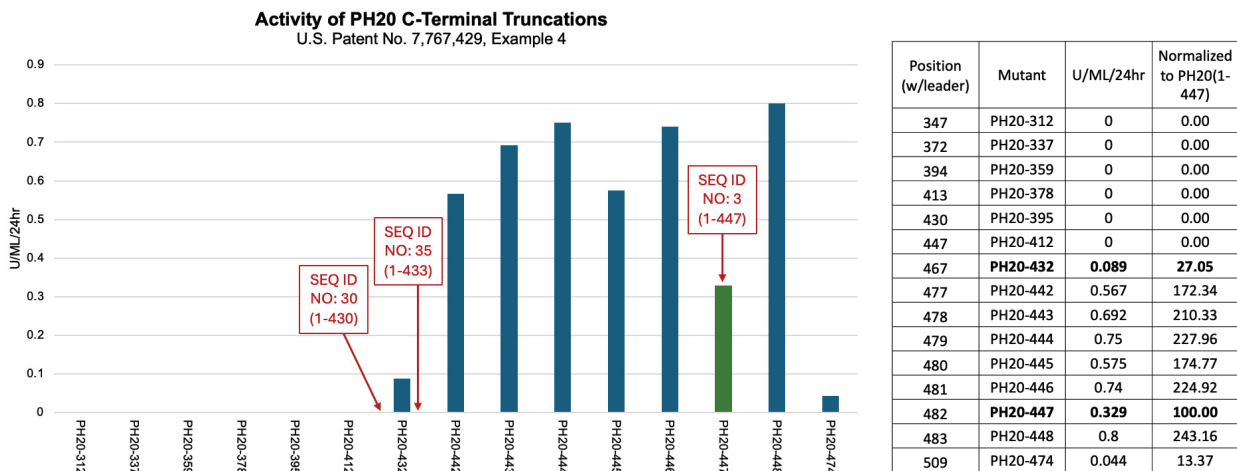
The common disclosure describes no multiply-modified “active mutant” PH20 polypeptides having fewer than 447 residues (or even an unmodified PH20 with such lengths) and provides no guidance about making enzymatically active mutants based on PH20 sequences ending before position 447 and containing 2 or more substitutions.⁹²

This omission creates significant uncertainty, because both the common disclosure and the prior art report that PH20 polypeptides with fewer than 442 residues significantly ***reduce or eliminate*** hyaluronidase activity in unmodified PH20 polypeptides. For example, Patentee’s prior art ’429 Patent reported that

⁹¹ EX1003, ¶¶ 151, 161-62, 169.

⁹² EX1003, ¶¶ 97, 167-69.

PH20 with fewer than 432 residues lacked hyaluronidase activity, while those with between 432 and 448 residues had widely varying activities (below):⁹³



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

⁹³ EX1005, 87:52-88:24 (activity of PH20₁₋₄₄₂ “decreased to approximately 10% of that found” in the PH20₁₋₄₄₇ polypeptides); EX1013, Figure 2, 430-32 (“soluble hyaluronidase activity could be recovered in the conditioned medium from deletion mutants terminating after amino acids 477 – 483 [442-448]” but “[l]ess than 10% activity was recovered when constructs terminated after amino acid 467 [432] or when using the full-length PH20 cDNA”).

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429.⁹⁴ The common disclosure concurs, stating that PH20 polypeptides must extend to at least position 429 to exhibit hyaluronidase activity:

A mature PH20 polypeptide ... containing a contiguous sequence of amino acids having a C-terminal amino acid residue corresponding to amino acid residue **464** of SEQ ID NO: 6 [position **429** without signal] ... *is the minimal sequence required for hyaluronidase activity.*⁹⁵

Before 2011, the C-terminal region of PH20 was known to contain a unique domain linked to a characteristic pattern of sequences first reported in 2007 by Chao (“Hyal-EGF”).⁹⁶ In PH20, the Hyal-EGF domain is found at positions 337-409, and it was shown in 2009 to be essential to hyaluronidase activity.⁹⁷

The C-terminus of PH20 is illustrated below, showing (i) the location where SEQ ID NOS: **3** (447), **32** (430) and **35** (433) terminate (arrows), (ii) the “minimally active domain” at 437-447 in green, and (iii) residues below position

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

⁹⁵ EX1001, 68:30-39 (emphases added).

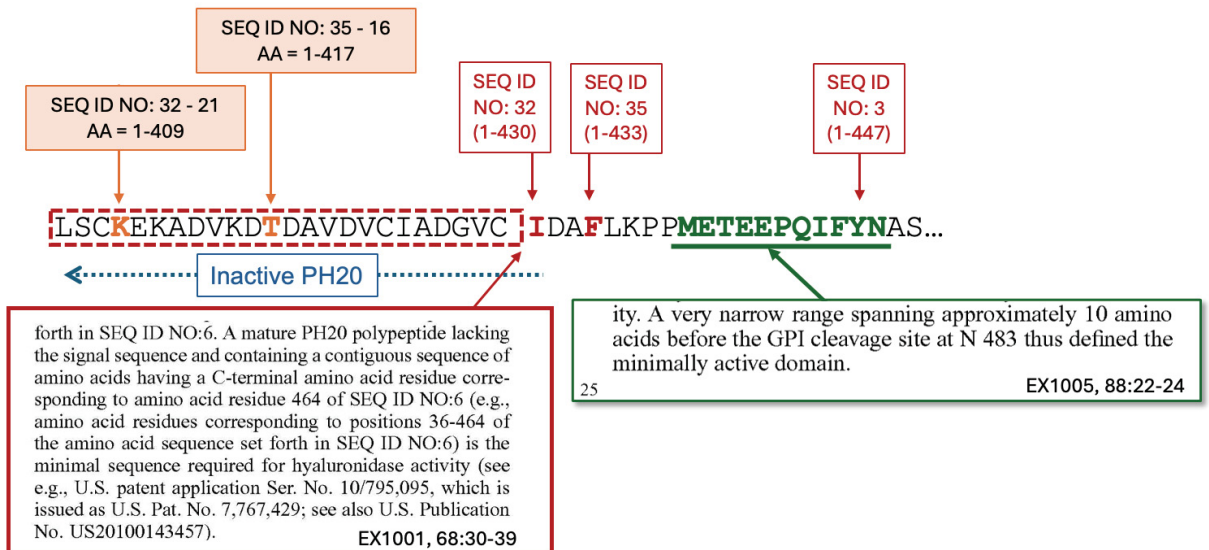
⁹⁶ EX1006, 6912; EX1003, ¶¶ 84-96, 153.

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

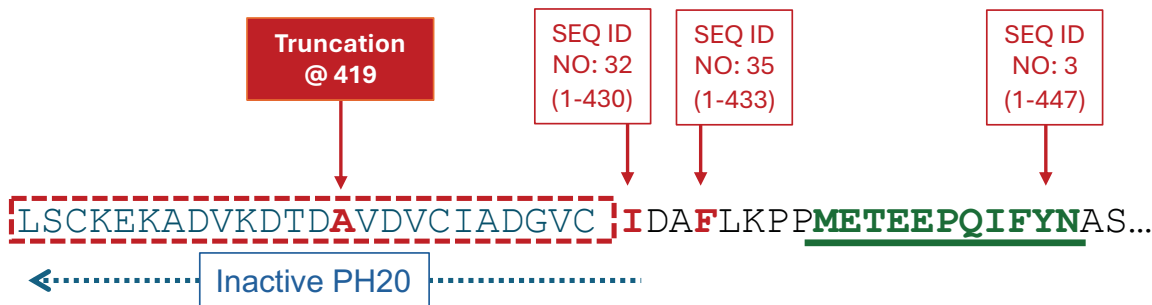
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429 in a red dashed box.⁹⁸ Positions that truncate 21 and 16 residues from SEQ ID

NOS: 32 and 35 are also shown ending before position 429.



From the prior art and the common disclosure, a skilled artisan in 2011 would believe that C-terminal deletions yielding PH20 polypeptides that terminate before position 430 would be inactive, yet the claims expressly encompass truncations down to and beyond position 419.⁹⁹



⁹⁸ EX1003, ¶ 153.

⁹⁹ EX1003, ¶¶ 160-65.

The common disclosure provides no examples of (and provides zero guidance concerning producing) such C-terminally truncated PH20 mutants that are enzymatically active, thus ignoring the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433.¹⁰⁰ And, again, the mathematical boundaries of the claims explicitly encompass modified PH20 polypeptides with these types of truncations.

3. Empirical Results from Testing Single-Replacement Modified PH20 Does Not Identify Multiply-Modified Enzymatically Active PH20 Polypeptides

The empirical results reported in the common disclosure provide no predictive guidance to a skilled artisan about the structural features of the vast genus of amino acid changes that can be combined to form multiply-modified PH20 polypeptides.

a) Data Showing Most Single-Replacements Were Inactive or Less Active Is Not Probative of Multiple-Replacement Mutants

The common disclosure reports results from testing a portion of a randomly generated library of ~6,743 single-replacement PH20₁₋₄₄₇ polypeptides.¹⁰¹ It explains the mutants were generated with a mutagenesis process which substituted

¹⁰⁰ EX1003, ¶¶ 143, 159, 167-69.

¹⁰¹ EX1001, 133:5-16, 200:31-33, 200:11-17.

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one of ~15 amino acids into random positions in PH20₁₋₄₄₇ “such that each member contained a single amino acid change.”¹⁰² Approximately 5,917 were tested, while ~846 were uncharacterized.¹⁰³ More than half (~57%) of these mutants were classified as “inactive mutants,” while ~30% (1335) were reported to have less activity than unmodified PH20₁₋₄₄₇ (20%-100%).¹⁰⁴ In other words, ~87% of the single-replacement PH20₁₋₄₄₇ polypeptides had *less* activity than unmodified PH20₁₋₄₄₇.¹⁰⁵

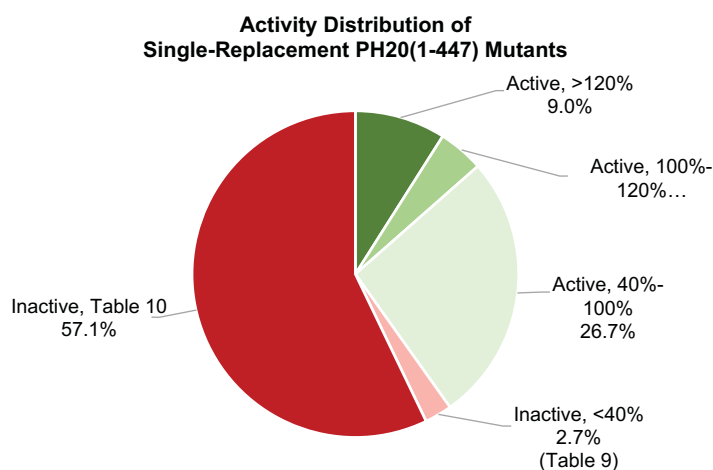
¹⁰² EX1001, 200:11-20.

¹⁰³ EX1003, ¶¶ 103-104. The common disclosure reports inconsistent numbers of tested mutants and classifications of mutants. Table 3 lists 2,516 single-replacement PH20₁₋₄₄₇ mutants as “active mutants,” but Table 9 identifies only 2,376 mutants that exhibit >40% hyaluronidase activity. Likewise, Tables 5 and 10 list 3,368 and 3,380 PH20₁₋₄₄₇ “inactive mutants,” respectively. The discrepancies are not explained.

¹⁰⁴ EX1003, ¶ 105.

¹⁰⁵ *Id.*

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



The measured activity of single-replacement PH20₁₋₄₄₇ mutants shows no trends or correlations even for single-replacement PH20₁₋₄₄₇ polypeptides.¹⁰⁶

Moreover, there are numerous examples in the dataset where the effects of introducing different amino acids into a single position in PH20₁₋₄₄₇ resulted in (i) increased activity, (ii) decreased activity, or (iii) inactive mutants (below).¹⁰⁷

¹⁰⁶ EX1003, ¶¶ 106, 142-43.

¹⁰⁷ Data from Tables 3, 5, 9, 10.

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

The data on activities of tested single-replacement PH20₁₋₄₄₇ mutants is not analyzed or explained in the common disclosure—it is simply presented. There is no attempt to extrapolate its results to particular combinations of substitutions in PH20 polypeptides, or to even assess the impact the single substitution had on the protein’s structure.¹⁰⁸ The quality of the data is also questionable: no control values are reported or statistical assessments.¹⁰⁹ The only realistic takeaway from the data is that most of the tested, random single-substitution mutants impaired PH20’s activity.¹¹⁰ Unlike single substitutions, multiple concurrent mutations can cause complex and unpredictable effects on a protein’s structure and resulting function.¹¹¹ The patent’s empirical set of test results provides no insights of value to a skilled artisan attempting to identify which of the many possible mutants with

¹⁰⁸ EX1003, ¶ 139.

¹⁰⁹ EX1003, ¶ 106.

¹¹⁰ EX1003, ¶ 138.

¹¹¹ EX1003, ¶¶ 139, 142.

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different sets of 2-22 substitutions will be enzymatically active modified PH20 polypeptides.¹¹²

b) Purported Stability Data is Not Reliable or Probative

The common disclosure reports results in Tables 11 and 12 from two runs of supposed “stability” testing of ~409 single-replacement PH20₁₋₄₄₇ polypeptides. Table 11 reports the hyaluronidase activity of single-replacement PH20₁₋₄₄₇ mutants tested at 4° C and 37° C, and in the presence of a preservative (m-cresol),¹¹³ while Table 12 compares relative activities under pairs of these conditions.¹¹⁴

The data in Tables 11 and 12 provides no meaningful insights.¹¹⁵ For example, it is unsurprising that single-replacement PH20₁₋₄₄₇ polypeptides showed higher activity at 37° C than at 4° C, given that PH20 exists at that temperature in

¹¹² EX1003, ¶¶ 140, 143.

¹¹³ EX1001, 263:41-270:20 (Table 11).

¹¹⁴ EX1001, 270:21-281:29 (Table 12).

¹¹⁵ EX1003, ¶ 76.

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humans.¹¹⁶ Testing with a phenolic preservative, on the other hand, showed that only a few mutants were able to resist its effects.¹¹⁷

More generally, the examples fail to demonstrate that measured activity data was attributable to improved stability in the PH20 structure, and do not identify to the skilled artisan which multiple substitutions may improve stability.¹¹⁸ They provide no probative insight regarding multiply-modified PH20 polypeptides.¹¹⁹

The values are also largely meaningless, as many of them fall within the huge variability measured for the positive control.¹²⁰ The chart below shows coloring reflecting relative percentage values from 0 to 120% for the positive controls from Tables 11/12 and plots those values below.¹²¹

¹¹⁶ EX1003, ¶ 73.

¹¹⁷ EX1003, ¶ 69.

¹¹⁸ EX1003, ¶¶ 75-76.

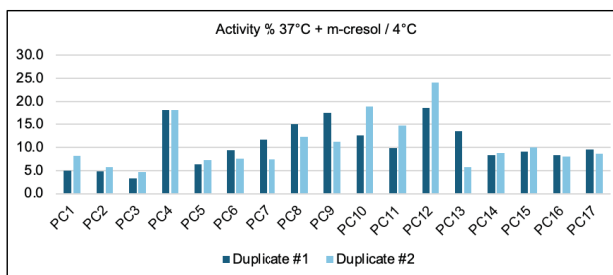
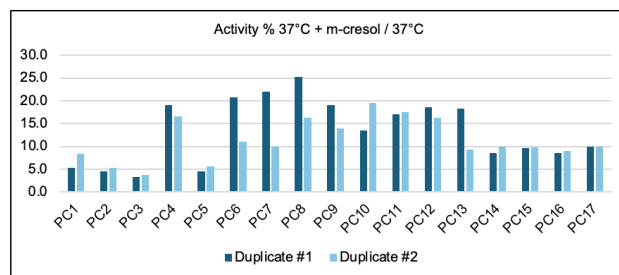
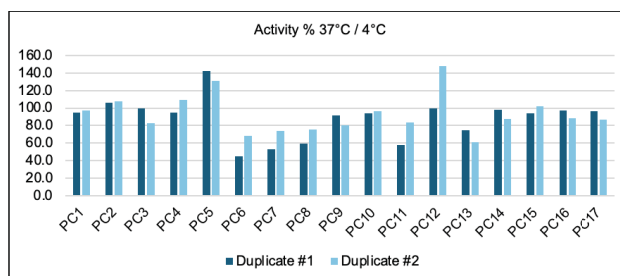
¹¹⁹ *Id.*

¹²⁰ EX1003, ¶ 71; EX1001, 281 (Table 12).

¹²¹ EX1003, ¶ 71, Appendix A-7, A-8.

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

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



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

The table and graphs above show the extensive variability observed for the positive control in the assay being used, with the range in values of almost 100%. As Dr. Hecht observes, the “significant variation raises serious doubts about how probative or instructive the values of individual tested mutants that fall within the range of variability observed for the control can possibly be,” meaning the data not only is uninformative, it is unreliable.¹²²

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

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

¹²² EX1003, ¶¶ 70-72.

performed. This prophetic method provides absolutely no insights into which multiply-modified PH20 polypeptides are active mutants.¹²³

The common disclosure merely outlines *the idea* of multiply-modified PH20 polypeptides. It declares that “[a] modified PH20 polypeptide can have up to 150 amino acid replacements,” “[t]ypically” contains between 1 and 50 amino acid replacements and “can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.”¹²⁴ In addition to PH20 polypeptides with single amino acid replacements, it contends that a modified PH20 polypeptide “having a sequence of amino acids that exhibits” between 68% and 99% sequence identity with any of unmodified Sequence ID Nos. 74-855 “*can* exhibit altered, such as improved or increased, properties or activities compared to the corresponding PH20 polypeptide not containing the amino acid modification (e.g., amino acid replacement).”¹²⁵

None of these statements identify *any* actual multiply-modified PH20 polypeptides—it does not identify *any* sets of specific amino acid substitutions.

¹²³ EX1003, ¶¶ 173, 184-85, 190.

¹²⁴ EX1001, 47:20-27.

¹²⁵ EX1001, 98:53-67 (emphasis added).

They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides.

The common disclosure then outlines an “iterative” make-and-test research plan for discovering modified PH20 polypeptides with multiple substitutions that might exhibit hyaluronidase activity. It too is prophetic, and states:

The method provided herein [] is *iterative*. In one example, after the method is performed, any modified hyaluronan-degrading enzymes identified as exhibiting stability ... *can be modified or further modified* to increase or optimize the stability. A secondary library *can be* created by introducing additional modifications in a first identified modified hyaluronan-degrading enzyme. ... The secondary library *can be* tested using the assays and methods described herein.¹²⁶

The guidance in this research plan is effectively meaningless. It says to make mutants, test them to find activity, and keep repeating the process until you find something via screening. It does not indicate that any useful multiply-modified PH20 polypeptides will be found, much less what their specific characteristics or activities are.¹²⁷

¹²⁶ EX1001, 140:35-47 (emphases added); *see also id.* at 41:17-24.

¹²⁷ EX1003, ¶¶ 187-90.

The specification also incorrectly portrays the experimental readout—hyaluronidase activity—as a measure of “stability.”¹²⁸ As Dr. Hecht explains, to assess a protein’s stability directly one performs experiments that measure the energy associated with the protein’s transition between its folded and unfolded states.¹²⁹ Activity may or may not be influenced by stability but is not itself a measure of stability.¹³⁰

An alternative focus is then proposed: mutations can be “targeted near” “critical residues” which supposedly “can be identified because, when mutated, a normal activity of the protein is ablated or reduced.”¹³¹ But Tables 5 and 10 show that at least one substitution at each of 405 positions between positions 1 and 444 of PH20₁₋₄₄₇ resulted in an inactive mutant.¹³² In other words, the guidance is to target locations “near” ~90% of the amino acids in PH20₁₋₄₄₇, which is no different

¹²⁸ EX1003, ¶¶ 67, 69, 179.

¹²⁹ EX1003, ¶¶ 63-66.

¹³⁰ EX1003, ¶ 67.

¹³¹ EX1001, 140:48-141:6.

¹³² EX1003, ¶ 180, Appendix A-3.

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than targeting every residue in the protein.¹³³ It is, like the first proposed “iterative” process, meaningless.

These prophetic research plans, based entirely on unfocused, iterative “make-and-test” experiments, provide no direction to the skilled artisan about which of the trillions and trillions of possible multiply-modified PH20 polypeptides are “active mutant” PH20 polypeptides. Instead, they require the skilled artisan to repeat the cycle of mutagenesis iteratively, screening and selecting until 10^{49} to 10^{66} modified PH20 polypeptides are produced and screened for activity.¹³⁴ That in no way demonstrates possession of the claimed genus.

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

The common disclosure does not identify the structural significance of any of the ~2,500 mutations that yielded single residue “active mutant” PH20₁₋₄₄₇ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are

¹³³ EX1003, ¶ 180.

¹³⁴ EX1003, ¶¶ 175-77, 181, 187-88.

responsible for the measured change in hyaluronidase activity.¹³⁵ Instead, it simply lists single replacements made across effectively the entire protein sequence that incorporate randomly selected amino acids being classified as “active mutants” in a hyaluronidase assay, without further explanation, and nothing is said about the effects (if any) of substitutions on the protein’s structure.¹³⁶

The common disclosure also does not identify any *sets* of specific amino acid replacements that correlate to structural domains or motifs that positively or negatively influence hyaluronidase activity, much less *predictably* increase activity to defined thresholds.¹³⁷ Again, it simply reported activity data from testing randomly generated *single*-replacement PH20₁₋₄₄₇ mutants.

The common disclosure’s empirically identified examples of “active mutant” single-replacement PH20₁₋₄₄₇ mutants also do not *by themselves* identify any “structure-function” relationship between “active mutants” and the set of single-replacement modified PH20₁₋₄₄₇ polypeptides.¹³⁸ And they plainly do not do so for the much larger genus of modified PH20 polypeptides having varying

¹³⁵ EX1003, ¶¶ 139-40, 151.

¹³⁶ EX1001, 232:40-67; EX1003, ¶¶ 139-40, 142.

¹³⁷ EX1003, ¶¶ 55, 142-43.

¹³⁸ EX1003, ¶¶ 61, 143, 157, 159.

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lengths and between 2 and 22 substitutions, with or without additions or deletions.¹³⁹

Critically, the common disclosure also *does not even contend* that a particular amino acid replacement at a particular position that makes a PH20₁₋₄₄₇ an “active mutant” will make any other modified PH20 polypeptide with that same amino acid replacement (plus between 2 to 22 additional replacements or truncations) an “active mutant.”¹⁴⁰ Such an assertion would have no scientific credibility—the activity of a protein such as PH20 is dictated by its overall structure, which can be influenced unpredictably by different combinations of changes to its amino acid sequence.¹⁴¹ Thus, even the inventors did not view their compilation of test results as identifying a structure-function correlation for multiply-modified PH20 polypeptides.

The common disclosure, thus, does not identify to a skilled artisan *any* structural features shared by the many, diverse “active mutant” modified PH20 polypeptides within the scope of the claims.¹⁴² As such, it cannot satisfy the

¹³⁹ EX1003, ¶ 157.

¹⁴⁰ EX1003, ¶¶ 168, 192-93.

¹⁴¹ EX1003, ¶¶ 56-57.

¹⁴² EX1003, ¶ 157.

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

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

The ~2,500 single-replacement PH20₁₋₄₄₇ polypeptides that are “active mutants” are not examples representative of the claimed genera of claims 1 to 4, much less its various sub-genera.¹⁴³

First, the single-replacement PH20₁₋₄₄₇ examples are not representative of the trillions and trillions of PH20₁₋₄₄₇ polypeptides with between **2 and 22 substitutions** at any of hundreds of positions within the protein.¹⁴⁴ The latter group of proteins is structurally distinct from single replacement PH20 polypeptides, both as to their sequence and due to the various structures within the folded protein that, when incorporating different amino acid substitutions, may alter their structures and their interactions with neighboring residues.¹⁴⁵ The effects of those numerous substitutions on a protein’s various secondary structures and structural motifs

¹⁴³ EX1003, ¶¶ 61, 143, 155, 159.

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

¹⁴⁵ EX1003, ¶¶ 54-56, 58, 120, 156, 159.

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within the protein is not described in the common disclosure, and the magnitude of concurrent substitutions encompassed by the claims was unknowable in 2011.¹⁴⁶

The overall activity of a protein with multiple substitutions also will not be due to one amino acid, but to the unique structure of each protein that reflects *the totality* of effects of those many substitutions.¹⁴⁷

More specifically, introducing a first amino acid substitution often affects the neighbors of that original/replaced amino acid by, for example, (i) introducing a stabilizing interaction, (ii) removing a stabilizing interaction, (iii) introducing a conflicting interaction (*e.g.*, adverse charge or hydrophobicity interactions).¹⁴⁸

Introducing a second substitution in that region may reverse those interactions (or not) with each neighboring residue, and a third substitution may do the same, up to 22 rounds each potentially impacting each interaction.¹⁴⁹ The data associated with a single amino acid substitution thus cannot be representative of the properties of any of these downstream, multiply-substituted mutants, which will have an

¹⁴⁶ EX1003, ¶ 224.

¹⁴⁷ EX1003, ¶¶ 36, 61, 140, 143, 151.

¹⁴⁸ EX1003, ¶¶ 56-58.

¹⁴⁹ EX1003, ¶¶ 58-60, 142.

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

Single-replacement PH20₁₋₄₄₇ polypeptides are also not representative of multiply-modified PH20 polypeptides that incorporate structural modifications that rendered the wild-type protein inactive, including polypeptides (i) with truncations terminating below position 429, and (ii) which incorporated a single substitution at a position that rendered PH20₁₋₄₄₇ inactive.¹⁵¹ Single-replacement PH20₁₋₄₄₇ polypeptides are not representative of those sub-genera of mutants because they do not have the additional structural features that are distinct from those in the wild-type sequence and that impart detrimental effects. For example, a single-replacement, active PH20₁₋₄₄₇ polypeptide would not be considered representative of a PH20 with multiple substitutions and a sequence with 409 to 433 residues (which would still be in the claims' scope).¹⁵² A skilled artisan could not have predicted—based on the disclosed data, all of which are in a PH20₁₋₄₄₇ sequence—whether a severely truncated mutant could be further modified to restore

¹⁵⁰ EX1003, ¶¶ 61, 142-43, 159, 169.

¹⁵¹ EX1003, ¶¶ 161-64.

¹⁵² EX1003, ¶¶ 167-69.

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hyaluronidase activity, much less what additional substitutions would restore activity.¹⁵³

The Patents thus provide a very narrow set of working examples relative to the diversity of modified PH20 polypeptides being claimed.¹⁵⁴ The examples are restricted to *one type of change* (a single amino acid replacement) in *one type of PH20 polypeptide* (SEQ ID NO: 3).¹⁵⁵ By contrast, the claims encompass changes in 35 different unmodified PH20 sequences, and include, in addition to one identified replacement, anywhere from 1 to 21 (claim 1), 1-16 (claim 3) or 1-20 (claim 4) additional changes.¹⁵⁶ A simple illustration demonstrates how *non-representative* the examples are: all of the Patents' examples of single-replacement PH20₁₋₄₄₇ mutants fit into one box of the array below.

¹⁵³ EX1003, ¶ 168.

¹⁵⁴ EX1003, ¶ 155.

¹⁵⁵ EX1003, ¶¶ 97, 99, 103.

¹⁵⁶ EX1003, ¶¶ 115-20.

	Number of Changes																					
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
3																						
32																						
33																						
34																						
35																						
36																						
37																						
38																						
39																						
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Consequently, the skilled artisan would not have viewed the Patents' examples of individual single amino acid replacements in PH20₁₋₄₄₇ as

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representative of the diversity of modified PH20 polypeptides encompassed by the claims.¹⁵⁷

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

Patentee's position on the breadth of the claims is unknown. However, by their literal language, the claims capture several sub-genera of "active mutant" modified PH20 polypeptides the common disclosure says caused single-replacement PH20₁₋₄₄₇ mutants to be rendered inactive (*i.e.*, those with replacements in Tables 5/10 or in PH20 sequences truncated below position 429). Likewise, the claim language captures modified PH20 polypeptides with the six combinations of replacements the common disclosure explicitly says to not make: P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, N333A/N358A and N47A/N131A/N219A.¹⁵⁸ The claims thus improperly capture subject matter the common disclosure affirmatively excluded from the genus of enzymatically active modified PH20 polypeptides having multiple substitutions and other changes.

The common disclosure provides no exemplification of multiply-modified species of PH20 polypeptides that violate these prohibitions in the common

¹⁵⁷ EX1003, ¶ 143.

¹⁵⁸ See § V.A.2.a; EX1001, 76:10-22.

disclosure.¹⁵⁹ There is no explanation of the types of substitutions that might be made to restore activity that, under the logic of the common disclosure, will result in enzymatically inactive PH20 polypeptides or which the specification teaches *not* to make.¹⁶⁰ Yet the claims encompass such proteins. The claims therefore independently violate the written description requirement for the reasons articulated by the Federal Circuit in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998)—if a disclosure “unambiguously limited” the invention, but the claims circumvent that limitation, those claims are “broader than the supporting disclosure” and are unpatentable.

8. The Dependent Claims Lack Written Description

a) Claims 5 and 6 Lack Written Description

Claims 5 and 6 add a purely functional requirement to the genus defined by claim 1: that the modified PH20 polypeptides exhibit increased (>100% (claim 5) or >120% (claim 6)) hyaluronidase activity relative to unmodified PH20₁₋₄₄₇.

The reasons provided in §§ V.A.1-V.A.7 explaining why claims 1-4 lack written description apply with full force to claims 5 and 6. Stated simply, the common disclosure’s recitation of a *desired* level of hyaluronidase activity in

¹⁵⁹ EX1003, ¶ 161.

¹⁶⁰ EX1003, ¶ 168.

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claims 5 and 6 does not identify *which* of the many trillions of PH20 polypeptides having 95% sequence identity with SEQ ID NOS: 3 or 32-66 and one of seven replacements at position 313 will exhibit those functional requirements.¹⁶¹

First, the identification of four PH20₁₋₄₄₇ mutations at position 313 that exhibit 120% or higher activity (A, H, K, R) of unmodified PH20₁₋₄₄₇ is not representative of each claim's genus of PH20 polypeptides with 2 to 22 additional substitutions and/or truncations.¹⁶² There is no description of multiply-modified PH20 polypeptides with the claimed substitutions at 313, much less one that identifies the 2 to 22 more substitutions and would retain this elevated enzymatic activity.¹⁶³ Indeed, the common specification does not identify even one multiply-modified PH20 polypeptide with any level of hyaluronidase activity.¹⁶⁴

Second, the common disclosure identifies no common structural feature shared by multiply-modified PH20 polypeptides and exhibiting the recited >100% or >120% activity.¹⁶⁵ Certainly, the mere presence of a M313K replacement in a

¹⁶¹ EX1003, ¶¶ 185, 191-92.

¹⁶² EX1001, 235 (Table 9); EX1003, ¶¶ 191-92.

¹⁶³ EX1003, ¶¶ 140, 190-93.

¹⁶⁴ EX1003, ¶¶ 130, 172.

¹⁶⁵ EX1003, ¶¶ 157, 190.

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multiply-modified PH20 does not dictate such a result, and the common disclosure makes no claim that it does.¹⁶⁶

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

b) Claims 7-9 Lack Written Description

Claims 7-9 employ claim 1's definition of the genus of modified PH20 polypeptides, and do not add requirements that limit the numbers of polypeptides in that genus. Claims 7-9 lack written description for the same reasons as claim 1.

c) Claims 10-21 Lack Written Description

Claims 10-21 employ claim 1's definition of the genus of modified PH20 polypeptides to define nucleotides, host cells, pharmaceutical compositions, methods of administering such compositions, and specify methods for using compositions containing modified PH20 polypeptides within that genus for treating cancer, including with anticancer drugs. Claims 10-21, however, contain no language that identifies *which* modified PH20 polypeptides within that immense genus can be used in the claimed methods, and thus do not remedy the § 112 deficiencies of claim 1.¹⁶⁷ Because each of claims 10-21 are directed to the same

¹⁶⁶ EX1003, ¶¶ 143, 168, 192.

¹⁶⁷ *Idenix*, 941 F.3d at 1155, 1165 (claims directed to method of treatment involving immense genus of modified proteins invalid for lack of written

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genus of polypeptides that are not adequately described in the written description of the common disclosure, they are unpatentable.

d) Claim 22 Lacks Written Description

Claim 22 defines a method of producing a genus of PH20 polypeptides that employs the same genus definition as claim 1, and thus lacks written description for the same reasons.

B. All Challenged Claims Are Not Enabled

All challenged claims are also unpatentable for lack of enablement.

“If a patent claims an entire class of ... compositions of matter, the patent’s specification must enable a person skilled in the art to make and use the *entire* class,” *i.e.*, “the *full scope* of the invention.”¹⁶⁸ So, the “more one claims, the more one must enable.”¹⁶⁹ “It is the specification, not the knowledge of one skilled in

description and non-enablement); *Boehringer*, PGR2020-00076, Paper 42, at 40-41 (because “the Specification does not provide an adequate written description of the composition of claim 1... we find that claims 12-16 [directed to methods of treatment using the compositions] lack written description for at least the same reasons”).

¹⁶⁸ *Amgen*, 598 U.S. at 610 (emphases added).

¹⁶⁹ *Id.*

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the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.”¹⁷⁰ “Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation.”¹⁷¹

Although not required, enablement may be assessed using the *Wands* factors, which consider: “(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention.”¹⁷²

Where the scope of the claims is large, there are few working examples disclosed in the patent, and the only guidance to practice “the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those

¹⁷⁰ *Idenix*, 941 F.3d at 1159.

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

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

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satisfying the claims’ functional limitations—the asserted claims are not enabled.”¹⁷³

Here, the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the $10^{49}+$ PH20 polypeptides having multiple amino acid replacements and/or truncations are “active mutant” PH20 polypeptides within the scope of the claims.¹⁷⁴

1. Claims 1 to 4 Are Not Enabled

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

¹⁷³ *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595, 615-16 (D. Del. 2022)

(Dyk, T., sitting by designation) *aff’d* 81 F.4th 1362 (Fed. Cir. 2023).

¹⁷⁴ EX1003, ¶¶ 170-71, 190.

a) Extreme Scope of the Claims

As explained in § IV.D.1, each of claims 1 to 4 defines an immense and structurally diverse genus of between 10^{49} and 10^{66} modified PH20 polypeptides, which introduces substantial scientific questions that are left unanswered by the common disclosure.

The claims encompass many modified PH20 polypeptides that terminate below position 429.¹⁷⁵ The common disclosure and the prior art, however, report that unmodified human PH20 must include residues through position 429 to have hyaluronidase activity.¹⁷⁶ Several of the claims (1-2, 5-22) also encompass modified PH20 polypeptides that, per the common disclosure's guidance, would be expected to be insoluble because they include all or some of the GPI anchor sequence.¹⁷⁷ And, to the extent Patentee contends the claims should be read as covering any polypeptide that falls within the mathematical "sequence identity" boundaries set by the claim language, they would capture modified PH20 polypeptides with 2-22 amino acid replacements the common disclosure instructs

¹⁷⁵ EX1003, ¶¶ 154, 164.

¹⁷⁶ EX1001, 68:30-39; EX1003, ¶¶ 93, 152-53.

¹⁷⁷ EX1001, 45:5-7, 70:39-40, 72:50-56, 73:47-49; EX1005, 2:56-61, 3:57-62.

“are less tolerant to change or required for hyaluronidase activity”¹⁷⁸ or which the common disclosure affirmatively says to not make.¹⁷⁹

In other words, the claims capture a massive genus of modified PH20 polypeptides, most of which would have unknowable properties absent individual production and testing.¹⁸⁰

Claims that capture a massive and diverse genus of proteins have routinely been found non-enabled. For example, the claims in *Amgen* covered “millions” of different, untested antibodies,¹⁸¹ while in *Idenix*, a skilled artisan would “understand that ‘billions and billions’ of compounds literally meet the structural limitations of the claim.”¹⁸² In both cases, the enormous claim scope was found non-enabled after being contrasted to the limited working examples in the patent, the existence of unpredictability, and the quantity of experimentation needed to practice the full scope of the claims (*Wands* Factors 1, 3, 4, and 7). And, as the *Idenix* court observed, one cannot rely on the knowledge and efforts of a skilled

¹⁷⁸ EX1001, 78:45-47.

¹⁷⁹ EX1001, 76:10-22.

¹⁸⁰ EX1003, ¶ 158.

¹⁸¹ 598 U.S. at 603.

¹⁸² 941 F.3d at 1157.

artisan to try to “fill the gaps in the specification” regarding which of the “many, many thousands” of possible compounds should be selected for screening, and which in this case is impossible.¹⁸³

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

The common disclosure provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement PH20₁₋₄₄₇ polypeptides, of which ~2500 were “active mutants.”¹⁸⁴ Those examples are a tiny fraction of the 10⁴⁹ to 10⁶⁶ modified PH20 polypeptides covered by the claims, and provide no guidance that would help a skilled artisan navigate the “trial-and-error” methodology the common disclosure describes using to make modified PH20 polypeptides; indeed, none incorporate more than one substitution and none truncate the PH20 polypeptide before position 447.¹⁸⁵

The common disclosure provides no credible guidance on the full scope of the genus comprising multiple combinations of changes to PH20 polypeptides.¹⁸⁶

¹⁸³ *Id.* at 1159.

¹⁸⁴ EX1003, ¶ 103.

¹⁸⁵ EX1003, ¶¶ 155, 159, 167.

¹⁸⁶ EX1003, ¶¶ 131, 139.

Instead, it describes an explicitly prophetic and “iterative” process for *discovering* active mutant PH20 polypeptides. *See* § V.A.4.

The purely prospective research plan in the common disclosure demands that a skilled artisan engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of *randomized* mutations (up to 21 rounds per starting molecule under the broadest claims) to *discover* which of the 10^{49+} possible modified PH20 polypeptides having 2 to 21 replacements to any of 19 other amino acids in any of 35 starting PH20 sequences might possess hyaluronidase activity.¹⁸⁷

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

¹⁸⁷ EX1003, ¶¶ 188-90; *see also* EX1018, 382 (noting that “combinatorial randomization of only five residues generates a library of 205 possibilities (3.2 x 10⁶ mutants), too large a number for manual screening”). Chica also credited a supposed “ground-breaking” advancement in predictive molecular modeling techniques. EX1018, 384, 382. That supposed advancement, however, was later shown to be false. EX1030, 569; EX1034, 258; EX1036, 275, 277; EX1048, 859.

- (i) it does not identify *any* specific combination of two or more replacements within any PH20 polypeptide that yield “active mutants”;
- (ii) it provides no data from testing *any* PH20 polypeptide with two or more substitutions;
- (iii) it does not identify any regions or residues that are “associated with the activity and/or stability of the molecule” or “critical residues involved in structural folding or other activities’ of the molecule” when two or more concurrent replacements have been made.¹⁸⁸

A skilled artisan could not predict whether a particular multiply-modified PH20 polypeptide will be enzymatically active without making and testing each one.¹⁸⁹

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

¹⁸⁸ EX1003, ¶¶ 144, 158, 172, 184-85.

¹⁸⁹ EX1003, ¶ 190.

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proteins.¹⁹⁰ Simply put, the common disclosure's prophetic, iterative and labor-intensive process requires making and screening an immense number of modified PH20 polypeptides, before which the skilled artisan will not know which multiply-modified PH20 polypeptides are within the claims' scope.¹⁹¹

c) Making Multiple Changes to PH20 Polypeptides Was Unpredictable

Like any protein, the activity of PH20 can be unpredictably influenced by changes to its amino acid sequence.¹⁹² Introducing changes can alter the local structure of the protein where the change is made, which may disrupt secondary structures or structural motifs within the protein that are important to its biological activity (*e.g.*, catalysis, ligand binding, etc.).¹⁹³

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

¹⁹⁰ *Idenix*, 941 F.3d at 1161-63 (emphasis added); *see also Amgen*, 598 U.S. at 612-15; *Wyeth*, 720 F.3d at 1384-86; *Baxalta*, 597 F. Supp. 3d at 616-19; *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 n.2 (Fed. Cir. 2020).

¹⁹¹ EX1003, ¶¶ 172, 184-85, 189.

¹⁹² EX1003, ¶ 61.

¹⁹³ *Id.*

tolerated within the PH20 protein structure with a reasonable (though not absolute) expectation of success.¹⁹⁴ That person, using a rational design approach, would have performed such an assessment by, *inter alia*, analyzing evolutionarily non-conserved positions and evaluating specific changed residues using a PH20 protein structure model using experimental evidence available before 2011 that is not disclosed in or referenced by the common disclosure.¹⁹⁵

By contrast, the skilled artisan could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011.¹⁹⁶ Introducing ***multiple*** concurrent changes into a particular region of a protein greatly increases the likelihood of disrupting secondary structures and structural motifs essential to the protein's activity, and can even introduce new ones into the protein.¹⁹⁷ Replacing multiple amino acids thus can introduce an immense number of simultaneous influences on a protein's structure that cannot be predicted.¹⁹⁸

¹⁹⁴ EX1003, ¶ 194.

¹⁹⁵ EX1003, ¶¶ 20-22, 49, 211-12, 216.

¹⁹⁶ EX1003, ¶ 224.

¹⁹⁷ EX1003, ¶¶ 59-60.

¹⁹⁸ EX1003, ¶ 58.

The cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure in 2011. For example, the further away the modeled amino acid sequence gets from an actual naturally occurring sequence and/or the original model's structure, the less reliable that model became.¹⁹⁹ In addition, depending on the structural template used to produce the model, regions of the protein not supported by a corresponding structure cannot be reliably used to assess particular changes.²⁰⁰ And the time required to carry out rational design techniques to "practice" the full scope of the claimed genus would be unimaginable.²⁰¹

Consequently, a skilled artisan could not have used conventional rational design techniques to identify, much less predict the outcome of attempts to make, the enormous number of PH20 polypeptide sequences that incorporate the myriad possible combinations of between 5 and 22 substitutions the claims encompass.²⁰² Stated another way, practicing the full scope of the claims would have been well

¹⁹⁹ EX1003, ¶¶ 158, 190, 224; EX1004, ¶¶ 167-168.

²⁰⁰ EX1003, ¶¶ 158, 224; EX1004, ¶¶ 157-59; EX1012, 4, 8.

²⁰¹ EX1003, ¶ 51, 190; EX1059, 1225-26; EX1018, 378.

²⁰² EX1003, ¶¶ 61, 158, 224.

beyond the ability of the skilled artisan's ability to reasonably predict which multiply-modified PH20 polypeptides would be enzymatically active, and, even if possible, doing so would have taken an extreme amount of time and effort even for a small handful of the vast universe of multiply-modified polypeptides within the claims.²⁰³

d) Other Wands Factors and Conclusion

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

For example, while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of multiply-changed PH20 polypeptides.²⁰⁴ Likewise, while there was significant knowledge in the public art about hyaluronidases, there was no solved structure of the PH20 protein, experimental reports generally reported on *loss of activity* from mutations, and did not predictably teach how to introduce changes that *enhanced* stability or activity. Indeed, the patent disclosure at issue in *Amgen* dates to the same 2011 timeframe as the common disclosure.

²⁰³ EX1003, ¶¶ 158, 190.

²⁰⁴ EX1003, ¶¶ 158, 224.

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

2. The Dependent Claims Are Not Enabled

a) Claims 5 and 6 Are Not Enabled

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

The reasons why claims 1-4 are not enabled (*see* § V.B.1) establish why claims 5 and 6 are also not enabled. Specifically, a skilled artisan could not have predicted which of the trillions of PH20 polypeptides having up to 21 changes in addition to a required change at position 313 would exhibit greater than 100% or 120% of the hyaluronidase activity of an unmodified PH20.²⁰⁵ Instead, a skilled artisan would need to make-and-test each of those molecules in order to practice the “full scope” of the claims.²⁰⁶

b) Claims 7-9 Are Not Enabled

Claims 7-9 employ the genus definition used in claim 1, and do not add requirements that limit the numbers of polypeptides in the claim 1 genus. Claims 7-9 are therefore not enabled for the same reasons as claim 1.

²⁰⁵ EX1003, ¶¶ 185, 190.

²⁰⁶ *Id.*

c) Claims 10-21 Are Not Enabled

Claims 10-21 employ the definition of the genus of modified PH20 polypeptides used in claim 1 to define nucleotides, host cells, and PH20-based pharmaceutical compositions and methods of administering them or using them to treat cancer. None of claims 10-21 limit the number of polypeptides in the claim 1 genus. Claims 10-21 are therefore not enabled for the same reasons as claim 1.²⁰⁷

d) Claim 22 Is Not Enabled

Claim 22 defines a method of producing a genus of PH20 polypeptides that employs the same genus definition in claim 1. Claim 22 is not enabled for the same reasons as claim 1.

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

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

First, it ignores that at least a portion of the claimed genus *does* require the modified PH20 polypeptides to be an “active mutant.” *See* § IV.D.3. Because dependent claims 5 and 6 require the modified PH20 polypeptides to exhibit increased hyaluronidase activity levels (>100% or 120% of unmodified PH20),

²⁰⁷ *See, e.g., Idenix*, 941 F.3d at 1155, 1165.

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parent claim 1 necessarily encompasses a sub-genus comprised of “active mutant” modified PH20 polypeptides. A failure to enable or describe a subgenus within the scope of the claims demonstrates that the claim *as a whole* is unpatentable for lack of written description and non-enablement.

Second, the common disclosure fails to provide any correlation between changes to PH20 polypeptides and *either* active or inactive mutants.²⁰⁸ Rather, it leaves to the skilled artisan the burdensome task of making and testing, through trial-and-error iteration, each of the 10⁴⁹+ candidate polypeptides within the claims’ scope to determine which exhibit hyaluronidase activity and which are inactive mutants.²⁰⁹

Third, the only putative utility identified for “inactive” polypeptides is as “antigens in contraception vaccines.”²¹⁰ This assertion is not scientifically credible, but regardless, the common disclosure provides no guidance about which epitopes on the PH20 protein must be preserved in an “inactive mutant” (if any) to induce contraceptive antibody production in a human subject.²¹¹ Notably, while

²⁰⁸ EX1003, ¶ 143.

²⁰⁹ EX1003, ¶¶ 173-74, 182-84.

²¹⁰ EX1001, 74:20-22, 193:14-33.

²¹¹ EX1003, ¶ 113.

the specification cites two studies in guinea pigs,²¹² it ignores numerous publications before 2011 that showed that immunizing mammals with PH20 did *not* cause contraception.²¹³ Moreover, Patentee's own clinical studies of the unmodified PH20₁₋₄₄₇ protein reported in 2018 that, despite producing anti-PH20 antibodies, those anti-PH20 antibodies *did not affect fertility* in humans:

Although some antisperm antibodies are associated with decreased fertility [], no evidence of negative effects on fertility could be determined in rHuPH20-reactive antibody-positive subjects of either sex.²¹⁴

Notably, Patentee reported this clinical result almost seven years before filing the application that issued as the '298 Patent.

Even if one considers the unlikely possibility that some epitope on human PH20 might induce contraceptive effects in a human, a skilled artisan could not

²¹² EX1001, 193:14-33; EX1022, 1142-43; EX1023, 1133-34.

²¹³ See EX1019, 325, 331-33 (“recombinant mPH20 is not a useful antigen for inclusion in immunocontraceptive vaccines that target mice”); EX1020, 179-81 (“immunization [of rabbits] with reproductive antigens ... are unlikely to result in reduced fertility ...”); EX1021, 30310, 30314 (“PH-20 is not essential for fertilization, at least in the mouse ...”).

²¹⁴ EX1024, 87-88; see also EX1061, 1154; EX1003, ¶¶ 110-11.

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have reasonably predicted from the common disclosure whether any “inactive mutant” modified PH20 polypeptides would preserve that epitope or induce antibody production that would confer (contrary to Patentee’s clinical evidence) contraceptive effects in humans.²¹⁵ Indeed, a skilled artisan would have expected the vast majority of “inactive mutant” PH20 polypeptides would have no utility at all.²¹⁶ Consequently, a skilled artisan would not have accepted the common disclosure’s assertion that “inactive mutants” are useful as contraceptive vaccines, particularly in humans.²¹⁷

Finally, and most significantly, the common disclosure does not identify a single inactive PH20 mutant (with any number of substitutions) that was shown to have contraceptive effect.²¹⁸ Therefore, at most, the common disclosure presents

²¹⁵ EX1003, ¶¶ 112-13.

²¹⁶ *Id.*; *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App’x. 26, 30 (Fed. Cir. 2007).

²¹⁷ EX1003, ¶¶ 112-13; *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005) (implausible scientific statements not entitled to weight).

²¹⁸ EX1003, ¶ 113.

only a “research proposal” to discover such “inactive mutants.”²¹⁹ It does not demonstrate possession of or enable the immense and diverse genus of PH20 polypeptides claimed, regardless of whether the claims are appropriately limited to “active mutants” or, instead, include “inactive mutants.”

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

The specifications of the pre-AIA '731 Application and AIA '298 Patent are substantially identical, and the challenged claims are not supported as § 112(a) requires by either. The claims are both PGR eligible and unpatentable under § 112(a).

The originally-filed claims of the '731 Application employed different claim formats but encompassed an equivalently large genus of multiply-substituted polypeptides. For example, original claim 1 required a “modified PH20 polypeptide” with an “amino acid replacement [that] confers ... increased stability” and having “85% sequence identity to SEQ ID NO: 3” (claim 3) or between “1 [and] 75 or more amino acid replacements” (claim 4). Dependent claims list positions (claim 12) or replacements (claims 13-16) in those

²¹⁹ See *Janssen Pharmaceutica N.V. v. Teva Pharms. USA, Inc.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) (“[t]he utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research”).

polypeptides. And, while certain claims contemplated 2-3 particular combinations of amino acid replacements (from dozens of locations), the claims also encompassed other unspecified substitutions at unspecified locations.²²⁰

The original claims provide no additional guidance or insight that would demonstrate written description of or would enable the claimed sets of modified PH20 polypeptides. As such, the original claims do not provide § 112 support for the challenged claims.²²¹

VI. Challenged Claims 1-4 and 7-22 Are Unpatentable Under § 103

As explained in § IV.D.2 above, claims 1-4 each define a genus that includes *one* specific modified PH20 polypeptide: M313K PH20₁₋₄₄₇. Because that particular modified PH20 polypeptide would have been obvious from the '429 Patent in view of Chao and the knowledge of a skilled artisan before 2011, each of claims 1-4 is unpatentable. Each of claims 7-22 also would have been obvious, as

²²⁰ EX1026, at 335.

²²¹ *See, e.g., Ariad Pharms.*, 598 F.3d at 1349 (“original claim language” does not “necessarily disclose[] the subject matter that it claims”); *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993) (original claim amounted to no more than a “wish” or “plan” for obtaining the claimed DNA and “attempt[ed] to preempt the future before it has arrived”).

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each specifies attributes that are met by the M313K modified PH20₁₋₄₄₇

polypeptide, or involve issues taught or suggested by the '429 Patent alone or with other prior art.

A. The Prior Art

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

Chao (EX1006) is an article published in the scientific journal "Biochemistry" in 2007. Chao is not discussed in the common disclosure of the '298 Patent and '731 Application, and was not cited or considered during examination of either.

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

B. Because M313K PH20₁₋₄₄₇ Would Have Been Obvious, Claims 1-4 Are Unpatentable

As explained below, Patentee's '429 Patent would have motivated a skilled artisan to produce modified PH20₁₋₄₄₇ polypeptides having a single amino acid substitution in a non-essential region of the protein. That person, guided by her familiarity with conventional rational protein design principles and the teachings of the '429 Patent and Chao, would have readily identified single amino acid substitutions in non-essential regions of PH20 that would be tolerated by the PH20

protein, such that the PH20 with the substitution would be expected to substantially retain its enzymatic activity. This process would have led the skilled artisan to identify M313K as one such single-amino acid substitution in PH20₁₋₄₄₇ that would be expected to retain hyaluronidase activity. Because claims 1-4 each encompass this obvious variant of PH20₁₋₄₄₇, each is unpatentable.

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

Patentee's '429 Patent, filed in 2003, describes as its invention soluble hyaluronidase glycoproteins ("sHASEGPs") based on PH20 that are enzymatically active at neutral pH.²²² It exemplifies and claims one such "sHASEGP" produced by truncating the human PH20 sequence at position 447 (positions 36-482 of SEQ ID NO: 1).²²³

The '429 Patent explains that sHASEGPs are useful in human therapy, including, *inter alia*, when combined with other therapeutic agents, and specifically illustrates administering such combinations subcutaneously to treat

²²² EX1005, 6:4-10, 10:30-59.

²²³ EX1005, 86:18-33, 86:64-87:13, 88:8, 89:52-90:15, 153:36-40.

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diseases including cancer.²²⁴ A PH20₁₋₄₄₇ was approved by the FDA as Hylenex[®] in 2005.²²⁵

The '429 Patent's teachings combined with the status of PH20₁₋₄₄₇ as an approved human therapeutic before 2011 would have induced a skilled artisan to focus on this particular PH20 polypeptide.²²⁶

Patentee's '429 Patent defines sHASEGPs as not only being the wild-type PH20₁₋₄₄₇ sequence, but as also including "equivalent" proteins "with amino acid substitutions that do not substantially alter activity" of the protein.²²⁷ It then expands on this guidance, explaining:

Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity, for example enzymatic activity, of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in

²²⁴ EX1005, 8:25-9:4, 56:36-43, 56:56-57:36, 63:41-61, 74:10-29, 76:19-77:36, 99:28-100:47.

²²⁵ EX1049, 1.

²²⁶ EX1003, ¶ 195.

²²⁷ EX1005, 9:65-10:13; *see also id.* at 18:64-19:6 ("equivalent" proteins).

non-essential regions of a polypeptide do not substantially
alter biological activity ...²²⁸

The '429 Patent explains that single amino acid substitutions can include “conservative” substitutions in Table 1, but that “[o]ther substitutions are also permissible and can be determined empirically or in accord with known conservative substitutions.”²²⁹ Notably, however, lysine is specifically identified as one of the exemplified “conservative” substitutions that Table 1 of the '429 Patent suggests for methionine in these non-essential positions of PH20.²³⁰

The '429 Patent thus teaches making a *particular* type of modification (a single amino acid substitution) at a *particular* location (non-essential regions of PH20) in a *particular* PH20 sequence (PH20₁₋₄₄₇) to yield equivalents of PH20₁₋₄₄₇ (*i.e.*, those that do not substantially alter the activity or function of PH20₁₋₄₄₇).²³¹

The '429 Patent also motivates skilled artisans to undertake this effort to design and produce such single-amino acid substituted PH20₁₋₄₄₇ proteins because

²²⁸ EX1005, 16:14-22.

²²⁹ EX1005, 16:24-36.

²³⁰ *Id.*; EX1003, ¶ 204.

²³¹ EX1003, ¶¶ 202-204; EX1004, ¶ 32.

it assures them their efforts will be successful.²³² As it states, skilled artisans recognized that such “single amino acid substitutions in non-essential regions” of PH20₁₋₄₄₇ “do not substantially alter biological activity” of PH20₁₋₄₄₇. As such, a skilled artisan would have expected a PH20₁₋₄₄₇ mutant with a single amino acid substitution in a non-essential region to have the same utility and therapeutic applications that the ’429 Patent identifies for wild-type PH20₁₋₄₄₇ and other sHASEGPs.²³³

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 recognized this type of change could best be accomplished using conventional rational design techniques, which involves determining (i) which regions are non-essential in PH20, and (ii) which single amino acids to substitute into positions in those non-essential regions.²³⁴

The ’429 Patent was written eight years before 2011. Given that, a skilled artisan would have looked for additional published insights into the structure of

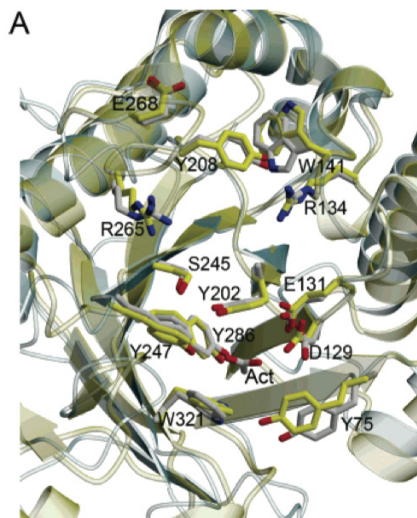
²³² EX1003, ¶¶ 203-204.

²³³ EX1003, ¶¶ 199, 203, 218.

²³⁴ EX1003, ¶¶ 209-10.

human hyaluronidase enzymes like PH20.²³⁵ That would have led the person directly to Chao (EX1006), which reported an experimentally determined structure for human HYAL1, and provided new insights into the shared characteristics of human hyaluronidase enzymes.²³⁶

First, by superimposing the HYAL1 and bee venom hyaluronidase structures, Chao showed that human and non-human hyaluronidases share a highly conserved catalytic active site structure and identified residues within this catalytic site that interact with the HA substrate.²³⁷



²³⁵ EX1003, ¶¶ 86, 205; EX1004, ¶ 88.

²³⁶ EX1003, ¶¶ 86, 205-207; EX1004, ¶ 88; EX1006, 6912-17.

²³⁷ EX1006, 6917 (Figure 4A); *see also id.* at 6914-16, Figure 2C; EX1004, ¶¶ 89-91; EX1003, ¶¶ 81-82.

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The '429 Patent likewise used the bee venom hyaluronidase structure to identify critical residues in PH20.²³⁸ It also taught that hyaluronidase domains share similarity among and between species, including certain residues in conserved motifs necessary for enzymatic activity.²³⁹

Second, using an alignment of five human hyaluronidases, Chao identifies predicted secondary structures in the proteins (*e.g.*, β -sheets, α -helices) (Figure 3, below), as well as, invariant conserved positions (blue), residues involved in catalysis (red), conserved cysteines that form disulfide bonds (gold) and conserved asparagine residues that are glycosylated (turquoise).²⁴⁰

²³⁸ EX1005, 4:12-22, 86:49-53, 88:14-24.

²³⁹ EX1005, 2:6-67, 4:11-22.

²⁴⁰ EX1006, 6916; EX1003, ¶ 83; EX1004, ¶¶ 92.

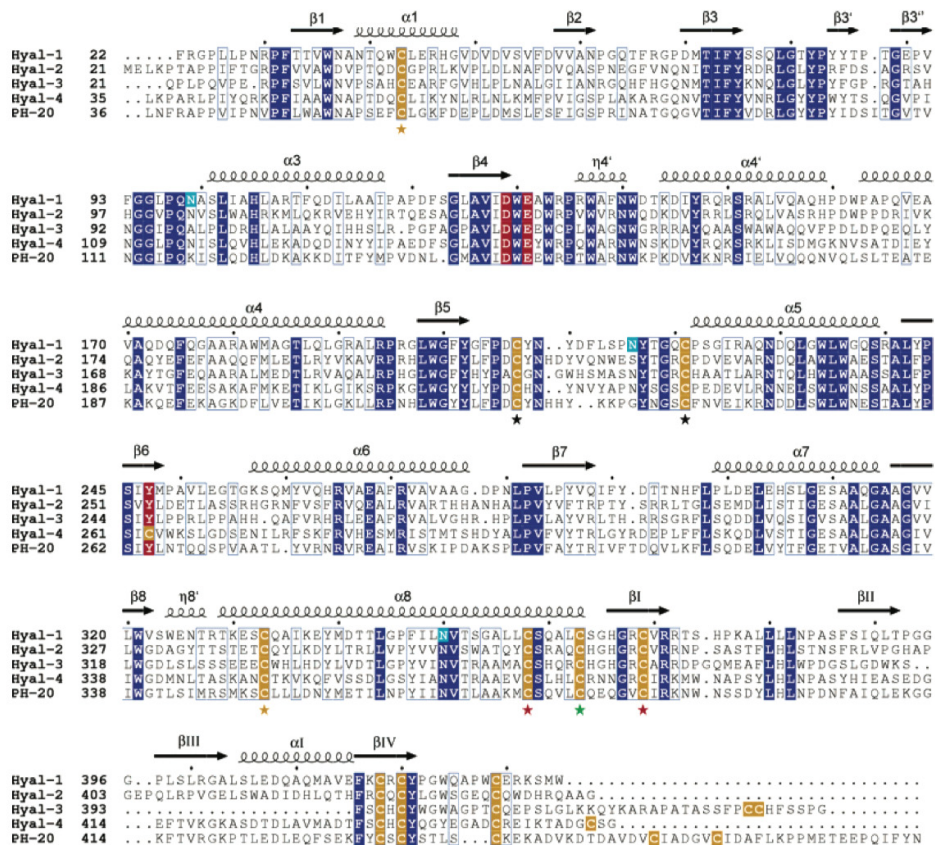


FIGURE 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative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

Third, Chao reported the presence of “a novel, EGF-like domain” in the C-terminal region of human hyaluronidases that was “closely associated” with the catalytic domain (discussed above, § V.A.2.cV.A.2.c). Of note here, Chao identifies a characteristic pattern for the Hyal-EGF domain in PH20 (at 337-409).²⁴¹

²⁴¹ EX1006, 6912; EX1004, ¶¶ 97-98; EX1003, ¶¶ 84-85.

3. A Skilled Artisan Would Have Identified M313K as Being in a Non-Essential Region of PH20₁₋₄₄₇ in 2011

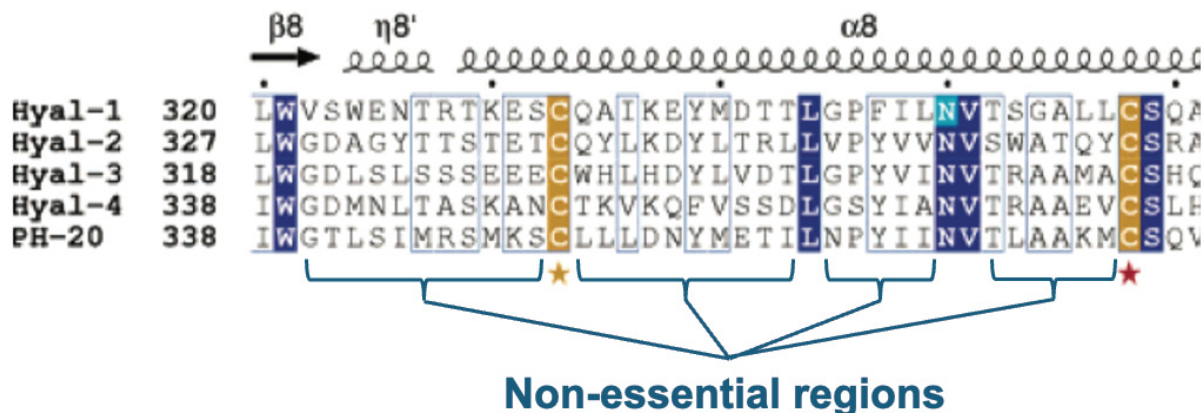
To implement the '429 Patent's suggestion to produce modified PH20₁₋₄₄₇ polypeptides with single amino acid substitutions in non-essential regions that retain hyaluronidase activity, the skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011.²⁴² The person would have done that using conventional sequence alignment tools in conjunction with the information in the '429 Patent and in Chao, as well as information publicly known in 2011.²⁴³

The multiple sequence alignment identifies the non-essential regions in PH20—they are the sequences between essential residues containing positions at which variations occur at a frequency above ~5% (illustrated in Chao for five homologous human hyaluronidase sequences below).²⁴⁴

²⁴² EX1003, ¶¶ 208-210; EX1004, ¶¶ 22, 25-30, Appendix D-3.

²⁴³ EX1003, ¶¶ 20-21, 209-211; EX1004, ¶¶ 22-24; EX1017, 224-26.

²⁴⁴ EX1004, ¶¶ 31-32, Appendix D-2; EX1003, ¶ 211; EX1006, 6916.

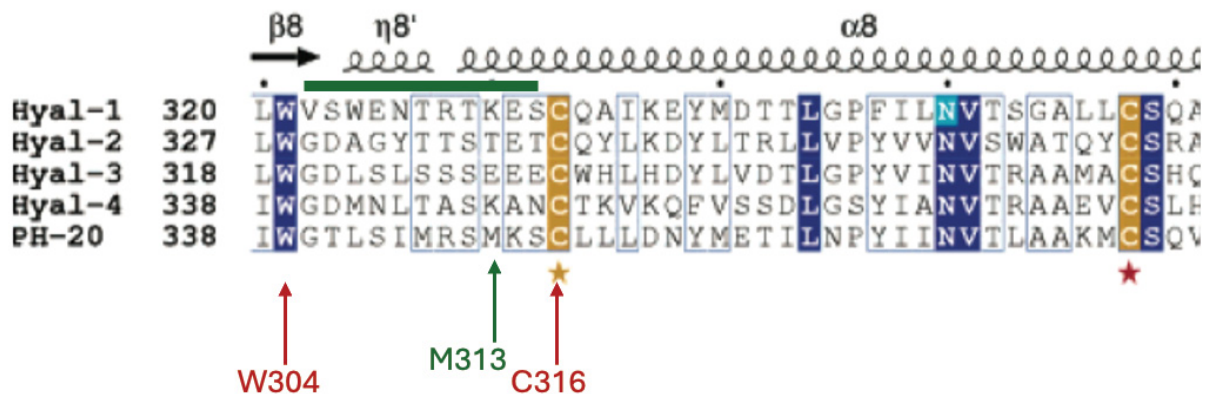


Dr. Sheldon Park, an expert in protein sequence and structure analysis with extensive personal experience before 2011, performed these steps on a set of 88 homologous hyaluronidase protein sequences he identified that had been published by December 29, 2011.²⁴⁵ Dr. Park then prepared a multiple-sequence alignment of these 88 homologous proteins, similar to what Chao did with the five human hyaluronidases, and from that alignment identified essential (Appendix D-3) and non-essential (Appendix D-2) residues.²⁴⁶

²⁴⁵ EX1004, ¶¶ 27, 149-152; EX1053; EX1054; EX1055; EX1056; EX1064, 1, 4, 10, 23-28.

²⁴⁶ EX1004, ¶¶ 28-32, 153-154, Appendix D; EX1057; EX1058; EX1043, 1-2, 4-5; EX1065, 1, 4.

Position 313 is within a non-essential region of PH20₁₋₄₄₇, which is shown not only by Dr. Park's analysis, but also by Chao's Figure 3; both report the same bounding essential residues (*i.e.*, W304 and C316) (below).²⁴⁷



Thus, following the guidance and information in the '429 Patent and Chao, and assessing information publicly available in December 2011 using conventional sequence analysis tools, a skilled artisan would have readily identified position 313 as a position in a non-essential region PH20₁₋₄₄₇.²⁴⁸

4. A Skilled Artisan Would Have Found Lysine to Be Suggested as an Obvious Single Amino Acid Substitution at Position 313 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

²⁴⁷ EX1003, ¶ 213; EX1004, ¶¶ 31-32, Appendix D-2; EX1006, 6916.

²⁴⁸ EX1003, ¶ 216; EX1004, ¶¶ 31-32, 104, Appendix D-2; EX1005, 16:14-22, 16:24-36; EX1006, 6916.

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acid sequence of homologous, stable and active naturally occurring hyaluronidase enzymes.²⁴⁹ This derives from evolutionary selection principles, which over the course of millions of years, function to eliminate from the genome of organisms those variations in the sequences of a protein that do not yield stable and active forms of the protein.²⁵⁰ Thus, a skilled artisan can readily compile a list of the specific amino acids that have been tolerated at positions within non-essential regions of PH20 using a multiple-sequence alignment of homologous hyaluronidase enzymes.²⁵¹

Dr. Park did this; he used the alignment he produced of the 88 hyaluronidase proteins known by December 2011 to identify and calculate the frequency of

²⁴⁹ EX1003, ¶¶ 20, 49, 210, 214, 216; EX1004, ¶ 21-22.

²⁵⁰ EX1003, ¶¶ 20, 210; EX1004, ¶¶ 25, 31, 41-42; EX1017, 224 (“Evolution provides a tremendously useful model for protein design. ... By considering the common features of the sequences of these proteins, it is possible to deduce the key elements that determine protein structure and function—even in absence of any explicit structural information.”); EX1014, 351.

²⁵¹ EX1003, ¶¶ 214, 216; EX1004, ¶ 21-22.

occurrence of each different amino acid that occurs at positions corresponding to each position in the non-essential regions of PH20₁₋₄₄₇.²⁵²

The amino acids appearing at position 313 of PH20 in the corresponding positions of the 88 naturally occurring hyaluronidase enzymes known by 2011 are shown below.²⁵³ The wild-type residue at position 313 in PH20 is methionine (M), which occurs in ~14% of the proteins (including PH20). As shown, the most prevalent amino acid found at position 313 in this set of homologous sequences is lysine (K) (~40%), which is present in 35 different hyaluronidase proteins.

	AA at position 348/313 in PH20 ₁₋₄₄₇		Most frequent AA at position in set of proteins
wt 348:	M	13.63	K 39.77
res387:	K	35 39.77	} % of occurrence of AA in set of proteins
res387:	E	15 17.04	
res387:	M	12 13.63	
res387:	T	5 5.68	
res387:	A	4 4.54	
res387:	R	4 4.54	
res387:	Q	4 4.54	
res387:	Y	2 2.27	
res387:	V	2 2.27	
res387:	N	2 2.27	
res387:	P	1 1.13	
res387:	L	1 1.13	
res387:	-	1 1.13	

Several amino acids other than methionine occur with significant frequency at a position corresponding to 313 in PH20 in known, homologous hyaluronidase

²⁵² EX1004, ¶¶ 30-32, 41-43, Appendix D-1.

²⁵³ EX1003, ¶ 214; EX1004, ¶¶ 43, 113, Appendix D-1.

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enzymes.²⁵⁴ A skilled artisan would have believed those amino acids would be the obvious choices to assess as single amino acid substitution for position 313 of PH20₁₋₄₄₇.²⁵⁵

More directly, a skilled artisan would have had specific reasons to substitute lysine (K) for methionine (M) at position 313 as a single amino acid substitution in a non-essential region of PH20₁₋₄₄₇.

First, lysine is the most prevalent amino acid at the position corresponding to position 313 in PH20 in the set of 88 homologous hyaluronidase enzymes known in 2011—it occurs in nearly 40% of those proteins (35 different naturally occurring hyaluronidase enzymes) and in 2 of the 5 human hyaluronidases.²⁵⁶ The high frequency with which lysine occurs in this position makes it an obvious candidate for being incorporated into position 313 of PH20, as it is tolerated in many naturally occurring hyaluronidase enzymes.²⁵⁷

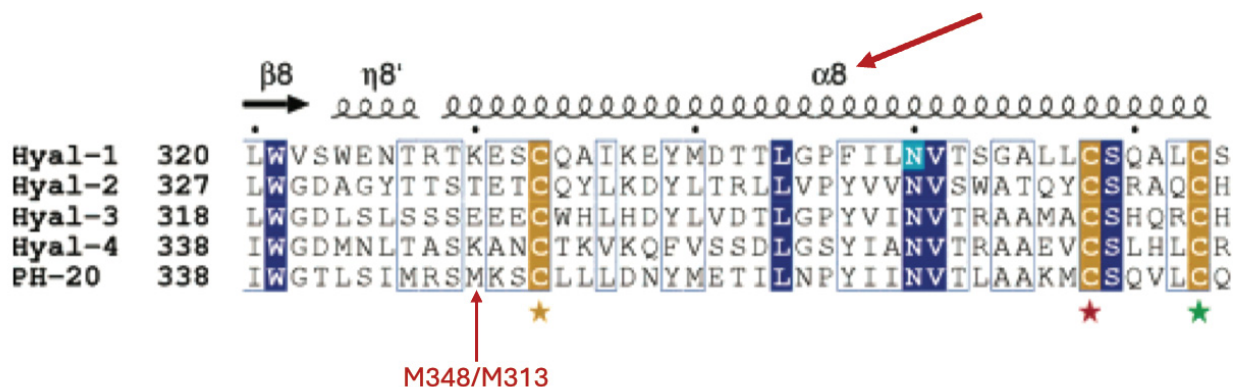
²⁵⁴ EX1004, ¶ 106.

²⁵⁵ EX1003, ¶¶ 210, 214, 216-17; EX1004, ¶¶ 41-42 106.

²⁵⁶ EX1004, ¶¶ 43, 106, 113; EX1003, ¶ 214.

²⁵⁷ EX1003, ¶¶ 214, 216-17; EX1004, ¶ 113.

Second, lysine was known to have a high helix propensity, meaning it is favored in sequences that form α -helix secondary structures.²⁵⁸ Chao identified the “ $\alpha 8$ ” helix sequence as one such α -helix forming sequence in PH20, and position 313 of PH20 is at the beginning of that $\alpha 8$ helix sequence (below).²⁵⁹ Given its high propensity for supporting α -helix secondary structures, a skilled artisan would have viewed lysine as a logical (and thus obvious) substitution for methionine at position 313, given its location within the $\alpha 8$ helix sequence in PH20₁₋₄₄₇.²⁶⁰



Third, the '429 Patent specifically identifies lysine as an example of a conservative amino acid substitution for methionine in non-essential regions of

²⁵⁸ EX1050, 422-24, Table 2; EX1003, ¶¶ 215; EX1004, ¶¶ 69-70, 117.

²⁵⁹ EX1006, 6916, Figure 3; EX1003, ¶ 192, 215; EX1004, ¶¶ 32, 108.

²⁶⁰ EX1003, ¶ 215; EX1004, ¶¶ 32, 108, 117-118.

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proteins like PH20.²⁶¹ A skilled artisan would find lysine to be an alternative to methionine pursuant to this guidance in the '429 Patent.²⁶²

For all of the reasons above, a skilled person would have found it obvious change the methionine (M) at position 313 to lysine (K) in PH20₁₋₄₄₇.²⁶³

5. A Skilled Artisan Would Have Reasonably Expected the M313K Substitution in PH20₁₋₄₄₇ Would Yield an Enzymatically Active PH20 Protein

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

Replacing the methionine (M) at position 313 with lysine (K) yields a PH20₁₋₄₄₇ with a single amino acid substitution in a non-essential region of the polypeptide.²⁶⁴ In its '429 Patent, Patentee stated:

Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.²⁶⁵

²⁶¹ EX1005, 16:4-32, Table 1, 10:9-13.

²⁶² EX1003, ¶¶202-204.

²⁶³ EX1003, ¶¶ 213-216.

²⁶⁴ See § VI.B.3; EX1003, ¶¶ 213-14; EX1004, ¶ 32.

²⁶⁵ EX1005, 16:17-20.

Patentee also represented in its '429 Patent that “conservative substitutions, such as those set forth in Table 1 ... do not eliminate proteolytic activity” and listed lysine for methionine as one such “conservative substitution.”²⁶⁶

Patentee then secured claims in the '429 patent to modified PH20₁₋₄₄₇ proteins with at least one substitution (*e.g.*, claim 1), even though it provided no examples of any PH20 proteins with any substitutions. Patentee, thus, made and relied on its affirmative statements that a skilled artisan would have expected *any* single amino acid substitution in *any* non-essential position of PH20₁₋₄₄₇ to not substantially affect the biological activity of the enzyme, and particularly ones listed in Table 1. Patentee should not be permitted to change its position now and contend that a skilled artisan would not have reasonably expected that making the M313K substitution in PH20₁₋₄₄₇ would yield an enzyme with substantially the same activity as unmodified PH20₁₋₄₄₇.

b) Skilled Artisans Would Reasonably Expect M313K to be Tolerated in PH20₁₋₄₄₇

Independently, a skilled artisan would have reasonably expected that the M313K substitution in PH20₁₋₄₄₇ would not substantially alter the biological activity (hyaluronidase activity) of PH20₁₋₄₄₇.

²⁶⁶ EX1005, 16:7-9, 27-32.

Both experts noted that many naturally occurring homologous hyaluronidase proteins contain lysine at the position corresponding to position 313 in PH20.²⁶⁷

The high frequency of occurrence of lysine at positions equivalent to 313 in naturally-occurring hyaluronidases, including in 2 of 4 human homologs of PH20 (Chao), along with lysine's high helix propensity, would have led a skilled artisan to reasonably expect the M313K substitution would be tolerated in PH20₁₋₄₄₇.²⁶⁸

c) The PH20 Structural Model Confirms that PH20₁₋₄₄₇ Would Tolerate Lysine at 313

Dr. Park further assessed whether a variety of single amino acid substitutions in PH20₁₋₄₄₇ would be tolerated, such as the M313K substitution, using a PH20 protein structural model generated by SWISS-MODEL from Chao's HYAL1 structure as the template, as would have been done in 2011 by a skilled artisan.²⁶⁹

²⁶⁷ EX1003, ¶ 214; EX1004, ¶ 113.

²⁶⁸ EX1003, ¶¶ 217-218; EX1006, 6916.

²⁶⁹ EX1004, ¶¶ 39-40, 156; EX1003, ¶ 221, 223; EX1006, 6915, Figure 2; EX1017, 229; EX1012, 1-2, 4; EX1014, 348, 370; EX1038, 3382.

Dr. Park explains that the PH20 model he used was reliable in the region of position 313 of PH20 based on QMEAN values,²⁷⁰ and would be very similar to a PH20 model generated by SWISS-MODEL in 2011 (*e.g.*, because it used 165 conserved positions in the backbone of the two proteins).²⁷¹

Dr. Park also devised a consistent, objective methodology for assessing substitutions using the PH20₁₋₄₄₇ model.²⁷² Factors he considered included, *inter alia*, the number of neighboring residues at position 313 (*i.e.*, those within 5 Å), the various types of possible interactions between neighbors (*e.g.*, hydrophobic, charged, van der Waals, steric, etc.), and solvent accessibility.²⁷³ Where interactions were observed, Dr. Park assessed the impact of them (*e.g.*,

²⁷⁰ EX1004, ¶¶ 157-59 (satisfactory local and global QMEAN values); EX1037, 346-47; EX1069, 3; EX1012, 4, 8.

²⁷¹ EX1004, ¶¶ 160-161, 165; EX1038, 3382-4; EX1017, 229-230; EX1012, 1-2; EX1014, 348, 370; EX1066, 5-11.

²⁷² EX1004, ¶¶ 102-103; *see generally id.* at § IV.C (description of Dr. Park's methodology).

²⁷³ EX1004, ¶¶ 44-47, 53-60, 65-85, Appendix D-5; EX1035, 1408, Table 2; EX1043, 2, Table 1.

hydrophobic-hydrophilic, effects on secondary structures, size related issues such as steric clashes or creation/filling of “holes” in the structure).²⁷⁴

Dr. Park assessed the environment of position 313 visually by comparing the wild-type with the version incorporating substituted amino acids at position 313 using functionality within the viewer (PyMol) and as a modeled sequence generated from the PH20₁₋₄₄₇ sequence incorporating the single substitution in SWISS-MODEL.²⁷⁵ Again, these technologies were available in 2011.²⁷⁶ He used his methodology to assess numerous substitutions representing diverse interactions, and confirmed that it provided a consistent, objective and unbiased evaluation of substitutions throughout the protein.²⁷⁷

Dr. Park assigned a score for each substitution reflecting the aggregate effect of the interactions he observed (below).²⁷⁸

²⁷⁴ EX1004, ¶¶ 62-63, 85.

²⁷⁵ EX1004, ¶¶ 61, 107, 115, 165-66; EX1003, ¶ 22, 49, 221, 223.

²⁷⁶ EX1004, ¶¶ 155, 160, 165-66, 171-172; EX1066, 1, 4, 7, 17, 25, 27, 35, 39, 41; EX1067, 1, 6-7, 53-57, 61-62; EX1012, 1-4.

²⁷⁷ EX1004, ¶¶ 102-103.

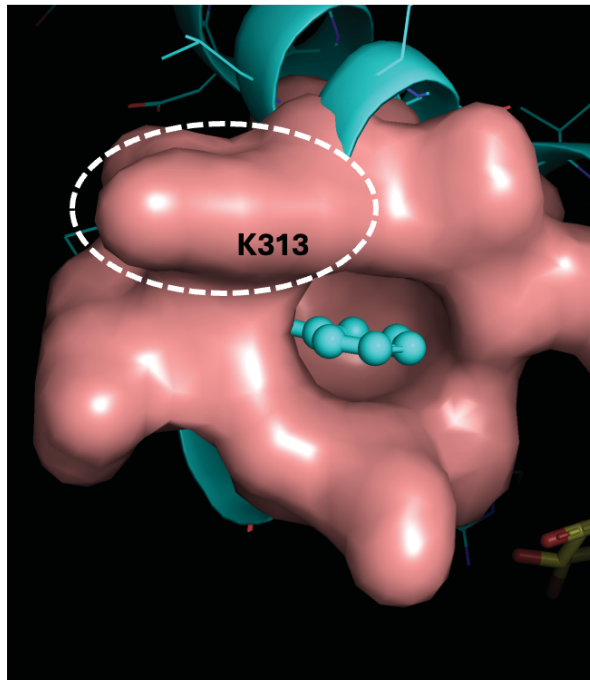
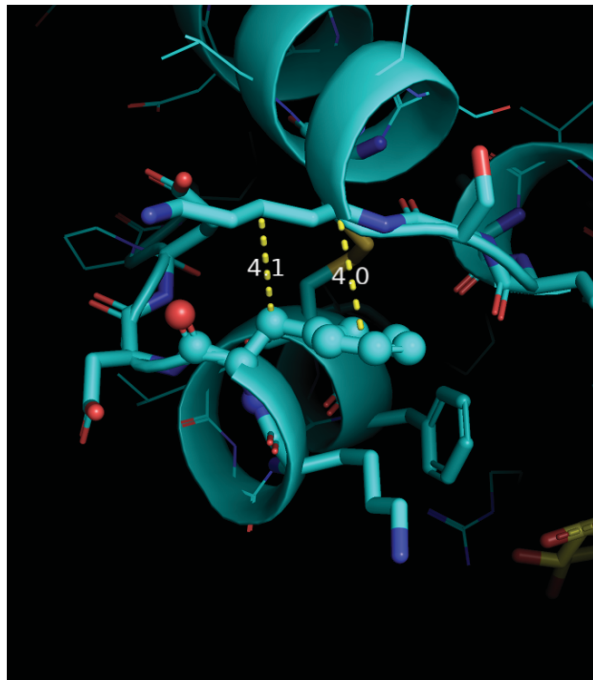
²⁷⁸ EX1004, ¶¶ 85-87.

<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 3 for the M313K substitution in PH20₁₋₄₄₇, indicating that the substitution would be expected to confer improved stability.²⁷⁹ He observed that in the wild-type environment, position 313 contributes to a hydrophobic pocket around the phenylalanine (F) at position 29, but that position 313 also has a high solvent exposure.²⁸⁰ He found that while lysine and methionine have chemically different classifications, lysine within the environment of position 313 would be seen as a conservative substitution as it maintains several structural roles of methionine at that position (below).

²⁷⁹ EX1004, ¶ 118-120, Appendix C.

²⁸⁰ EX1004, ¶¶ 108-11.



First, due to their similar aliphatic side-chains, when lysine is substituted for methionine at position 313, it maintains the three interactions that occur between the C- α , C- β and C- γ carbons of methionine with phenylalanine at position 29.²⁸¹ Also, the C- α through C- γ atoms in lysine (like in methionine) help form a solvent-limited pocket around PH20 through interactions with F29 and H47, which is also comparable to lysine's role at position 330 in HYAL1.²⁸² Second, the terminus of lysine is hydrophilic, making it more compatible in a solvent environment than the thiol group in methionine, and it may also form a salt-bridge with glutamic acid (E)

²⁸¹ EX1004, ¶ 118.

²⁸² *Id.*

at position 66.²⁸³ Dr. Park thus concluded that because the net effect of the interactions associated with substituting lysine for methionine at position 313 in PH20₁₋₄₄₇ would be stabilizing, the M313K substitution in PH20₁₋₄₄₇ would be tolerated and thus expected to retain the hyaluronidase activity of the unmodified PH20₁₋₄₄₇.²⁸⁴

Dr. Park's visualization-based assessment is a technique that was prevalent in 2011.²⁸⁵ Similarly, his technique of assessing interactions between neighbors and assigning an overall score reflecting the aggregate effects of those interactions is consistent with methods reported in peer review publications (*e.g.*, Dr. Moul't's

²⁸³ EX1004, ¶ 119.

²⁸⁴ EX1004, ¶ 120.

²⁸⁵ EX1017, 228 (“... a structural biologist's intuition is often an important tool in the design of the desired variants, an approach that may be termed structure-based protein design to borrow a term from the drug design field. Visualization of the known reference structure is a key component of this.”); EX1004, ¶¶ 22, 33-36; EX1003, ¶¶ 22, 49, 221, 223.

group reported using this technique to assess single substitutions caused by single-nucleotide polymorphisms, and classified the net effects on a 3-point scale).²⁸⁶

Dr. Hecht reviewed Dr. Park's analysis and conclusions, and agreed with both.²⁸⁷ Through his own assessment, he observed that lysine substituted into position 313 would have a stabilizing effect due to (i) the compatibility of the shape of lysine with the solvent-exposed pocket at that location, and (ii) the fact that the M313K substitution would introduce a hydrophilic residue (L) into a solvent-exposed position in the protein, all without disturbing pre-existing interactions with neighboring amino acids.²⁸⁸

The common disclosure defines an "active mutant" as a modified PH20 polypeptide with as little as 40% of the activity of unmodified PH20₁₋₄₄₇.²⁸⁹ Dr. Hecht and Dr. Park each independently concluded that the M313K substitution would have been tolerated by PH20₁₋₄₄₇, meaning it would exhibit comparable

²⁸⁶ EX1004, ¶¶ 48-52; EX1031, 439, 462-64, 469-71, Table 3; EX1032, 265-66; EX1003, ¶ 223.

²⁸⁷ EX1003, ¶¶ 225.

²⁸⁸ EX1003, ¶¶ 226-227.

²⁸⁹ EX1001, 74:11-16; *also id.* at 77:61-65.

hyaluronidase activity to unmodified PH20₁₋₄₄₇ (*i.e.*, activity well above 40%).²⁹⁰

A skilled artisan considering the M313K substitution in PH20₁₋₄₄₇ thus would have reasonably expected the M313K PH20₁₋₄₄₇ mutant would exhibit comparable activity to unmodified PH20₁₋₄₄₇ protein.²⁹¹

Based on the '429 Patent, Chao, and information available in 2011, the M313K PH20₁₋₄₄₇ mutant polypeptide would have been obvious to a skilled artisan in 2011. And because claims 1-4 each encompass the single-replacement modified M313K PH20₁₋₄₄₇ polypeptide, each claim is unpatentable.

C. Dependent Claims 7-19 and Claims 20-22 Are Obvious

None of the dependent claims or claim 22 define subject matter that is independently patentable from claims 1-4. For the reasons below, each would have been obvious to a skilled artisan.

1. Claims 7-9

Claims 7-9 require the modified PH20 polypeptide to “comprise[] one or more modifications” including glycosylation (claims 7-8) and be a “glycoprotein that comprises an N-acetylglucosamine moiety linked to each of at least three asparagine residues” (9).

²⁹⁰ EX1003, ¶¶ 225-27, 229; EX1004, ¶¶ 115-120.

²⁹¹ EX1003, ¶ 229.

The '429 Patent teaches (i) that human PH20 must be glycosylated to exhibit activity, and (ii) expression of PH20₁₋₄₄₇ in mammalian (CHO) host cells that yield active forms of PH20₁₋₄₄₇.²⁹² It further teaches that “N- and O-linked glycans are attached to polypeptides through asparagine-N-acetyl-D-glucosamine ... linkages,” and claims PH20 polypeptides (including PH20₁₋₄₄₇) having asparagine-linked sugar moieties.²⁹³ Frost reports that the recombinant production of PH20₁₋₄₄₇ in CHO cells “resulted in a 447 amino acid 61 kDA glycoprotein with a properly processed amino terminus and 6 N-linked glycosylation sites.”²⁹⁴

Based on the '429 Patent and knowledge in the art, a skilled artisan would have found it obvious to produce M313K PH20₁₋₄₄₇ in a CHO cell, and that doing so causes six N-linked glycosylation sites to be glycosylated.²⁹⁵

2. Claims 10-12 and 22

Claims 10-12 broadly specify a nucleic acid encoding any modified PH20 polypeptide of claim 1, an expression vector comprising that nucleic acid, and a host cell comprising that vector. Claim 22 similarly claims methods of

²⁹² EX1005, 95:13-30; 40:41-51, 89:53-91:67; 88:5-9.

²⁹³ EX1005, 3:27-35, claims 1, 6.

²⁹⁴ EX1013, 432.

²⁹⁵ EX1003, ¶¶ 197-98, 200-201.

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recombinantly producing a genus that includes M313K PH20₁₋₄₄₇ by transfecting a plasmid containing a cDNA encoding it into a host cell, culturing the cells, and harvesting the protein from the cell culture.

The '429 Patent teaches the recombinant production of PH20₁₋₄₄₇ in CHO cells comprising (i) preparing a nucleic acid encoding PH20₁₋₄₄₇, (ii) inserting it into a plasmid expression vector, and (iii) transfecting CHO cells with the plasmid to produce the PH20₁₋₄₄₇ protein.²⁹⁶ It also teaches “nucleic acid molecules that encode a polypeptide ... that have at least” 95% sequence identity with a full length PH20 (*i.e.*, up to 22+ substitutions).²⁹⁷

From their training and experience, and the guidance in the '429 Patent, a skilled artisan would have found it obvious to prepare and insert into a plasmid a nucleic acid encoding a single-replacement (*e.g.*, M313K) PH20₁₋₄₄₇, transfect a CHO host cell with it, express and then harvest the protein from the cell culture.²⁹⁸ For example, Arming and Zhang both reported recombinant production of single-substitution forms of active soluble PH20 polypeptides.²⁹⁹

²⁹⁶ EX1005, 89:54-90:15, 90:19-91:67.

²⁹⁷ EX1005, 11:60-66.

²⁹⁸ EX1003, ¶¶ 198, 200.

²⁹⁹ EX1011, 810-11; EX1010, 9433-35.

3. Claims 13-21

Claims 13-21 specify a pharmaceutical composition comprising any modified PH20 polypeptide in the genus of claim 1, alone (claim 13) or in combination with a therapeutic agent (14), several genera of agents, (15) an antibody (16), and “a small molecule drug” (17). Claims 18 and 19 concern methods of administering the compositions of claim 14 (18) and doing so subcutaneously (19). Claims 20 and 21 concern methods of treating cancer by administering the composition of claim 14 to a patient (claim 20) including a patient being treated with an anticancer drug (21).

The '429 Patent provides extensive guidance concerning and claims pharmaceutical compositions comprising soluble, neutral PH20 polypeptides (*e.g.*, PH20₁₋₄₄₇), alone or in combination with other therapeutic agents including antibodies, small molecule drugs, and agents used in treating cancer.³⁰⁰ It similarly describes and claims methods of administering them subcutaneously via formulations that combine an enzymatically active hyaluronidase protein with the

³⁰⁰ EX1005, 8:60-9:4, 54:52-55:35, 56:28-57:21, 55:61-56:9, 56:66-57:21, 73:4-74:29, claims 14, 29, 33.

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other therapeutic agent, which together enable “spreading” of the therapeutic agent after injection.³⁰¹

A skilled artisan would have appreciated that a single-replacement PH20₁₋₄₄₇ polypeptide with comparable hyaluronidase activity to PH20₁₋₄₄₇ (such as the M313K mutant) would be equivalently useful in the therapeutic compositions, methods of administration, and methods of treatment described in the '429 Patent for PH20₁₋₄₄₇.³⁰² Indeed, in the '429 Patent, Patentee secured claims encompassing pharmaceutical compositions containing certain modified PH20 polypeptides and chemotherapeutic agents despite the absence of any exemplification.³⁰³ Claims 13-21 also impose no restrictions on the makeup of the pharmaceutical compositions, and claim only categories of therapeutic agents. A skilled artisan would have found such agents and methods of administration and treatment to have been obvious from the '429 Patent for the above reasons.³⁰⁴

³⁰¹ EX1005, 8:25-38, 56:28-56, 57:22-36, 58:59-59:12, 63:40-64:4, 76:18-77:37, claim 27.

³⁰² EX1003, ¶¶ 199, 203, 217-18, 229.

³⁰³ EX1005, claims 29, 30, 50.

³⁰⁴ EX1003, ¶¶ 199, 203.

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

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

Patentee is likely to dispute that the M313K PH20₁₋₄₄₇ is obvious because it is reported to have unexpectedly high hyaluronidase activity as a single substitution mutant. Demonstrating that result for one mutant out of the $\sim 10^{49}$ - 10^{66} modified PH20 polypeptides encompassed by the claims, however, utterly fails to establish a nexus between that evidence and the claims. As explained above, the single-substitution M313K PH20₁₋₄₄₇ is not representative of the numerous, structurally different proteins that are encompassed by the claims, particularly those that would be expected to be inactive. *See* § V.A.2. No evidence or explanation is provided in the common disclosure that resolves this confusion.

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

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

Discretionary denial is assessed using the factors set forth in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020). None weigh in favor of denial as there is currently no parallel litigation regarding the '298 Patent.

Also, during examination, no patentability issues relevant to the grounds were considered.³⁰⁵ Notably, Chao was not cited to the Office, and the Examiner did not have the benefit of Dr. Hecht or Dr. Park's detailed expert testimony. The Examiner also did not consider Petitioner's § 112 arguments regarding the lack of support for the immense genus of claimed modified PH20 polypeptides (or any substantially similar arguments) during prosecution.³⁰⁶ Rather, the first § 112 rejection concerned whether a dependent claim to a soluble PH20 polypeptide was further limiting, which was mooted when the Applicant cancelled the claim.³⁰⁷ The second concerned whether an independent pharmaceutical composition claim

³⁰⁵ The Examiner's double patenting rejections were mooted by the filing of terminal disclaimers, not on the merits. *Supra* § IV.C.

³⁰⁶ *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7-11 (P.T.A.B. Feb. 13, 2020).

³⁰⁷ EX1002, 436-39, 555-57.

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and its dependent claims were definite, which was withdrawn after the Applicant amended the independent claim to cover only a single composition.³⁰⁸

VIII. CONCLUSION

For the foregoing reasons, the challenged claims are unpatentable.

Dated: November 26, 2024

Respectfully Submitted,

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³⁰⁸ EX1002, 440, 531, 555-57.

EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,018,298
1002	File History of U.S. Patent No. 12,018,298
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
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1015	Table Associating Citations from the '298 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

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1045	Redline Comparison of the '731 and '298 Specifications
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1063	[Reserved]

No.	Exhibit Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with M313K Mutation
1071	Swiss Model Printout of PH20 Model with M313A Mutation
1072	Swiss Model Printout of PH20 Model with M313R Mutation
1073	Swiss Model Printout of PH20 Model with M313Y Mutation
1074	Swiss Model Printout of PH20 Model with M313P Mutation
1075	Swiss Model Printout of PH20 Model with M313L Mutation

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,676 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

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Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 26th day of November, 2024, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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