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Paper 100
Date: October 15, 2026

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

HALOZYME, INC.,
Patent Owner.

PGR2025-00030
Patent 12,054,758 B2

Before SUSAN L. C. MITCHELL, CYNTHIA M. HARDMAN, and MICHAEL A. VALEK, Administrative Patent Judges.

MITCHELL, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 328(a)

I. INTRODUCTION

This is a Final Written Decision in a post-grant review challenging the patentability of claims 1, 2, and 6–30 of U.S. Patent No. 12,054,758 B2 (Ex. 1001, "the '758 patent").[1] We have jurisdiction under 35 U.S.C. § 6.

Petitioner has the burden of proving unpatentability of the challenged claims by a preponderance of the evidence. 35 U.S.C. § 326(e). Having reviewed the parties' arguments and cited evidence, for the reasons discussed below, we find that Petitioner has demonstrated by a preponderance of the evidence that claims 1, 2, and 6–30 are unpatentable.

A. Procedural History

Petitioner Merck Sharp & Dohme LLC filed a Petition requesting post-grant review of all claims of the '758 patent. *See* Paper 1 ("Pet."). Patent Owner Halozyme, Inc. filed a Preliminary Response. *See* Paper 20. The parties also filed briefs directed to discretionary denial issues. *See* Papers 17, 19. The Director ruled on discretionary denial issues and referred the case to a Board panel to consider the merits and non-discretionary considerations and determine whether to institute a post-grant review. *See* Paper 25.

We determined, based on the arguments and evidence of record, that the '758 patent was eligible for post-grant review and that at least one of the challenged claims was more likely than not unpatentable. *See* Paper 26 ("Inst. Dec."). Thus, on October 16, 2025, pursuant to 35 U.S.C. § 324, the

[1] Petitioner originally challenged claims 1–40 of the '758 patent, but Patent Owner statutorily disclaimed claims 3–5 and 31–40, leaving claims 1, 2, and 6–30 ("challenged claims") of the '758 patent at issue in the Petition. *See* Ex. 2003.

Board instituted trial of all challenged claims (claims 1, 2, and 6–30). *Id.* at 55.

Following institution, Patent Owner filed a Patent Owner's Response to the Petition (Paper 43, "PO Resp."), Petitioner filed a Reply to Patent Owner's Response (Paper 78, "Reply"), and Patent Owner filed a Sur-reply (Paper 94, "Sur-reply").

Patent Owner filed a Motion for Additional Discovery (Paper 42), Petitioner opposed the motion (Paper 44), and the Board denied the motion (Paper 47).

Patent Owner filed a Motion to Terminate (Paper 51, 65), Petitioner filed an opposition (Paper 57), Patent Owner filed a reply (Paper 60), and the parties filed authorized supplemental briefing regarding the Motion to Terminate (Papers 73, 75). The Board denied Patent Owner's Motion to Terminate. Paper 89. Patent Owner requested Director Review of the Board's order denying its Motion to Terminate (Paper 95), but that request was not considered because the request "is outside the scope of Director Review" (Ex. 3101).

The parties filed, and the Board resolved, various motions to seal. A motion to seal remains pending and will be resolved in due course.

We held an oral hearing July 23, 2026, a transcript of which is of record. Paper 99.

B. Real Parties-In-Interest

Petitioner identifies Merck Sharp & Dohme LLC as the real party-in-interest. Pet. 6. Patent Owner identifies Halozyme, Inc. and Halozyme Therapeutics, Inc. as the real parties-in-interest. Paper 3, 1.

C. Related Matters

The '758 patent is subject to a civil action in *Halozyme, Inc. v. Merck Sharp & Dohme LLC f/k/a/ Merck Sharp & Dohme Corp.*, 2:25-cv-03179 (D.N.J.), along with the following related U.S. patents: 10,865,400; 11,041,149; 11,066,656; 12,018,298; 12,037,618; 12,049,652; 11,952,600; 12,091,692; 12,104,185; 12,110,520; 12,152,262; 12,077,791; 12,195,773; and 12,264,345 5. Paper 97, 1.

The '758 patent is also related to a number of patents subject to post-grant review proceedings including those in the Table below:

U.S. Patent No.	PGR No.	PGR Petition Filed	At Issue In Civil Action
11,952,600	PGR2025-00003	Nov. 12, 2024	Yes
12,018,298	PGR2025-00004	Nov. 26, 2024	Yes
12,152,262	PGR2025-00006	Dec. 10, 2024	Yes
12,123,035	PGR2025-00009	Dec. 27, 2024	No
12,110,520	PGR2025-00017	Jan. 17, 2025	Yes
12,060,590	PGR2025-00024	Feb. 21, 2025	No
12,049,652	PGR2025-00033	Mar. 7, 2025	Yes
12,104,185	PGR2025-00039	Mar. 28, 2025	Yes
12,037,618	PGR2025-00042	Apr. 15, 2025	Yes
12,091,692	PGR2025-00046	Apr. 29, 2025	Yes
12,077,791	PGR2025-00050	May 7, 2025	Yes
12,264,345	PGR2025-00052	Jun. 27, 2025	Yes
12,195,773	PGR2025-00053	Jun. 6, 2025	Yes
12,371,685	PGR2025-00087	Nov. 20, 2025	Yes
10,865,400	IPR2026-00312	Mar. 23, 2026	Yes
11,041,149	IPR2026-00313	Mar. 23, 2026	Yes
11,066,656	IPR2026-00314	Mar. 23, 2026	Yes

See Paper 97, 2. Petitioner also "filed petitions for *inter partes* review of related U.S. Patent Nos. 10,865,400 (IPR2026-00312), 11,041,149 (IPR2026-00313), and 11,066,656 (IPR2026-00314), which are at issue in the above-referenced civil action." *Id.* at 1.

Patent Owner states that the '758 patent is related to the following pending U.S. Patent Applications and patents:

Application No.	Filed
18/922,889	Oct. 22, 2024
19/071,005	Mar. 5, 2025
19/071,055	Mar. 5, 2025
19/075,092	Mar. 5, 2025
19/071,264	Mar. 5, 2025
19/546,132	Feb. 20, 206
19/550,132	Feb. 25, 2026
19/550,136	Feb. 25, 2026
19/551,393	Feb. 26, 2026
19/551,420	Feb. 25, 2026
19/720,762	Jun. 25, 2026
19/720,766	Jun. 25, 2026
19/722,345	Jun. 26, 2026
19/722,335	Jun. 26, 2026

Paper 97, 2–3.

D. The '758 Patent

The '758 patent issued August 6, 2024, from U.S. Application 18/066,960, filed December 15, 2022. Ex. 1001, codes (21), (22), (45). The '758 patent is a division of U.S. Application 17/327,568, filed on May 21, 2021, which is a continuation of U.S. Application 16,912,590, filed on June 25, 2020, now U.S. Patent 11,066,656 B2, which is a continuation in a lengthy set of applications claiming continuity to U.S. Application 13/694,731 ("the '731 Application"), filed on Dec. 28, 2012, now U.S. Patent No. 9,447,401 B2. *Id.* at code (60). The '731 Application claims the priority benefit of provisional applications U.S. 61/796,208, filed November 1, 2012, and U.S. 61/631,313, filed Dec. 30, 2011. *Id.*

The '758 patent is drawn to "[m]odified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity." Ex. 1001, 4:16–19. The '758 patent teaches "[h]yaluronan (hyaluronic acid; HA) is a polypeptide that is found in the extracellular matrix of many cells, especially in soft connective tissues." *Id.* at 4:23–25. The '758 patent teaches "[c]ertain diseases are associated with expression and/or production of hyaluronan. Hyaluronan-degrading enzymes, such as hyaluronidases, are enzymes that degrade hyaluronan. By catalyzing HA degradation, hyaluronan-degrading enzymes (e.g., hyaluronidases) can be used to treat diseases or disorders associated with accumulation of HA or other glycosaminoglycans." *Id.* at 4:30–36. The '758 patent teaches that "[v]arious hyaluronidases have been used therapeutically . . . . Many of these are ovine or bovine forms, which can be immunogenic for treatment of humans." *Id.* at 4:41–47.

The '758 patent states that modifications for PH20 polypeptides include amino acid replacement, deletion, and/or insertions. Ex. 1001, 4:56–58. With regard to modified PH20 hyaluronidase polypeptides, the '758 patent further teaches:

> [P]rovided are modified PH20 polypeptides that contain one or more amino acid replacements that result in a PH20 polypeptide that retains activity and/or exhibits increased or altered stability under a variety of conditions. . . . Exemplary modifications are amino acid replacements. For purposes herein . . . amino acid replacements are denoted by the single amino acid letter followed by the corresponding amino acid position in SEQ ID NO:3 in which the replacement occurs. Single amino acid abbreviations for amino acid residues are well known to a skilled artisan . . . and are used herein throughout the description and examples. For example, replacement with P at a position corresponding to position 204 in a PH20 polypeptide

> with reference to amino acid residue positions set forth in SEQ ID NO:3 means that the replacement encompasses F204P in a PH20 polypeptide set forth in SEQ ID NO:3, or the same replacement at the corresponding position in another PH20 polypeptide.

Id. at 4:62–5:15.

The '758 patent teaches "modified PH20 polypeptides provided herein exhibit altered activities or properties compared to a wildtype, native or reference PH20 polypeptide." *Id.* at 75:49–51. The '758 patent further provides:

> Included among the modified PH20 polypeptides provided herein are PH20 polypeptide that are active mutants, whereby the polypeptides exhibit at least 40% of the hyaluronidase activity of the corresponding PH20 polypeptide not containing the amino acid modification (e.g., amino acid replacement). In particular, provided herein are PH20 polypeptides that exhibit hyaluronidase activity and that exhibit increased stability compared to the PH20 not containing the amino acid modification. Also provided are modified PH20 polypeptides that are inactive, and that can be used, for example, as antigens in contraception vaccines.

Id. at 75:51–62.

E. Illustrative Claims

Claim 1, the sole independent claim, is illustrative of the challenged claims in the '758 patent and is reproduced below.

> 1. A modified PH20 polypeptide, comprising one or more amino acid modifications in an unmodified PH20 polypeptide, wherein:
>
> the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7 and 32–66;

> amino acid modifications are selected from the group consisting of amino acid replacements(s), deletion(s), and/or insertion(s);
>
> the modified PH20 polypeptide comprises an amino acid replacement at a position corresponding to residue 317, with reference to amino acid positions set forth in SEQ ID NO:3;
>
> the replacement at the position corresponding to residue 317 is selected from the group consisting of A, I, K, M, Q, and R;
>
> corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the amino acid sequence of SEQ ID NO:3; and
>
> the modified PH20 polypeptide has at least 91% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32–66.

Ex. 1001, 303:2–26.

F. Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable based on the four grounds listed below.

Ground	Reference(s)/Basis	35 U.S.C. §	Claim(s) Challenged[2]
1	Written Description	§ 112	1, 2, 6–30
2	Enablement	§ 112	1, 2, 6–30
3	'429 patent[3], Chao[4]	§ 103	1, 2, 6, 8, 10–30

[2] Petitioner originally challenged claims 1–40 for lack of written description and enablement, and challenged claims 1, 2, 5, 6, 8, and 10–40 for obviousness. *See* Pet. 7. We have adjusted the claims challenged to only those that remain in effect following Patent Owner's disclaimer.
[3] US 7,767,429 B2, issued Aug. 3, 2010 (the "'429 patent"; Ex. 1005).
[4] Chao et al., *Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis*, 46 Biochemistry 6911–6920 (2007) (Ex. 1006).

See Pet. 7. Petitioner relies on the Declarations of Michael Hecht, Ph.D., Sheldon Park, Ph.D., James Naismith, Ph.D., and Garnett Kelsoe, Ph.D. *See* Exs. 1003, 1004, 1133, 1134, respectively. Patent Owner relies on the Declarations of Melanie Simpson, Ph.D., Gregory Petsko, Ph.D., Gary Cherr Ph.D., and James Moon, Ph.D. *See* Exs. 2068, 2070, 2072, 2074, respectively.

II. ANALYSIS

A. Level of Ordinary Skill in the Art

We consider the grounds of unpatentability in view of the understanding of a person of ordinary skill in the art (sometimes referred to herein as "POSA") as of the effective filing date of the challenged claims. Petitioner contends that one of ordinary skill in the art would

> have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to [the] 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.).

Pet. 15–16 (citing Ex. 1003 ¶ 13).

Patent Owner responds "[s]olely for the purposes of the analysis herein, Patentee applies Petitioner's POSA definition (Pet., 15-16; EX1003, ¶13) and Patentee's, both of which were addressed in the Institution Decision (ID, 8-10). Petitioner's declarant Dr. Hecht agreed that POSAs under Petitioner's definition 'would have been able to speak with someone

with hyaluronidase experience as part of a multi-disciplinary team.'" PO Resp. 31 (citing Ex. 2076, 63:8–64:2).

We find that Petitioner's undisputed proposal is sufficiently comprehensive to encompass the prior art relevant to the '758 patent. It is reasonably clear that, in indicating that a POSA would have an advanced degree (like a Ph.D.) and years of experience in analysis of protein structure, the parties agree that knowledge of proteins generally is sufficient to understand the types of problems encountered in the art and the prior art solutions to those problems, and the ordinary artisan need not be an expert in hyaluronidases. We also agree with Patent Owner that a POSA would be able to apply key scientific concepts (e.g., biochemistry, recombinant biology, sequence analysis and protein modeling) to enzymes such as hyaluronidases and speak with a multidisciplinary team about these enzymes. *See, e.g.*, *id.* at 31, 58–59, 64. We find that all of the experts of record in this proceeding have sufficient technical training and experience to meet these requirements and are qualified to testify from the perspective of a POSA.

We consider the POSA level as of the 2011–2012 timeframe, which includes the Dember 28, 2012, priority date Patent Owner asserts for the written description and enablement challenges. *See, e.g.*, PO Resp. 11 n.8 (Patent Owner indicating that it "applies the December 28, 2012, filing date of the '731 application for purposes of responding to Petitioner's written description and enablement challenges (Ground I–II)," and "the December 30, 2011, priority date for purposes of responding to Petitioner's obviousness challenge (Ground III)"). Patent Owner alleges that for its written description and enablement challenges, "Petitioner and its experts

erroneously rely upon a December 30, 2011, date (Pet. 26-84; *see also,* Pet. 39–41, 55, 72, 74; EX1003, ¶11), rather than the proper December 28, 2012, date." PO Resp. 44 n.12. However, Petitioner does not restrict the § 112 analyses to December 2011; rather, Petitioner states that the claims are not entitled to claim priority to either the provisional application filed on December 30, 2011, or the '731 Application filed on December 28, 2012. Pet. 15. Petitioner then states, "Regardless, the prior art of the grounds was published before December 2011, and the obviousness grounds use that date to assess the knowledge and perspectives of the skilled artisan." *Id.* In any event, the record does not reflect any material difference in the state of the art between the December 30, 2011, and December 28, 2012, priority dates that would change our findings herein.

B. Claim Construction

In a post-grant review, we interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.200(b). Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*

In our Institution Decision we construed the term "modified PH20 polypeptide" as encompassing polypeptides with some hyaluronidase activity. Inst. Dec. 17. In reaching this conclusion, we primarily relied on the intrinsic evidence in a definitional passage in the '758 Specification, which states:

> As used herein, "modified PH20 polypeptides" or "variant PH20 polypeptide" refers to a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino

> acid replacement as described herein, in its sequence of amino acids compared to a reference unmodified PH20 polypeptide. A modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.

Ex. 1001, 48:38–46.

> Based on the evidence of record at that time, we determined that
>
> the '758 patent recognizes a broad understanding of a "modified PH20 polypeptide" as encompassing PH20 sequences from a variety of different mammalian species, with or without precursor or signal sequences, with or without post-translational modifications, and with up to 150 amino acid replacements. . . . On the current record, we therefore adopt the definition for "modified PH20 polypeptide" as recited in the '758 patent to encompass polypeptides with some hyaluronidase activity.

Inst. Dec. 17. Following institution, the parties continue to dispute this term, and we now address the parties' contentions regarding the term "modified PH20 polypeptides" on the complete record.

a) Petitioner's Position

Petitioner asserts the common disclosure[5] "describes two mutually exclusive categories of 'modified PH20 polypeptides,'" i.e., "active mutants" and "inactive mutants."' Pet. 21. Petitioner contends that the

[5] Petitioner uses the term "common disclosure" to refer to the specifications of the '758 patent and the '731 application. *See* Pet. 6 n.5. Petitioner states, and Patent Owner does not dispute, that these two specifications "are highly similar," with the following three changes in the '758 patent: "(i) it removes positions 282, 298, and 431 from the list of positions to avoid changing in enzymatically active PH20 proteins relative to the '731 Application (EX1045, 78), (ii) it removes the mutant designated 'I083K' from Table 9's list of 'Active' mutants and added I208K (*id.*, 218), and (iii) it modifies Table 3 to remove substitutions L and W from position 288 (*id.*, 80)." *Id.*

claims are limited to one only one category, the "active mutant" embodiment, for three reasons:

> First, every claim requires modified PH20 polypeptides with one of nine replacements at position 317 that were reported to yield an "active mutant" as a single-replacement $PH20_{1-447}$ polypeptide (*i.e.*, L317A, L317I, L317K, L317M, L317Q, or L317R). All six mutants are identified as "Active Mutants" in Table[] 3 and all have >100% activity per Table 9.
>
> Second, claim 4 restricts the genus of active mutants in claim 1 (*i.e.*, those with hyaluronidase activity) to modified PH20 polypeptides that have at least 100% of the activity of unmodified PH20.
>
> Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one amino acid modification," but can also "have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***." This aligns with the specification's prophetic methodology for discovering PH20 polypeptides with multiple changes, which selects "active mutants" with one substitution, randomly introduces another, and then screens to find "double mutants" that ***retained*** hyaluronidase activity. This also tracks the claims, which require one substitution and permit others.

Id. at 24–25.

b) Patent Owner's Response

Patent Owner asserts that it "does not dispute that the claims encompass PH20s with hyaluronidase activity," but "does contend that the claims are defined by structure only and encompass ***both*** enzymatically active and enzymatically inactive PH20s." PO Resp. 31. Patent Owner states "[t]here is no language in the claim requiring the polypeptide to perform a specific function. The parties do not dispute this." *Id.* at 31 (citing Ex. 2076, 172:21–173:9).

Regarding the definitional passage in the Specification, Patent Owner asserts that "the definition of 'modified PH20 polypeptide' is limited to the first sentence." PO Resp. 33. According to Patent Owner,

> [t]he definition provided in the first sentence is also consistent with the usage of the term "modified PH20 polypeptide" throughout the specification, which describes the invention by reference to amino acid sequences, regardless of function or whether the modified PH20s are "active" or "inactive."
>
> If Petitioner were correct and the second sentence also is part of the definition, then the term "modified PH20 polypeptide" as used in the specification and claims would be limited to enzymatically active PH20 polypeptides, which Petitioner argues must have at least 40% activity. But that interpretation contradicts how the term is used in the specification. The specification repeatedly uses the term "modified PH20 polypeptide" to refer to inactive polypeptides.

Id. at 35; *see also id.* at 37 (citing Ex. 1001, 79:28–30, 115:52–59; 75:51–56, 75:60–62; 116:3–45, 116:53–60, 187:56–60, 261:60–262:24; Ex. 2068 ¶¶ 266–268). Patent Owner asserts:

> Petitioner's expert, Dr. Hecht, admitted that he did not even 'consider this [disclosure]' referring to inactive modified PH20 polypeptides in forming his opinion 'because [it] seemed contradictory' to his 'interpretation' that the claims require activity. But a proper claim construction analysis involves examining how the term is used throughout the entire specification, without disregarding sections of the specification that may conflict with a preconceived interpretation.

Id. at 37 (citing Ex. 2076, 189:1–192:16).

Patent Owner concludes that "the patent makes clear that 'modified PH20 polypeptide' encompasses both active and inactive polypeptides" and that "inactive PH20s do have a credible utility" as antigens in contraception

vaccines. *Id.* at 38–39 (citing Ex. 2068 ¶¶ 266–268, 392; Ex. 2074; Ex. 2072).

c) Petitioner's Reply

Petitioner responds that:

> The claim construction dispute is narrow: are the claims limited to a "***structurally and functionally distinct genus***" of PH20s (*i.e.*, "properly folded" and enzymatically active modified PH20 polypeptides), or do they ***also*** include 10^{59}+ other PH20 sequences in the claim parameter's "sequence space" (*i.e.*, a genus outweighing Earth)?

Reply 1–2 (citing PO Resp. 31; Ex. 2068 ¶ 33; Ex. 2070 ¶¶ 51, 58, 128 n.12; Ex. 1130, 62:13–23; 68:6–69:5; Ex. 1133 ¶¶ 77–80, 44–46, 55–58, 92–101; Reply § III.C.1(b); Ex. 1003 ¶¶ 122–23). Petitioner asserts that a POSA would read "the claims ***as a whole*** as directed to properly folded, active PH20s." *Id.* at 3–4 (citing Pet. 24–25; Ex. 1026, 90:33–34; Ex. 1003 ¶¶ 127–129; Ex. 1133 ¶¶ 105–110; *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008)).

Petitioner cites the testimony of Patent Owner's expert Dr. Simpson, where she testified that "'PH20' ***provides context*** to 'modified PH20 polypeptide.'" *Id.* at 2 (citing Ex. 1130, 57:9–58:4; *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 952 (Fed. Cir. 2006)). Petitioner also cites the testimony of Patent Owner's expert Dr. Petsko, stating: "***POSAs think of PH20 as a folded protein***," and expert Dr. Simpson, stating that the Specification's definition of PH20 refers to properly folded and enzymatically active proteins. *Id.* at 2–3 (citing Ex. 2070 ¶ 345; Ex. 1026, 50:31–32; Ex. 1130, 60:14–61:12, 61:19–23; Ex. 2070 ¶ 128 n.12; Ex. 1133 ¶¶ 92–104; Ex. 1133 ¶¶ 87–89; Ex. 1131, 32:8–37:20; Ex. 2068 ¶¶ 283, 353, 376; Ex. 2070 ¶¶ 50, 426).

d) Patent Owner's Sur-Reply

Patent Owner asserts that the "claimed modified PH20 polypeptides are defined by their structure—an L317A, L317I, L317K, L317M, L317Q, or L317R mutation and 91% sequence identity—not by their function," and that "Petitioner's expert, Dr. Kelsoe, admitted as much" in the following testimony: "'Q So you don't read claim 1 to require any hyaluronidase activity, right? **A. To the best of my understanding, no.**'" Sur-reply 1 (quoting Ex. 2302, 41:6–12; 48:1–4). Patent Owner asserts that "Petitioner's expert, Dr. Hecht, admitted at deposition that the term 'modified PH20 polypeptide' is used in the specification to refer to both active and inactive PH20s." *Id.* at 1–2 (citing Ex. 2076, 189:1–194:12, 172:21–173:17, 213:1–215:19, 221:8–223:22). Patent Owner further asserts that Petitioner's expert "Dr. Naismith admits that 'the definition of "modified PH20 polypeptide" in the common disclosure considered in isolation does not explicitly state that each modified PH20 polypeptide is enzymatically active.'" *Id.* at 2 (citing Ex. 1133 ¶ 109).

According to Patent Owner, Petitioner's argument that proper folding is required for a "modified PH20 polypeptide" conflicts with the Specification "because the term 'modified PH20 polypeptide' is itself a defined term," "Petitioner improperly imports the constituent term 'PH20' into the separately defined 'modified PH20 polypeptide,'" the "PH20 definition imposes no 'properly folded' or any folding requirement," and "the specification uses 'PH20' to refer to both active and inactive polypeptides." Sur-reply 2–3 (citing Ex. 1001, 115:53–116:2, 79:30–33).

e) Evidence and Analysis

"The construction of claims is simply a way of elaborating the normally terse claim language in order to understand and explain, but not to change, the scope of the claims." *Embrex, Inc. v. Serv. Eng'g Corp.*, 216 F.3d 1343, 1347 (Fed. Cir. 2000).

We first turn to the intrinsic evidence because "the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc). "[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Id.* at 1316.

> [T]he definition in the patent documents controls the claim interpretation. . . . Any other rule would be unfair to competitors who must be able to rely on the patent documents themselves, without consideration of expert opinion that then does not even exist, in ascertaining the scope of a patentee's right to exclude.

Southwall Tech., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1578 (Fed. Cir. 1995).

(1) Intrinsic evidence

Our analysis begins with the claims and Specification of the '758 patent. In relevant part, claim 1 recites a "modified PH20 polypeptide." The '758 patent states: "PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active."[6] Ex. 1001, 45:54–

[6] The Specification defines "neutral active" as "the ability of a PH20 polypeptide to enzymatically catalyze the cleavage of hyaluronic acid at

55; *cf. id.* at 68:47–51. The '758 patent further explains that "[r]eference to PH20 includes precursor PH20 polypeptides and mature PH20 polypeptides (such as those in which a signal sequence has been removed), truncated forms thereof that have activity, and includes allelic variants and species variants, variants encoded by splice variants, and other variants." *Id.* at 46:4–9. The '758 patent states that "PH20 polypeptides also include those that contain chemical or posttranslational modifications and those that do not contain chemical or posttranslational modifications." *Id.* at 46:13–16.

The '758 patent has a detailed "Definitions" section (*id.* at 44:55–68:45) which states the following regarding the term "modified PH20 polypeptide":

> As used herein, "modified PH20 polypeptide" or "variant PH20 polypeptide" refers to a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement as described herein, in its sequence of amino acids compared to a reference unmodified PH20 polypeptide. A modified PH20 polypeptide can have up to 150 amino acid replacements, ***so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity***. Typically, a modified PH20 polypeptide contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 amino acid replacements. It is understood that a modified PH20 polypeptide also can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.

Id. at 48:38–53 (emphasis added).

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neutral pH, such as at a pH between or about between pH 6.0 to pH 7.8." Ex. 1001, 50:39–42.

The "Definitions" section further addresses other terms that relate to "modified PH20 polypeptide." In particular, the "Definitions" section states:

> As used herein, activity refers to a functional activity or activities of a polypeptide or portion thereof associated with a full-length (complete) protein. Functional activities include, but are not limited to, biological activity, catalytic or enzymatic activity, antigenicity (ability to bind or compete with a polypeptide for binding to an anti-polypeptide antibody), immunogenicity, ability to form multimers, and the ability to specifically bind to a receptor or ligand for the polypeptide.

Id. at 50:9–17. The term "hyaluronidase activity" is more narrowly defined such that it specifically "refers to the ability to enzymatically catalyze the cleavage of hyaluronic acid." *Id.* at 50:18–19.

Other portions of the "Definitions" section also refer to the activity of the protein. For example, in its definition of a "denaturing condition," the '758 patent states that "a condition is denaturing if the activity of the protein is reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or more in the presence of the condition than in its absence." *Id.* at 51:15–18. The "Definitions" section also states that

> "increased stability" with reference to a modified PH20 hyaluronidase means that, in the presence of the same denaturing or denaturation condition(s) (e.g., presence of a denaturing excipient such as a preservative), the modified PH20 hyaluronidase exhibits ***greater hyaluronidase activity*** compared to an unmodified PH20 hyaluronidase not containing the amino acid replacement(s).

Id. at 52:41–47 (emphasis added).

The "Definitions" section defines both "phenophile" and a "thermophile" as proteins that "exhibit[] at least or about at least 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%,

300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% or more of the activity of the unmodified or reference PH20 hyaluronidase" in the presence of a phenolic preservative or under elevated temperatures, respectively. *Id.* at 54:59–55:22. The "Definitions" section also states that "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 of the resulting molecule." *Id.* at 57:58–61. The "Definitions" section explains, regarding "substantially pure," that "further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance." *Id.* at 62:1–3.

The "Definitions" section also states that "a conjugate refers to a modified PH20 polypeptide linked directly or indirectly to one or more other polypeptides or chemical moieties . . . whereby at least one modified PH20 polypeptide is linked, directly or indirectly to another polypeptide or chemical moiety ***so long as the conjugate retains hyaluronidase activity***." *Id.* at 63:39–46 (emphasis added). The "Definitions" section further states:

> As used herein, a co-formulation refers to a composition containing two or more active or pharmaceutical or therapeutic agents and one or more excipients. For example, a co-formulation of a fast-acting insulin and a hyaluronan degrading enzyme contains a fast-acting insulin, a hyaluronan degrading enzyme, and one or more excipients.

Id. at 64:16–21.

After the "Definitions" section, in a different section discussing the PH20 polypeptide, the '758 patent states: "Due to the role of PH20 in fertilization, PH20 can be used as an antigen for immunocontraception." *Id.* at 72:63–65. The '758 patent also states that "provided are modified PH20

polypeptides that are inactive, and that can be used, for example, as antigens in contraception vaccines." *Id.* at 75:60–62.

In sum, considering the intrinsic evidence as a whole, the Specification of the '758 patent supports an understanding that some activity is required for a polypeptide to be a "modified PH20 polypeptide," and it is the enzymatic activity of hyaluronidase specifically that is the most frequently identified activity recited in the Definitions section of the '758 patent. Indeed, both the definitions of "PH20" and "modified PH20 polypeptide" require hyaluronidase activity. *See* Ex. 1001, 45:54–55, 50:39–41 ("PH20 refers to a type of hyaluronidase that . . . is neutral-active" and "neutral active refers to the ability . . . to enzymatically catalyze the cleavage of hyaluronic acid at neutral pH"); 48:43–46 ("A modified PH20 polypeptide can have up to 150 amino acid replacements so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity."). Similar language is used later in the definition of a "conjugate" to explain that even when the modified PH20 polypeptide is linked to another polypeptide or chemical moiety it "retains hyaluronidase activity." *Id.* at 63:39–46. In contrast, the discussion regarding the potential use of "modified PH20 polypeptides that are inactive" as antigens in contraception vaccines appears only in non-definitional sections of the '758 patent. *Id.* at 72:63–65, 75:60–62. Accordingly, we find that this disclosure does not modify the definition's explicit requirement that the claimed "modified PH20 polypeptide" exhibit hyaluronidase activity. *Id.* at 48:38–46.

(2) Extrinsic evidence

Both Petitioner and Patent Owner cite prior art references replete with disclosures demonstrating that PH20 is a polypeptide with hyaluronidase activity. We cite a selection of this evidence below.

"PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active." Ex. 1007, 10:31–32; *cf.* Ex. 1011, 810 ("PH-20 hyaluronidase from human sperm"); Ex. 1013, 429–430 ("expression of the PH20 enzyme . . . demonstrated the hyaluronidase activity associated with the cell membrane"); Ex. 1021, 30310 ("glycosylphosphatidylinositol-anchored sperm hyaluronidase PH-20"); Ex. 1024, 84 ("Recombinant human PH20 (rHuPH20) is a soluble recombinant form of human PH20 that can be used to depolymerize hyaluronan."); Ex. 2035, 33654 ("Among the six HAases [hyaluronidases], HYAL1, HYAL2, and PH20 are well characterized"); Ex. 2086, 171 ("While plasma membrane PH-20 shows hyaluronidase activity only at neutral pH, inner acrosomal membrane PH-20 was found to be active both at neutral and acidic pH."); Ex. 2100, 542 ("macaque sperm surface protein PH-20 is a hyaluronidase"); Ex. 2107, 151 ("PH-20 is a sperm plasma-membrane protein that has been shown to have hyaluronidase activity in several mammalian species including nonhuman primates."); Ex. 2108, 80 ("PH-20 has a hyaluronidase activity that is required for sperm penetration through the cumulus cell layer that surrounds the oocyte.").

The parties cite a subset of references showing that PH20, as well as being a hyaluronidase, has also been considered for use an antigen in contraceptive vaccines. "[F]ormulations of recombinant mouse PH20 (mPH20, SPAM-1) were therefore produced as part of an effort to develop

immunocontraceptive vaccines for use as biological control agents for mice." Ex. 1019, 331; *cf.* Ex. 1022, 1146 ("immunization of male guinea pigs with PH-20 reproducibly leads to infertility"); Ex. 1023, 1133 (same).

Turning to the expert testimony, Petitioner's experts Dr. Hecht and Dr. Naismith testify that a POSA reading the Specification would understand the challenged claims to encompass enzymatically active mutants, i.e., modified PH20 polypeptides with hyaluronidase activity. *See, e.g.*, Ex. 1003 ¶¶ 127, 132–134 (interpreting claim 4 as affirmatively requiring modified PH20 polypeptides that exhibit hyaluronidase activity); Ex. 1133 ¶ 100 (agreeing with Dr. Hecht).[7] When asked on cross-examination, "How are you drawing the line between what's a definition and what's not a definition [in the Specification]?", Petitioner's expert Dr. Hecht answered:

> Because the first sentence that you just read is, "as used herein," okay, a modified PH20 polypeptide, okay. And then it continues saying a modified PH20 – that it's – it's now giving us more detail and saying it can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.

[7] Another of Petitioner's experts, Dr. Kelsoe, was asked in his deposition "if claim 1 [of a related patent] requires the modified PH20 polypeptides to contain any hyaluronidase activity?" and he replied, "It does not. It simply claims 95 percent identity." Ex. 2302, 41:6–12. However, unlike Petitioner's other experts, Dr. Kelsoe was not asked to consider a POSA's understanding of the definitions provided in the Specification. *See* Ex. 1134 ¶¶ 15–16 (stating that he was instructed to apply an understanding of "modified PH20 polypeptides" that did not require activity and that based on the "understanding of the term provided by counsel" he assumed it includes both properly folded and misfolded, inactive polypeptides).

Ex. 2076, 181:9–18. When a further question asked, "the specification, in fact, uses the term[] modified PH20 polypeptides to refer to inactives?", Dr. Hecht recognized a distinction in the '758 patent and stated:

> I think it seems to contradict itself because it seems elsewhere to define it, as I read earlier. And then in the paragraph you read, it seems to violate that definition.
>
> It says "as used herein" on my declaration, page 70, which appears, to me, to be a definition of how it is used herein and so – which says, "so long as the resulting polypeptides exhibit hyaluronidase activity." That seemed a pretty strong statement to me in terms of how it is used herein whereas the paragraph you read seems to contradict that.

Id. at 191:18–192:11.

Patent Owner's expert Dr. Simpson disagrees with Dr. Hecht.[8] Dr. Simpson states, "[i]n my opinion, a POSA would have understood the claims do not require hyaluronidase enzymatic activity, let alone ≥ 40% hyaluronidase enzymatic activity." Ex. 2068 ¶¶ 26, 256. Dr. Simpson relies on the fact that claim 1 does not expressly reference hyaluronidase activity and on statements in the '758 patent discussing "inactive mutants" (which do not appear the "Definitions" section of the Specification) to support her position that "a POSA would understand that modified PH20 polypeptides with a L317A, L317I, L317K, L317M, L317Q, or L317R substitution are

[8] We note that Patent Owner's experts Dr. Moon and Dr. Petsko did not independently analyze claim construction. Dr. Moon stated, "I understand that PH20 is a sperm-associated protein having hyaluronidase activity and is involved in fertilization in mammals." Ex. 2074 ¶ 38. Dr. Petsko stated, "I have not been asked to opine regarding claim construction and do not do so in this declaration." Ex. 2070 ¶ 246.

not always active." *Id.* ¶¶ 261, 264, 266–268, 272. However, in deposition, Dr. Simpson acknowledged that in the Specification "PH20 is defined as a type of hyaluronidase that occurs in sperm and is neutral-active." Ex. 1130, 62:2–3.

Petitioner's expert Dr. Naismith states, "Dr. Simpson is reading the phrase 'modified PH20 polypeptide' to have the identical meaning as the phrase 'modified polypeptide.' This reading effectively strikes the word 'PH20' out of the claims." Ex. 1133 ¶ 103. Dr. Naismith states, "PH20 is expressly defined in the common disclosure to have a form a POSA would understand is folded." *Id.* ¶ 104. Dr. Naismith states that "the defined meaning of PH20 would have led a POSA to conclude that 'modified PH20 polypeptides' are those that (i) contain at least one amino acid modification and (ii) are properly folded proteins, as that is the form that the PH20 protein exists in on the surface of sperm cells." *Id.* Dr. Naismith stated in deposition that "when I use just PH20 that conveys to me, as it does in the common disclosure, that is a folded active form of the protein." Ex. 2301, 64:20–22.

f) Analysis

The instant claims differ from many of the claim sets previously considered by the Federal Circuit because they do not expressly recite a function for the polypeptide. *See, e.g.*, *In re Kubin*, 561 F.3d 1351, 1353 (Fed. Cir. 2009) ("wherein the polypeptide binds CD48"); *Bayer Healthcare LLC v. Baxalta Inc.*, 989 F.3d 964, 971 (Fed. Cir. 2021) ("a functional factor VIII polypeptide"); *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1072 (Fed. Cir. 2005) ("[a]n isolated polypeptide having DNA polymerase activity").

However, as discussed above, the definition of the term "PH20" in the '758 patent states that "PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active"—meaning that it is understood to have activity at neutral pH. Ex. 1001, 45:54–55. Further, the second sentence of the definition of "modified PH20 polypeptide" in the '758 patent allows mutations in the PH20 polypeptide "***so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity***." *Id.* at 48:38–46 (emphasis added). Thus, we agree with Petitioner that the term, interpreted in light of the Specification, requires at least some hyaluronidase activity.

We disagree with Patent Owner's argument that Petitioner's reliance on the "PH20" definition "improperly imports the constituent term . . . into the separately defined 'modified PH20 polypeptide.'" Sur-reply 3. Here, the "modified PH20 polypeptide" definition follows and builds upon the "PH20" definition. Moreover, the fact that both definitions specifically refer to the protein's hyaluronidase activity supports Petitioner's position that the claimed "modified PH20 polypeptide" must exhibit such activity.

Patent Owner's argument that the claims should not be read to exclude the use of enzymatically-inactive peptides as contraceptives (the only other possible utility recited in the '758 patent) is unavailing. PO Resp. 36–40; *cf.* Ex. 1001, 115:54–58. First, "[t]he fact that a patent asserts that an invention achieves several objectives does not require that each of the claims be construed as limited to structures that are capable of achieving all of the objectives." *Phillips*, 415 F.3d at 1327 (citing *Liebel–Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 908 (Fed. Cir. 2004)). Second, unlike the definitions of "PH20" and "modified PH20 polypeptide" in the "Definitions" section of the Specification, the passages describing

possible contraceptive use do not contain any characteristics suggesting they are definitional in nature. *See Alnylam v. Moderna*, 138 F.4th 1326, 1333 (Fed. Cir. 2025) (enumerating "characteristics" of definitions such as the fact that the text appears in the "Definitions" section, sets the term off in quotation marks, and uses phrases like "refer to" that indicate that specification language is definitional in nature). Accordingly, the statement that "[a]lso provided are modified PH20 polypeptides that are inactive, and that can be used, for example, as antigens in contraception vaccines" does not redefine the term, nor otherwise void the definitional language in the Specification stating that a "modified PH20 polypeptide can have up to 150 amino acid replacements, ***so long as*** the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***." Ex. 1001, 75:60–62, 48:38–46 (emphasis added).

The extrinsic evidence also supports that "PH20" is understood by POSAs to refer to the protein's hyaluronidase activity, and not just its structure. Indeed, virtually every publication cited by both parties references the enzyme's hyaluronidase activity. And while Patent Owner's expert Dr. Simpson suggests that the term "PH20" does not impose any particular function on the polypeptide, Dr. Simpson also acknowledged that in the Specification "PH20 is defined as a type of hyaluronidase that occurs in sperm and is neutral-active." Ex. 1130, 62:2–3.

We agree with Dr. Naismith that excluding any function from the term "PH20" "effectively strikes the word 'PH20' out of the claims." Ex. 1133 ¶ 103. That is, by electing to include the defined term "PH20" in the claims of the '758 patent, Patent Owner chose to inform POSAs that the claimed polypeptides would have the properties that the '758 patent expressly

defines as being part of a "PH20" polypeptide, which include hyaluronidase activity. Just as the phrase "steel baffles" in *Phillips* required that "the baffles must be made of steel," the term "PH20 polypeptide" requires a compound that is both a polypeptide and that has the activity conferred by the term "PH20." *See Phillips*, 415 F.3d at 1324.

For these reasons, we reject Patent Owner's position that the claims recite a modified PH20 polypeptide in purely structural terms, and construe "modified PH20 polypeptide" to require a polypeptide that has hyaluronidase activity.

g) Conclusion

For the reasons discussed above, we construe the claim term "modified PH20 polypeptide" to require a polypeptide that has hyaluronidase activity.

We determine that we need not expressly construe any other claim terms. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

C. Ground I - Written Description

1. Principles of Law

In a post-grant review, as in an *inter partes* review, "the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). This burden of persuasion never shifts to

Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

"A specification that 'reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date' has adequate written description of the claimed invention." *Novartis Pharm. Corp. v. Accord Healthcare, Inc.*, 21 F.4th 1362, 1368 (Fed. Cir. 2022) (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)). "[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.* at 1368–69 (alteration in original).

We analyze the asserted grounds of unpatentability in accordance with these principles to determine whether Petitioner has met its burden to establish by a preponderance of the evidence that the claims fail to comply with the written description requirement.

2. Petitioner's Position

Petitioner asserts that the claims capture a massive and diverse genera of enzymatically active PH20 polypeptides because they capture

> PH20 mutants with 2 substitutions, 3 substitutions, and so on up to a number set by the sequence identity boundary (*i.e.*, 21 for the narrowest claims (*e.g.* claims 25 and 26) to 42 for the broadest (claim 1)). The optional substitutions can be anywhere in the sequence (*i.e.*, clustered in a narrow region, spaced apart in groups, or spread randomly throughout the sequence), to any of 19 other amino acids, and arranged in any manner.
>
> Each claim also encompasses substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 37 alternative sequences that terminate at positions 430 to 474. The claims' sequence identity language also captures PH20 polypeptides that

> terminate at positions before 430. For example, claims referencing SEQ ID NO:32 that allow between 21 and 42 changes (and can be any mixture of deletions and substitutions will capture a PH20 terminating at position 416 or below. But removing so many residues from the C-terminus of PH20 can render it inactive, and the disclosure does not describe or suggest that the claimed position 317 substitution renders such mutants active. The claims, however, capture such polypeptides.

Pet. 31–32 (citing Ex. 1003 ¶¶ 119–120, 164–167; Ex. 1001, 60:61–61:1, 47:43–47, 47:56–58, 42:3–9).

Petitioner asserts the '758 patent provides "a prophetic research plan requiring 'iterative' make-and-test experiments that *might discover* multiply-modified enzymatically active PH20 polypeptides." *Id.* at 49 (citing Ex. 1001, 42:48–55, 135:27–32, 142:13–26; Ex. 1003 ¶¶ 173–177). Petitioner acknowledges that the '758 patent identifies double mutations to avoid and indicates "the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides," but Petitioner notes that the "sequence identity claim parameters, however, capture such mutants." *Id.* at 36 (citing Ex. 1001, 60:61–61:1, 47:43–47, 47:56–58, 42:1–7; Ex. 1003 ¶¶ 119–120, 164–167).

Petitioner asserts that "a skilled artisan in 2011 would have believed that PH20 polypeptides that terminate before position 430 would be inactive (*e.g.*., at position 419)," but asserts that the '758 patent "provides no examples of (or guidance concerning) PH20 mutants truncated below position 447 with one or more substitutions and that are enzymatically active. It thus ignores the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433," but the claims "capture modified PH20 polypeptides with truncations down to and

beyond position 419." *Id.* at 39 (citing Ex. 1003 ¶¶ 92–93, 95, 97, 164–166, 168).

Petitioner asserts that "~87% of the single-replacement $PH20_{1-447}$ polypeptides had *less* activity than unmodified $PH20_{1-447}$." *Id.* at 41 (citing Ex. 1003 ¶¶ 103–105). Petitioner asserts that the data shows the unpredictability of mutations where "introducing different amino acids at the same position in $PH20_{1-447}$ resulted in (i) increased activity, (ii) decreased activity, or (iii) inactive mutants." *Id.* at 42 (citing Ex. 1001, Tables 3, 5, 9, 10; Ex. 1003 ¶¶ 106, 142–143). Petitioner asserts that

> The results from single substitutions provide no insights into PH20 polypeptides with multiple concurrent mutations, which together can cause complex and unpredictable effects on a protein's structure and resulting function. The patent's empirical test results thus provide no guidance to a skilled artisan about which of the many possible PH20 mutants with different sets of 2–42 substitutions will be enzymatically active.

Id. at 43–44 (citing Ex. 1003 ¶¶ 139, 140, 142, 143). Petitioner asserts that the '758 patent "does not identify which *combinations* of substitutions improve stability. It thus provides no probative insight regarding multiply-modified PH20 polypeptides with increased stability." *Id.* at 45 (citing Ex. 1003 ¶¶ 75–76).

Petitioner asserts that the disclosures in the '758 patent fail to "identify ***any*** actual multiply-modified PH20 polypeptides (*i.e.*, particular sets of specific amino acid substitutions), much less provide results from testing any. They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides." *Id.* at 48. Petitioner asserts that the '758 patent provides "a prophetic research plan requiring 'iterative' make-and-test experiments that ***might discover*** multiply-modified enzymatically

active PH20 polypeptides . . . . This prophetic research plan is effectively meaningless—it does not indicate that any active mutant multiply-modified PH20 polypeptides will be found, much less identify ***which*** multiply-modified PH20 polypeptides are active mutants." *Id.* at 48–49 (citing Ex. 1003 ¶¶ 173–177, 184–185, 190; Ex. 1001, 42:46–53, 44:1–3, 127:22–67, 128:1–6, 128:9–129:51, 130:11–134:54).

Petitioner asserts the '758 patent does not identify

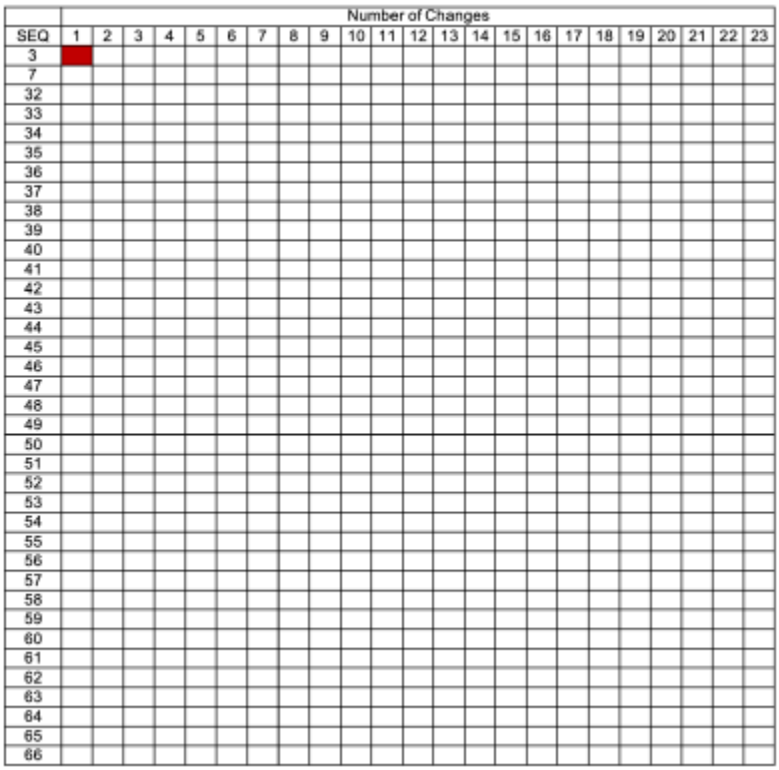
> the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.

Id. at 51 (citing Ex. 1003 ¶¶ 139–140, 151).

Petitioner asserts that the "[s]ingle-replacement $PH20_{1-447}$ examples are not representative of the trillions and trillions of $PH20_{1-447}$ polypeptides with between ***2 and 42 substitutions*** at any of hundreds of positions within the protein." *Id.* at 54 (citing Ex. 1003 ¶¶ 61, 143, 159). Petitioner asserts: "Enzymatically active single-replacement $PH20_{1-447}$ polypeptides also are not representative of enzymatically active, multiply modified PH20 polypeptides that incorporate changes that alone render PH20 proteins inactive (e.g., truncations terminating below position 429, or single substitutions that rendered $PH20_{1-447}$ inactive)." *Id.* at 56 (citing Ex. 1003 ¶¶ 161–164).

Petitioner asserts that "[a] simple illustration demonstrates how ***non-representative*** the examples are: all of the examples of single-replacement

$PH20_{1-447}$ mutants fit into one box of the array below (which depicts the scope of claim 2)."[9] *Id.* at 57.



The figure depicts a 23 x 37 array with a single shaded red box representing all of the tested single nucleotide mutations in SEQ ID NO: 3. *Id.* at 58.

Petitioner asserts that the remaining challenged claims in the '758 patent lack written descriptive support for the same or similar reasons. *See id.* at 60–65.

[9] Claim 2 depends from claim 1, reciting: "The modified PH20 polypeptide of claim 1, wherein the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NO: 3, 7, and 32–66." Ex. 1001, 313:44–47. Thus, claim 2 increases the percent identity required from 91% to 95%.

3. Patent Owner's Response

Patent Owner asserts that "Petitioner uses the math of permutations like a parlor trick, focusing on pure numbers, to distract from the fundamental fact that the scope of the claims is confined to the nine L317 variants and 91% identical subvariants." PO Resp. 4. Patent Owner asserts:

> Record evidence in this case demonstrates that the patent's specification describes both a representative number of species *and* common structural features of the narrow set of claimed modified PH20 variants such that POSAs could "'visualize or recognize' the members of the genus," under either the Board's preliminary construction or Patentee's proposed construction. Thus, the specification would have conveyed to POSAs that the inventors indeed had possession of the full scope of 91% identical subvariant polypeptides as of December 28, 2012.

Id. at 44 (citing Ex 2068 ¶¶ 277–342, 419).

Patent Owner asserts that "[t]he specification describes and characterizes the common structural features of the nine L317 variants recited in the claims (L317A, L317I, L317K, L317M, L317Q, and L317R) and their 91% identical subvariants." *Id.* at 45. Patent Owner asserts that POSAs "would have understood the claimed PH20s exhibit the same mechanism of action and share the same characteristic PH20 alpha-beta barrel tertiary structure, including a common active site and the same key catalytic residues, absent changes of the type the patent identifies as inactivating." *Id.* at 45. Patent Owner asserts that

> Dr. Petsko generated homology models of multiply-modified PH20s identified in the patent with the claimed L317 mutation, including chimpanzee PH20, gibbon PH20, orangutan PH20. EX2070, ¶¶57, 413-431. The modified chimpanzee PH20 contains six modifications when compared to SEQ ID NO: 3. Similarly, the modified orangutan and gibbon PH20s differ at 14 and 17 positions compared to SEQ ID NO: 3, respectively

> and the modified gibbon PH20 has 21 changes as compared to SEQ ID NO: 44 (which, as Dr. Simpson and Dr. Petsko explain, the '457 publication[10] teaches is active).

Id. at 45–46. Patent Owner contends that "these multiply-mutated L317Q subvariants all share a common tertiary alpha-beta barrel structure." *Id.* at 46.

Patent Owner points out that the Specification identifies specific amino acids necessary for enzymatic activity, amino acids involved in disulfide bridges, and sites involved in substrate binding. *Id.* at 48 (citing Ex. 1001, 70:17–29, 70:37–44, 70:49–57; Ex. 2068 ¶ 303). Patent Owner asserts that "because the specification discloses the structural features necessary for activity, POSAs would have understood them as common to active L317 variants and subvariants (further would have been able to reasonably and reliably distinguish inactive PH20s by changes of the kind identified in the patent as destroying them)." *Id.* at 49.

Patent Owner asserts:

> Through the comprehensive mutagenesis data (Tables 9-10), the patent shows, for each of the 447 positions in SEQ ID NO: 3, the tolerance of each position to substitution as it relates to enzymatic activity. This allows POSAs to distinguish between positions that are (1) critical to activity, (2) generally intolerant in that they permit only very limited substitution, (3) generally tolerant in that they permit a broad range of substitutions.

Id. at 50 (citing Ex. 2070 ¶¶ 44–56, 263–388; Ex. 2068 ¶¶ 305–306). Patent Owner asserts that "[t]hese data collectively would have provided more than

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[10] The "'457 publication" is U.S. Patent Application Publication No. 2010/0143457 A1 to Wei et al., published June 10, 2010 (Ex. 2165). It is referenced in the '758 patent. *See, e.g.*, Ex. 1001, 70:2–11, 70:67–71:4, 71:43–48, 74:13–19, 128:50–53.

sufficient blaze marks for POSAs to visualize or recognize all the members of the claimed genus, reliably distinguishing actives from inactives." *Id.* at 52 (citing Ex. 2068 ¶ 311). Patent Owner asserts that unlike the situations in *Ariad* and *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014),

> [a] "later actually invented" protein does not fall into the claims merely by showing hyaluronidase activity; it would have to fall within the narrow structural scope of the claims—the L317 mutation and 91% identity—to be covered. And, as the inventors identified by sequence and structure-function mapping the full scope of the narrow set of claimed L317 variants and subvariants, they in fact possessed the full scope of the genus.

Id. at 53.

Patent Owner asserts that "Dr. Petsko's and Dr. Simpsons' analyses show that in fact the claimed subvariants are structurally homogenous. And the large number of inactivating mutations are not evidence of unpredictability." *Id.* at 56 (citing Ex. 2068 ¶¶ 379–380). Patent Owner asserts that "the patent solves this problem; the inventors performed the work to identify those positions amenable to substitution. POSAs with the patent in hand can identify active singly and multiply modified subvariants." *Id.* at 57 (citing Ex. 2070 ¶¶ 343–365; Ex. 2068 ¶¶ 316–323).

Patent Owner asserts, as to C-terminal truncations, that the '758 patent provides data

> showing the effect that serial single amino acid C-terminal truncations had on activity—truncations that run ***from position 465 in the mature sequence all the way down to 430***. In other words, the '457 publication [referenced in the Specification of the '758 patent] provides activity data for all of the truncated polypeptide sequences listed in the claims.

> As Drs. Simpson and Petsko further explain, POSAs would have reasonably known based on [the] '457 publication's results what the activity would be for each recited sequence in the '758 claims.

Id. at 58–59 (citing Ex. 2068 ¶¶ 324–335; Ex. 2070 ¶¶ 218–230).

Patent Owner asserts, as to multiply-modified polypeptides, that "POSAs would have expected the resulting multiply modified PH20 polypeptide to be active because the '457 publication teaches that the multiply modified proteins (without the modification at position 317) were active." *Id.* at 61 (citing Ex. 2068 ¶¶ 338–339; Ex. 2070 ¶¶ 214–215). Patent Owner asserts that

> the genus of the claims here contains structurally homogeneous modified PH20s. The claims are thus not directed to a structurally diverse genus, as in *AbbVie*, but to nine variants and their 91% identical sub-variants. Moreover, the working examples comprehensively characterize the structure-function of PH20 (SEQ ID NO: 3) through the mutagenesis data.

Id. at 62.

4. Petitioner's Reply

Petitioner responds that its

> description of the claims' "sequence space"[11] is not a "parlor trick"—Halozyme's experts ***confirmed*** it was correct (~10^{59} to ~10^{112} sequences). Also undisputed is that the claims permit (i) modifications at any position, (ii) additions/deletions, and (iii) substitutions to any of 19 other amino acids.

[11] Petitioner and its experts use the term "sequence space" to refer to the size of the potential genus "defined by the sequence identity claim parameters," *i.e.*, "at least 91% sequence identity to one of SEQ ID NOS: 3, 7, and 32–66, and one position 317 change to A, I, K, M, Q or R." Ex. 1133 ¶ 48 (citing Ex. 1003 ¶¶ 115–125). We use this term the same way herein.

Reply 4 (citing Ex. 1003 ¶¶ 119–122; Ex. 1004 ¶¶ 165–169; Ex. 1026, 53:1–7, 68:18–34; Ex. 1130, 90:1–16, 90:25–91:5, 91:18–92:1; Ex. 1131, 54:24–55:6, 58:18–59:19, 61:6–8, 65:18–66:3; Ex. 2070 ¶¶ 235–236).

Petitioner asserts that "[p]roperly folded PH20s are the only PH20s in the sequence space that could have a common set of structural features, but the disclosure fails to identify what those common features are and which of the 10^{59}+ sequences will fold to have them." *Id.* at 11. Petitioner asserts that "[a]s a ***claim element***, the 91% identity requirement simply defines the boundaries of the 'sequence space'—the set of amino acid sequences within which the claimed PH20 polypeptides must be found." *Id.* at 11–12 (citing *Ariad*, 598 F.3d at 1349).

Petitioner asserts that Patent Owner

> anchors its "common structural feature" arguments on the "α/β barrel" motif in human PH20. But the disclosure nowhere mentions a "PH20 α/β barrel," discusses this motif, or portrays it as a common structural feature of any set of modified PH20s. It also does not identify any amino acid sequences for the PH20 α/β barrel motif or its elements. Nor does it reference the "distorted" (α/β) barrel motif in human PH20, explain that it does not contain PH20's active site, or explain how it differs from the canonical α/β structure.

Id. at 14 (citing Ex. 1133 ¶¶ 151–158, 165–170; Ex. 1008, 824–825, 829, 833; Ex. 1006, 6911–6913; Ex. 1033, 1027; Ex. 2068 ¶¶ 294–295, 305; Ex. 2070 ¶¶ 51, 128, 396, 422). Petitioner asserts that a POSA "could not have used knowledge of the ***canonical*** 'α/β barrel' motif to visualize the ***structurally distinct*** PH20's α/β motif because the two ***are materially different***." *Id.* at 15–16 (citing Ex. 1133 ¶¶ 136–139, 144, 150–152; Ex. 2070 ¶ 52). Petitioner asserts that the "disclosure contains no description of the Hyal-EGF domain or its sequence, despite its essential

role in the structure and function of enzymatically active PH20s.'" *Id.* at 16–17 (citing Ex. 1003 ¶ 84–88; Ex. 1133 ¶¶ 185, 187, 190–193, 198).

Petitioner asserts that Patent Owner is wrong that "examples of singly-substituted PH20s 'provide structure/function correlations POSAs can use to identify the active 91% identical' PH20s" for two reasons:

> First, effects on PH20 folding and activity from single substitutions cannot predict effects of ***combinations*** of changes. Even positions Dr. Petsko labeled "100% tolerated" varied extensively in activity, demonstrating the unpredictability of single substitutions.
>
> Second, listing options and leaving a POSA to figure out which combinations yield active PH20s does not describe species of multiply-modified PH20s.
>
> Finally, problems with the disclosure's experimental data and their reporting negate the 'functional' insights [Patent Owner] contends exist, and the disclosure does not describe the PH20 tertiary structure that must be maintained. Both halves of the 'structure-function' equation are missing here.

Id. at 20–21 (citing PO Resp. 50; Ex. 1003 ¶¶ 54–61, 67–76, 103–106, 140–143, Ex. 1133 ¶¶ 115, 151, 232–233, 246–259, 264–269, 307–309).

Petitioner asserts that Patent Owner "points to 7 alleged 'examples' of 'L317 variants.' None are described in the disclosure. Three are based on native ***primate*** sequences with known activity, while four were tested. None of the 7 illustrate the unpredictability of making 5+ changes to a native sequence." *Id.* at 21 (citing PO Resp. 53–55, Ex. 2070 ¶¶ 426–429; Ex. 1133 ¶¶ 114–119; Ex. 1003 ¶¶ 54–61).

5. Patent Owner's Sur-Reply

Patent Owner responds that

> the parties' primary dispute is whether the patent data could be used to predict the effects of multiple changes in the PH20 sequence such that the POSA could visualize and recognize the claimed genus and practice the full scope of the claims without undue experimentation.
>
> The evidence shows a POSA could do so.

Sur-reply 5. Patent Owner asserts that "an accurate homology model of PH20's structure, showing the distorted PH20 alpha-beta barrel fold and location of each amino acid in the structure, was available to a POSA," and "[w]ith this information, Dr. Simpson, a PH20 expert, and Dr. Petsko explained how POSAs could, ***using the patent's disclosure***, visualize and recognize the genus and predictably practice the full scope of the claims." *Id* at 5–6 (citing Pet. 11–15, 74, 101–107; Ex. 1004 ¶¶ 36, 104–164; Ex. 2077, 176:2–5; Ex. 1130, 97:14–99:10; Ex. 2070 ¶¶ 112–230, 343–441; Ex. 2068 ¶¶ 95–157).

Patent Owner asserts that the "disclosure provides a granular structure/function correlation that teaches, on a position-by-position basis, the effect on activity of substituting different amino acids into every position within the primary structure." *Id.* at 7. Patent Owner asserts that

> Drs. Petsko and Simpson testified that a POSA's ability to practice the claims was not limited to independent changes at highly tolerated positions. Instead, POSAs could evaluate additional substitutions or "make informed decisions about making several changes close together on the protein using the data in the '758 patent regarding which substitutions were tested and the results for each, combined with an assessment of the local environment of the residues in question."

Id. at 10 (citing Ex. 2070 ¶ 324; Ex. 1130, 97:14–98:10, 101:21–102:21, 190:12–195:25). Patent Owner asserts that "[i]t is undisputed that POSAs understand the characteristics of amino acids, such as their charge/size/

polarity and propensity to be present in secondary structures, and could evaluate their replacement using routine techniques, including visualizing interactions at the atomic level." *Id.* at 11 (citing Ex. 2070 ¶¶ 61–67, 343–431). Patent Owner asserts that "with the patent data in hand, the POSA can avoid the billions of PH20s that will be inactivated by changes identified in the patent." *Id.* at 12.

Patent Owner asserts that "Petitioner, unlike in other §112 cases, has a complete failure of proof in this regard: it does not point to a single example of a modified PH20 that contradicts what a POSA would predict using the data in the patent." *Id.* at 14. According to Patent Owner, Petitioner "identifies no prior art or post-filing evidence showing that combining mutations, including through epistasis or otherwise, renders visualizing, making, and using multiply-mutated PH20s unpredictable in light of the mutagenesis data." *Id.* at 16. Patent Owner asserts that numerosity is not a basis for invalidity under Section 112 and that a "POSA could 'reliably predict' actives and practice the claims without 'undue' experimentation." *Id.* at 18–19.

Patent Owner asserts that the

> specification discloses the common structural features based on that primary structure and the related mutagenesis data:
>
> - 91% sequence identity to the primary structure of the recited SEQ IDs;
> - The L317A, L317I, L317K, L317M, L317Q, and L317R mutations;
> - And for actives:
>   - A PH20 alpha-beta barrel fold, with known catalytic and binding sites.
>   - Lack of the inactivating changes identified in the disclosure.

Id. at 20–21. Patent Owner asserts that "[t]here is no dispute that there are several highly active representative species disclosed in the specification. Moreover, Petitioner's new expert [Dr. Naismith] admitted that all actives within the genus fold to the same PH20 alpha-beta barrel fold with catalytic and binding residues properly positioned, just as in the representative species." *Id.* at 23 (citing Ex. 2301, 213:10–18, 85:19–99:18, 101:11–20, 159:13–25).

6. Evidence and Analysis

a) Description in the '758 patent

Our review begins with the claims and Specification of the '758 patent.[12] Claim 1 recites a "modified PH20 polypeptide" that also requires the polypeptide sequence to be 91% identical to one of the 37 recited SEQ ID Nos and with at least one modification at position 317 of one of six specified amino acids. *See* Ex. 1001, 313:18–43. As set forth above, we interpret the claim to require hyaluronidase activity. *See supra* Section II.B.

The Specification generally discloses polypeptides with single point mutations at a variety of positions. *See, e.g.*, Ex. 1001, 14:9–18:42. The Specification identifies several short regions within the PH20 sequence that encode catalytic sites for the PH20 hyaluronidase enzyme in the Peptide 1 and Peptide 3 regions. *Id.* at 73:7–13. Significantly, the Specification details single modifications at a large percent of positions of the mature,

[12] Because there is no dispute that the specifications of the '758 patent and the '731 application are "highly similar" (*see supra* n.5), for expediency we refer herein to disclosures in the Specification of the '758 patent, with the understanding that the same disclosures appear in the "common disclosure."

soluble PH20 polypeptide with analysis showing whether the modification impacted hyaluronidase activity. *See id.* at 194:34–223:47, 226:61–261:59. The '758 patent also references an earlier patent application publication (the '457 publication), which discloses three double mutations and a single example of a triple mutation in the PH20 hyaluronidase enzyme, which all show hyaluronidase activity. *See* Ex. 2068 ¶¶ 338–340; Ex. 2165, Table 16.

The Specification, however, does not provide any other information regarding PH20 polypeptides with more than one mutation nor does it provide any information regarding the three-dimensional structure of any PH20 polypeptide or any hyaluronidase enzyme. *See generally* Ex. 1001; Ex. 1003 ¶¶ 100–101, 131 ("there are no 'double' or 'triple' (or more) mutants that combined sets of single mutations classified as causing both 'active' mutants and 'inactive' mutants or were within particular regions of the PH20 sequence"), 229 ("[T]he PH20 model built with SWISS-MODEL could not reliably assess[] multiple amino acid changes, and would have very low reliability when assessing modified sequences containing 10-20 concurrent changes.").

As an alternative utility, the '758 patent states that "[m]odified PH20 polypeptides provided herein can be used as vaccines in contraceptive applications." Ex. 1001, 187:41–42. The '758 patent further states that "[i]mmunization with PH20 has been shown to be an effective contraceptive in male guinea pigs (Primakoff et al. (1988) *Nature* 335:543-546, Tung et al. (1997) *Biol. Reprod.* 56:1133-1141). It also has been shown to be an effective contraceptive in female guinea pigs." *Id.* at 187:51–55.

b) Expert testimony

There is agreement among the experts, and we find, that the claims encompass (i) modifications at any position in the primary structure of the recited SEQ ID NOs so long as at least one of those modifications is one of the substitutions at position 317, and (ii) a number of additional modifications, including substitutions, deletions, and additions, that varies based on the particular sequence identity and SEQ ID NO recited in the claim. Ex. 1003 ¶¶ 103–107; *See* Ex. 1130, 90:25–91:12 (agreeing changes "could be substitutions, deletions, or additions of amino acids"); Ex. 1131, 54:15–56:23 (agreeing that a claim reciting 95% sequence identity would permit "up to 21 to 23 changes" that could be substitutions, deletions, or additions).

(1) Hyaluronidase activity

The experts disagree on the impact of the claimed 10^{59}+ different polypeptide sequences on hyaluronidase activity and enzyme structure.

(a) Petitioner's Evidence

Dr. Hecht states that "[t]he effects of these myriad sets of combinations of multiple substitutions within PH20 could not have been predicted by a skilled artisan in the 2011 timeframe using the tools that were available then." Ex. 1003 ¶ 158. Dr. Naismith concurs with Dr. Hecht, stating that "[t]here is no teaching in the patent or modelling software that would allow sets of 21 combined [multiple] substitutions that differ by more than around five changes from a known stably folded active PH20 to be predictably active." Ex. 1133 ¶ 117. Dr. Naismith continues, stating that "[o]ther than these 7 hypothetical mutants, neither Dr. Petsko nor Dr. Simpson identify or discuss any multiply modified PH20 polypeptide

within the claim parameter sequence space in their declarations, particularly ones having 5, 10, 15 or 20 changes." *Id.* ¶ 119.

Dr. Hecht notes that the sequence identity language of claim 1 allows "up to 21-42 changes, with each additional change (except at position 317) being to 1 of 19 other amino acids. But the up to 21-42 changes also can be at any of between 430 and 465 (or, in the case of the broadest claims, 474) different positions." Ex. 1003 ¶ 120. Dr. Park calculates that "95% sequence identity to $PH20_{1\text{-}465}$ means that the protein can have 23 total changes."[13] Ex. 1004 ¶ 168. Where one of those changes is at position 317 as required by claim 1, Dr. Park calculates based on a 95% sequence identity that the number of possible PH20 polypeptides with twenty-two additional changes ranges from 10^{59} to 10^{112}. *See* Ex. 1004 ¶¶ 168–169. Dr. Hecht characterizes the number of possible mutations as "astronomical in size." Ex. 1003 ¶ 125.

In the context of structure modeling, Dr. Park states that "the PH20 model from SWISS-MODEL that I used in my analysis should be very similar to what a skilled artisan would have obtained in 2011." Ex. 1004 ¶ 156. Dr. Park states "[i]n 2011, a second or third substitution could possibly be considered, but modeling multiple substitutions is more challenging and predictions can quickly become unreliable. This is

[13] We note that while claim 1 in the '758 patent recites 91% sequence identity, much of the evidence and testimony in this case was shared between related proceedings with different sequence identity recitations, which results in small differences in the number of changes that may be permitted. Thus, where an expert cites 95% sequence identity in later citations in this decision, we understand that the claimed 91% sequence identity will result in a larger genus of polypeptides.

especially true if the mutated residues are close to each other, either in sequence or in space, so that they interact with each other." *Id.* ¶ 158. Dr. Park cites Zhang (Ex. 1010), which states, "analysis of Hyal1 point mutants highlights the importance of specific conserved residues in catalytic function, but also identifies active site conformation as a critical factor. Disrupted activity resulted from the R265L mutation but not from N216A or global disulfide reduction." Ex. 1010, 9441. Dr. Park notes that Zhang found "a mutation at Asn350 in the 'c-terminal EGF-like domain' abolished hyaluronidase activity but one at Asn216 did not." Ex. 1004 ¶ 96; Ex. 1010, 9438–39. Dr. Park also cites Ex. 1011 (Arming), which states:

> *In vitro* mutagenesis of the Glu113 or Glu249 to glutamine yielded PH-20 polypeptides without detectable enzymatic activity in two different assay systems. A third mutant, where Asp111 was changed to asparagine, had about 3% of the activity of the wild-type enzyme. These three acidic amino acids lie within clusters of amino acids that are conserved between mammalian and hymenopteran hyaluronidases.

Ex. 1011, 813; Ex. 1004 ¶ 101. According to Petitioner, these prior art references demonstrate that even conservative mutations may significantly impact the PH20 polypeptide hyaluronidase function.

Dr. Naismith states that "[i]f the set of polypeptides being claimed includes any polypeptide with an amino acid sequence that meets only the . . . two claim requirements, it is both enormous and highly heterogeneous." Ex. 1133 ¶ 40. Dr. Naismith states:

> Dr. Petsko's textbook references Dr. Dobson's work and provides an illustration of the impact of even a single mutation to the structure and stability of a globular protein (*e.g.*, PH20). In this example, the single mutation does not prevent secretion of the globular protein but disrupts its stability to the degree that

> the original folded protein partially or completely unfolds in the extracellular environment.

Id. ¶ 76 (citing Ex. 2164, 160; Ex. 1140, 329 (Fig. 1)). Dr. Naismith states: "as Dr. Petsko's textbook explains, 'the partially unfolded form is prone to aggregation, which results in the formation of fibrils [] and other aggregates that accumulate in the extracellular space.'" *Id.* (citing Ex. 2164, 160 (Figs. 4–53)). Dr. Naismith states, "[l]arge numbers of those amino acid sequences will exist in an unfolded state that exhibit myriad three-dimensional structures, while other sequences will adopt misfolded or partially folded (*e.g.*, molten globules) structures." *Id.* ¶ 79 (citing Ex. 1014, 91–92, 92 (Fig. 6.2)).

Dr. Naismith states:

> I do not agree that the 91% sequence identity requirement is a "structural feature" of a modified PH20 polypeptide. It is a claim requirement that is determined mathematically. . . . It does not define any particular physical characteristic of a modified PH20 molecule. It functions solely to limit the size of the sequence space of the modified PH20 polypeptides.

Id. ¶ 83. Dr. Naismith states that a "POSA would consider 'structural features' of a protein to be the physical characteristics of the protein molecule." *Id.* ¶ 85.

Dr. Naismith states that "Drs. Petsko and Simpson identified seven examples of PH20 polypeptides with more than one change . . . . These limited examples do not meaningfully probe the combinatorial sequence space covered by the claims. They are also not representative of the breadth of modified PH20 polypeptides within the scope of the claims." *Id.* ¶¶ 114–115. Dr. Naismith states: "I do not believe a POSA in the 2011-2012 timeframe could have visualized from the common disclosure the set

of modified PH20 polypeptides with more than about 5 changes within the claim parameter sequence space that will fold and be enzymatically active." *Id.* ¶ 123.

Dr. Naismith states that "[c]omputational tools available in the 2011-2012 timeframe also were not capable of identifying and predicting the myriad types of subtle disruptions to a protein structure that collectively determine if a particular mutated sequence will properly fold and remain stably folded." *Id.* ¶ 128 (citing Ex. 1003 ¶¶ 49–50; Ex. 1004 ¶ 159).

In deposition, when Dr. Hecht was asked "what is your interpretation for why the inventors used a 95 percent sequence identity claim language?", Dr. Hecht answered: "[t]he inventors are trying to capture a genus. They're not giving a substantial, written description of that genus, but they're attempting to capture that." Ex. 2076, 196:10–18. Dr. Hecht further stated: "my sense was that the . . . patent lists a minuscule and highly biased sample of what would be within that fence, in the sense that it only lists single amino acid substitutions while at the same time it's attempting to claim things that have 20 or more substitutions." *Id.* at 203:6–12. When asked what "the skilled person would expect that if they made five changes in HYAL1", Dr. Hecht stated: "if one made all these mutations simultaneously in the same sequence, one would anticipate a huge reduction in activity." *Id.* at 227:6–21.

In deposition, Dr. Park acknowledged that a "homology model can help you to evaluate the impact of a substitution." Ex. 2077, 54:4–5. Dr. Park stated that a POSA in 2011 would have performed "multiple sequence alignment to identify non-essential regions, and reasonably expect

that the amino acids found at those positions may be introduced without substantially altering biological activity." *Id.* at 71:11–16.

When discussing characterizing a sequence with two mutations at the time of invention, Dr. Park noted that

> [t]he problem is when you're looking at one substitution, there are only so many interactions that a single amino acid can make, and those are relatively straightforward to discern for an expert.
> . . .
> Once you start introducing the mutations, more than one mutation . . . if those substitutions happen to be very close to each other, what happens is now suddenly you have to deal with many more possible changes in the interactions . . . .
> So now that results in both positive and negative interactions, all of which need to be tracked and estimated. Unfortunately, a person viewing the structure would not be able to differentiate many of these subtle changes, especially if there are multiple mutations nearby.

Id. at 198:12–199:19. Dr. Park later stated that "[a]s you introduce more and more mutations, the number of possible favorable and unfavorable interactions increases exponentially, and can quickly overwhelm a person's ability to evaluate them." *Id.* at 202:9–13.

When asked whether for multiple mutations "you could submit that sequence for PH20 into SWISS-MODEL, and you download a PBD [protein data bank] file with the resulting homology model, right?", Dr. Park answered: "sure, you can download it. But what do you do with it? The problem is you can't do anything, and there's no methodology that will allow you to compare two structures containing substitutions that are near each other if it's a large number." *Id.* at 204:9–205:14. Dr. Park further noted that "modeling is not just generating the PBD file, but also looking at it and making sense of it. And you will -- one will run into a combinatorial,

combinatorially intractable situation very quickly if mutations occur close to each other." *Id.* at 205:20–206:3. Dr. Park noted that this "is a struggle that the whole community has to deal with, and was not a solved problem back in 2011." *Id.* at 212:16–18.

In deposition, Dr. Naismith addressed the issue of how sequence differences would impact protein folding and stated: "what is really interesting with that is despite the fact that they have the same fold, they actually have some differences in function, which shows you it is quite difficult to detect." Ex. 2301, 86:14–17. When asked "Did you look at the experimentally determined PH20 structure?", Dr. Naismith answered: "I don't believe there is experimentally. There certainly wasn't one at 2011/2012." *Id.* at 87:19–23. When asked "Is there any limit to the structure, the three-dimensional structure that an unfolded protein could take?", Dr. Naismith stated: "I can't give you a number but it is exponentially large if you consider 15 mutations, for example. For unfolded proteins I would expect them to be very large." *Id.* at 92:19–93:6.

When asked about multiple mutations, Dr. Naismith stated, "So this is something all of the experts talk about, which is as you make an increasing number of single site mutations, so you go from 1 to 2 to 3 to 4 to 5, that you can't assume that the mutations do not interact with one another in unpredictable ways." *Id.* at 106:17–22.

The Scientific Background for the 2024 Nobel Prize in Chemistry ("Scientific Background") states, regarding protein structure prediction, that

> the reliability of contact prediction [i.e., pairs of amino acids in contact with each other in 3D] remained low for many years,

> until $CASP_{12}$[14] in 2016, when the accuracy suddenly increased dramatically. It turned out that the methods used to analyse correlated mutations had been oversimplified and could not distinguish between directly and indirectly correlated residues.

Ex. 1027, 7. The Scientific Background further states that in 2020, "while the contact and distance prediction performance remained at around 70% in $CASP_{14}$, the GDT [global distance test] score for the best predictions on difficult targets had now reached about 90%, and this was due to the new $AlphaFold_2$ (AF_2) program." *Id.* at 9.

(b) Patent Owner's Evidence

Dr. Petsko states that the "patent data show, for each of the 447 positions in SEQ ID NO: 3, the tolerance of each position to substitution. . . . The POSA would expect that single or multiple changes in positions that tolerate mutations will generally maintain activity." Ex. 2070 ¶¶ 54–55. Dr. Petsko states:

> PH20, Hyal-1 and bee venom hyaluronidase share several common features, including a common mechanism of action, common active site, and common critical residues involved in structure and function. Hyal-1 and PH20 also share a common alpha-beta barrel fold, with bee venom hyaluronidase adopting a similar fold. . . . The similarities shared by these three different proteins provide key insight into how POSAs in the 2012 time frame would think about concepts like common structural features, structure/function correlation and representative examples disclosed across the scope of a claimed set of protein variants.

[14] CASP (Critical Assessment of protein Structure Prediction) was a series of biannual challenges designed to assess the state of the art in protein structure prediction. Ex. 1027, 6.

Id. ¶¶ 126–127. Dr. Petsko states: "a POSA would have expected that a folded modified PH20 that is 91% identical in sequence to wild type ('WT') would adopt the same alpha-beta barrel fold as WT PH20." *Id.* ¶ 101. Dr. Petsko states that a "POSA could select 23 residues to change and reasonably expect to obtain an active PH20 as those changes were based on the data in the patent. For example, there are 40 positions that tolerated all tested substitutions, 87 that tolerated 90% or more and 158 that tolerated 60% or more." *Id.* ¶ 359.

Dr. Simpson states that

> one can illuminate common structural features of hyaluronidases (and other enzymes) through mutagenesis studies, by modifying the primary structure and determining the impact of the change on activity.
>
> In particular, as a conceptual matter, POSAs can experimentally assess potential common structural features of the three-dimensional protein by introducing mutations to its primary structure and seeing what abolishes activity, and then evaluating the results in the context of an experimental structure (*e.g.,* a crystal structure) or a homology model.

Ex. 2068 ¶¶ 155–156. Dr. Simpson states that the "patent data provide a POSA with an extremely powerful tool to engage in further modification of the protein in a reasonably predictable manner." *Id.* ¶ 157.

In deposition, Dr. Petsko was asked regarding the genus of claim 1 whether it would have been "possible to experimentally determine which ones are properly folded and enzymatically active in 2011 or 2012?"; he answered: "Not from experimenting on the entire ensemble." Ex. 1131, 64:12–17.

As to the tertiary structure of PH20, Dr. Petsko was asked, "When you reviewed the common disclosure, did you see a description of the PH20

polypeptides that used alpha-beta barrel fold to describe it?"; he answered: "Not in the text of the specification, but the structure of the bee venom hyaluronidase was referenced in the patent application." *Id.* at 94:14–20. When asked whether a POSA in 2012 "would be able to predict the change to a protein's net free energy of stabilization[15] associated with a set of 10 or 15 or 20 mutations?", Dr. Petsko answered: "No. They would not be able to predict the number. They would be able to get a sense of whether those were likely to be destabilizing or not." *Id.* at 102:1–9. Despite that statement, when asked whether "you would be able to predict whether that mutated 15 or 20 residue-mutated PH20 will exhibit the activity that you are hoping to get?", Dr. Petsko answered: "My opinion is that you could do so." *Id.* at 111:9–16. Dr. Petsko also stated that "[t]he information content of that particular set of substitutions is enormous. And when combined with the structural information from modeling the PH20 structure, it allows you to

[15] "Every biochemist or molecular biologist who has worked with proteins knows by experience that they are unstable. Slight changes in pH or temperature can convert a solution of biologically active protein molecules in their **native state** to a biologically inactive **denatured state**." Ex. 1014, 90. "[T]he 'net free energy of stabilization' is the difference in free energy between folded and unfolded states of a protein." Ex. 1133 ¶ 74 (citing Ex. 1003 ¶ 63); *see also* Ex. 1014, 90; Ex. 2164, 26 ("the net free energy of stabilization of most folded proteins—the difference in free energy between the folded and unfolded states—is actually rather small" meaning they are only "marginally stable"). "Mutations introduced into an amino acid sequence can . . . alter the net free energy of stabilization of the protein," and if they "decrease the net free energy of stabilization . . . the folded protein will be more prone to partial or complete unfolding" and thus loss of "biological activity (*e.g.*, to bind the HA substrate and hydrolyze it)." Ex. 1133 ¶ 75.

visualize and make predictions about much more of the dataset than just what you see here." *Id.* at 113:2–18.

In deposition, Dr. Simpson stated that a POSA "would have all the information they needed with respect to its activity to create a sequence that was 95% identical, that would either adopt the fold and be enzymatically active, or adopt the fold and not be enzymatically active, or not adopt the fold." Ex. 1130, 99:5–10.

(c) Review

As to hyaluronidase activity, the evidence of record shows that a POSA, in 2012, would not have predictably been capable of determining which PH20 polypeptides having modifications in addition to the recited modification at position 317 would have retained hyaluronidase activity, i.e., we credit Petitioner's evidence above that is more consistent with the evidence of record over Patent Owner's competing evidence. As Dr. Park explained, SWISS-MODEL (and other then-available computational modeling techniques) would not reliably provide such information. Ex. 1004 ¶¶ 156–159; *see also* Ex. 2077, 202:9–207:4 (explaining the limits of such techniques because "[a]s you introduce more and more mutations, the number of possible favorable and unfavorable interactions increases exponentially, and can quickly overwhelm a person's ability to evaluate them"). And this is confirmed by Scientific Background, which noted that prior to significant scientific innovations occurring after 2012, "the methods used to analyse correlated mutations had been oversimplified and could not distinguish between directly and indirectly correlated residues." Ex. 1027, 7. That is, in the 2011–2012 timeframe, a POSA employing the then-available analytical techniques in view of the written description in the

'758 patent could not have determined which of the many multiply-modified PH20 polypeptides within the scope of claim 1 would retain hyaluronidase activity and which would not, and the Specification does not reasonably convey to those skilled in the art that the inventors had possession of that subject matter. Ex. 1003 ¶ 171; Ex. 1004 ¶¶ 62, 158; Ex. 1131, 102:1–9; Ex. 1133 ¶¶ 59, 76.

Patent Owner's evidence does not overcome Petitioner's showing. While Dr. Petsko testified that the single substitution data in the Specification shows that there are a number of positions that tolerated most of the tested substitutions, there were also many that did not. *See* Ex. 2070 ¶ 359. More importantly, the data do not show results for polypeptides having multiple modifications, which greatly complicates the interactions involved, undermining predictability. *See, e.g.*, Ex. 1133 ¶ 129; Ex. 2077, 198:12–199:19, 202:9–13, 204:7–206:3, 212:16–18; Ex. 2301, 106:17–22. This unpredictability is further evidenced by Dr. Naismith's testimony, quoting Dr. Petsko's textbook as teaching that a "single mutation does not prevent secretion of the globular protein but disrupts its stability to the degree that the original folded protein partially or completely unfolds in the extracellular environment." Ex. 1133 ¶ 76 (citing Ex. 2164, 160; Ex. 1140, 329). This shows that even a single mutation can dramatically impact the protein's structure and stability and in turn its activity. *Id.* Indeed, Petitioner cites references demonstrating this specifically for PH20 polypeptides. Ex. 1010, 9441; Ex. 1011, 813.

While Dr. Petsko and Dr. Simpson suggest that a POSA would have been able to use the data in the Specification to make reasonable predictions about the effect of multiple modifications on hyaluronidase activity, we view

this testimony to at most describe a research plan (i.e., a "tool to engage in further modification"[16]) for finding the recited polypeptides rather than demonstrating the inventors were in possession of the full scope claimed. This is particularly so given the limits of the then-available analytical tools noted above and the fact that the structural connections and three dimensional modeling Patent Owner's experts attempt to make (*see, e.g.*, Ex. 2070 ¶¶ 129–213; Ex. 2068 ¶¶ 123–125) do not appear in the written description itself. To the extent the experts disagree on this point, we credit the testimony of Petitioner's experts over that of Patent Owner's. *See* Ex. 1133 ¶¶ 111–251 (identifying problems with the approaches proposed by Patent Owner's experts). For these reasons, we find that a preponderance of the evidence of record better supports a finding that in the 2011–2012 timeframe, it would have been unpredictable to identify which multiple mutants retained hyaluronidase activity, even with the single substitution data provided by the '758 patent.

(2) Contraceptive effect

As explained above, we construe the term "modified PH20 polypeptides" to require peptides that exhibit hyaluronidase activity. *See supra* Section II.B. But even if we were to accept Patent Owner's position that the term is broader and includes inactive versions of such peptides that can be used as antigens to provide a contraceptive effect, the preponderance of the evidence before us does not demonstrate this to be a credible utility. And in any event, it does not demonstrate that the inventors were in possession of the full scope of the claimed polypeptides—which is the

[16] Ex. 2068 ¶ 157.

relevant inquiry here. We address the parties' evidence regarding the potential contraceptive effect of these polypeptides below.

(a) Petitioner's Evidence

Dr. Kelsoe states regarding Tung, cited in the '758 patent for contraceptive activity, that "Tung 1997 (EX1023), reports that the majority of male guinea pigs developed experimental autoimmune orchitis (EAO), and that the observed infertility was due to the absence of sperm in the epididymis." Ex. 1134 ¶ 50. Dr. Kelsoe states this suggests that "the cause of infertility in male guinea pigs arising from immunization with PH20 was likely due to autoimmune inflammation rather than specific antibody-mediated responses against native PH20." *Id.* Dr. Kelsoe states: "Similar irregularities between antibody titer and contraceptive effect were observed in female guinea pigs." *Id.* ¶ 55. Dr. Kelsoe states that "[o]ther groups that tested recombinant PH20 in rabbits (Pomering 2002) and in mice (Hardy 2004) failed to achieve infertility *in vivo*. . . . This demonstrates that merely eliciting a polyclonal antibody response is insufficient to achieve functional neutralization of the target antigen; more is required." *Id.* ¶ 57 (citing Ex. 1020, 178, 180; Ex. 1019, 330, 331).

Dr. Kelsoe states: "a POSA would have understood that there are differences across species in terms of at least PH20's importance to fertilization, location of PH20 expression, and the predominant structural form of PH20 relevant to fertilization." *Id.* ¶ 60. Dr. Kelsoe states:

> In 2022, a group of scientists with the first author Printz investigated the risk that antibodies reactive to recombinant human PH20 (rHuPH20) would interact with endogenous PH20. . . . Although the mouse monoclonal antibody and rabbit polyclonal antibody bound to separate peptides from human

> PH20, with the rabbit polyclonal antibody binding to several such peptides, the human polyclonal IgG did not bind to ***any*** peptide.

Id. ¶ 69. Dr. Kelsoe further states that the "Printz 2022 authors also reported immunogenicity findings from clinical trials where rHuPH20 was co-administered subcutaneously with a variety of therapeutic molecules" and found "[n]o neutralizing antibodies were detected in any subject from this study." *Id.* ¶ 71 (quoting Ex. 1122, 9). Dr. Kelsoe states "[b]oth Printz 2022 and Nolan 2024 confirm what a POSA would have recognized from the totality of evidence available before the relevant timeframe: that PH20 was unlikely to be useful as an antigen in an immunocontraceptive vaccine in humans or mammals other than guinea pigs." *Id.* ¶ 73.

In deposition, Dr. Kelsoe acknowledged that "to determine the target of the immunocontraceptive, I would certainly, since that lies outside of my field of expertise, I would rely on a reproductive biologist, yes." Ex. 2302, 30:13–17.

Exhibit 1189 (Martin-DeLeon) states:

> Taken together, the data from non-primate and primate models (where there are no known redundant reproductive hyases) suggest that PH-20 is not a useful antigen for inclusion in immunocontraceptive vaccines. The absence of critical epitopes in recombinant PH-20 has been considered as an explanation for a lack of sterility after immunization in mice (Hardy et al., 2004). However, it is possible that the strong immunocontraceptive effect reported for affinity purified guinea pig PH-20 could reflect a fundamental difference in the autoimmune response in guinea pigs compared to other species.

Ex. 1189, 119.

(b) Patent Owner's Evidence

Dr. Cherr states that "POSAs would have known that antibodies that bind to sperm (antisperm antibodies) caused infertility." Ex. 2072 ¶ 32 (citing Ex. 2116, Abstract; Ex. 2114, 3). Dr. Cherr states:

> POSAs would have known that the binding of anti-PH20 antibodies to epitopes of PH20 polypeptide on the sperm surface would prevent sperm from fertilizing the oocyte by, *e.g.*, inhibiting sperm motility, inducing sperm agglutination, reducing penetration of cervical mucus by sperm, interfering with sperm capacitation or the acrosome reaction, or stimulating sperm lysis via the complement pathway.

Id. ¶ 33 (citing Ex. 2114, 3, 18–19; Ex. 2117, Abstract; Ex. 2116, 172, 173). Dr. Cherr states: "POSAs would have further known that the binding of anti-PH20 antibodies to epitopes of sperm PH20 polypeptide in the female reproductive tract would prevent PH20's hyaluronidase activity by allosteric effects irrespective of where the antibodies bound on PH20 polypeptides." *Id.* ¶ 34.

Dr. Cherr states that "[i]n *in vivo* studies, female guinea pigs were less fertile when immunized with guinea pig PH20 polypeptide." *Id.* ¶ 35 (citing Ex. 2010). Dr. Cherr states: "POSAs would have known, as Hardy 2004 and Pomering 2002 also acknowledge, that the poor contraception seen after administering PH20 polypeptides via non-mucosal routes in Hardy 2004 (intraperitoneal route in mice) and Pomering 2002 (subcutaneous route in rabbits) reflect the reproductive biology of mice and rabbits." *Id.* ¶ 51.

Dr. Moon states "POSAs would have expected that polyclonal antibodies would have been generated in human females in response to vaccination with any one of the modified PH20 polypeptides and bind to the

wild-type PH20 polypeptide of human sperm introduced into the female reproductive tract." Ex. 2074 ¶ 43.

In deposition, Dr. Cherr responded to a question about the safety of PH20 as a contraceptive, stating that in "the guinea pig males that were injected with PH20 . . . there was epididymitis and orchitis in the testes with massive inflammation. And that was what was deemed to be responsible for the contraceptive effect rather than any sort of antibody binding to cells, per se." Ex. 1129, 38:6–12. In response to being asked "you wouldn't want to cause epididymitis or orchitis in humans?", Dr. Cherr stated: "I would not." *Id.* at 38:13–16.

(c) Review

As to their potential contraceptive effect, the evidence of record fails to demonstrate an expectation that any human PH20 polypeptide, much less the modified PH20 polypeptides claimed, would function as contraceptives in humans. The common disclosure does not identify any particular modified PH20 polypeptide that can be used in a contraceptive, nor does it describe any testing of such. Ex. 1003 ¶ 122. While we acknowledge the expertise of Dr. Cherr and Dr. Moon, the only evidence of any efficacy of a PH20 polypeptide as a contraceptive vaccine are the Primakoff and Tung studies, cited in the Specification, which describe studies of native PH20 in guinea pigs. Ex. 1001, 187:40–60 (citing Primakoff (Ex. 2010) and Tung (Ex. 1023)).

We credit the testimony of Dr. Kelsoe disputing the opinions offered by Dr. Cherr and Dr. Moon regarding whether a POSA would have expected the modified PH20 polypeptides in the challenged claims to be useful as contraceptives. *See* Ex. 1134 ¶¶ 48–73. In particular, Dr. Kelsoe points to

Martin-Deleon, which includes experimental evidence showing that PH20 polypeptide vaccines were ineffective as contraceptives in rabbit, mouse, and macaque. Ex. 1189, 119. This evidence showing significant interspecies variability is further supported by the statement in Exhibit 1189 (Martin-DeLeon) that "it is possible that the strong immunocontraceptive effect reported for affinity purified guinea pig PH-20 could reflect a fundamental difference in the autoimmune response in guinea pigs compared to other species." *Id.*

The failure of PH20 polypeptides as contraceptive vaccines in three of four species tested, and particularly in a primate model that is physiologically more similar to humans, shows that a POSA would not have understood even unmodified PH20 polypeptides to provide a contraceptive effect in humans and most other species. At most, the references Patent Owner relies upon show an immunocontraceptive effect for unmodified PH20 polypeptides limited to guinea pigs. They do not evidence that a POSA would have understood that PH20 polypeptides would provide such an effect or otherwise be useful in a contraceptive vaccine.

Moreover, the common disclosure of the '758 patent does not provide any example of a modified PH20 polypeptide that can be used for contraception. Ex. 1003 ¶ 122. Dr. Moon testifies that a POSA would have expected that "polyclonal antibodies would be generated in a human female against ***any*** of the modified PH20 polypeptides" and that "such polyclonal antibodies would bind to the wild-type human PH20 polypeptide." Ex. 2074 ¶ 47 (emphasis added). But even so, Dr. Kelsoe persuasively explains that "a POSA would have expected the location of amino acid changes to matter to the nature of an immune response elicited by a modified PH20

polypeptide" (Ex. 1134 ¶ 79) and would not have expected all modified PH20 polypeptides to elicit the relevant biological response. *See id.* ¶¶ 77–98, 101. To the extent their testimony conflicts, we credit Dr. Kelsoe for the reasons explained in his declaration. *Id.*

For these reasons, the record does not show that a POSA in the 2011–2012 timeframe would have understood that the recited modified PH20 polypeptides would provide a contraceptive effect or otherwise be useful in a contraceptive vaccine, notwithstanding the discussion of such in the common disclosure.

In addition, Petitioner cites Exhibit 1190 (Nolan),[17] a 2024 journal article authored by scientists employed by Patent Owner, which is not prior art, but confirms that PH20 polypeptides (and by extension the *modified* PH20 polypeptides recited in the challenged claims) are not useful as a contraceptive. *See* Reply 41; Ex. 1134 ¶ 72. As such, it further undermines the competing testimony offered by Patent Owner's experts on this point. In particular, Nolan states that "rHuPH20 exposure and the resulting development of neutralizing ADAs [anti-drug antibodies] did not negatively alter fertility parameters in adults." Ex. 1190, 373. Nolan further states that after weekly administration of rHuPH20 to obtain antibodies, "[t]reated males were mated with nontreated females and there were no statistically significant differences in fertility." *Id.* at 375. Nolan concludes by stating "[a]dministration of rHuPH20 resulted in the generation of ADAs that had no detrimental effects on fertility as measured by sperm concentration and

[17] We note that neither Patent Owner nor its experts appear to have addressed or confronted this exhibit of Petitioner. *See* PO Sur-Reply, PO Resp., generally.

motility, litter size, litter viability, and development. . . . [T]hese studies demonstrate that prolonged exposure to rHuPH20 and circulating anti-rHuPH20 antibodies is well tolerated without impacts on reproduction or development." *Id.* at 381.[18]

Accordingly, even if the term "modified PH20 polypeptides" were interpreted to include inactive polypeptides that can serve as antigens to provide a contraceptive effect, the preponderance of the evidence does not show that a POSA would have understood the inventors to be in possession of the full scope of the recited polypeptides capable of such use.

7. Analysis

We find the preponderance of the evidence supports a finding that the claims fail to comply with the written description requirement. "Every patent must describe an invention. It is part of the *quid pro quo* of a patent." *Ariad*, 598 F.3d at 1345.

In determining compliance with the written description requirement for nucleic acid genus claims, the Federal Circuit has identified two extremes. In *Capon*, claims relying on known nucleotide sequences with known functions were found to satisfy the written description requirement. *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005). At the other end, *Juno* found that for broad claims to a nucleic acid encoding a chimeric T cell receptor with a functional requirement to bind a target, "the written description 'must demonstrate that the applicant has made a generic

[18] While we discuss Nolan in the context of our written description analysis here, we note that it strongly supports a conclusion that, even given the state of the art in 2024, the use of modified PH20 polypeptides as contraceptives has not been enabled by the Specification of the '758 patent.

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.'" *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1337 (Fed. Cir. 2021) (quoting *Ariad*, 598 F.3d at 1349).

As explained above, claim 1 requires modified PH20 polypeptides with some hyaluronidase activity. *See supra* Section II.B. Based on this claim interpretation, we find the evidence in this case closer to *Juno* than *Capon*, and that the '758 patent does not disclose sufficient structural features in the PH20 sequences associated with hyaluronidase or contraceptive activity to allow an ordinary artisan to distinguish which multiply mutated sequences will result in inactive polypeptides and which will retain activity. Indeed, Patent Owner's own expert conceded that it would not have been possible to experimentally determine properly folded and enzymatically active polypeptides in 2011 or 2012 over the entire claim scope. *See* Ex. 1131, 64:12–17.

And while *Capon* expressly allows reliance on prior art for description (*see Capon*, 418 F.3d at 1357–58), Patent Owner is trying to extend that to include that which is obvious from the prior art, not just that which is described. That is, it may have been obvious to a POSA to align PH20 sequences with other known hyaluronidase enzymes and obvious to use the crystal structure of a different hyaluronidase in SWISS-PROT to generate a three-dimensional structure, but neither that alignment nor a structure for PH20 is disclosed in the '758 patent. "[A] description that merely renders the invention obvious does not satisfy the [written description] requirement." *Ariad*, 598 F.3d at 1352. While a POSA might be able to embark on their own research program to try to find suitable multiply-modified PH20

polypeptides, the four corners of the written description do not demonstrate possession of such. *See id.* at 1356 (recognizing that "[p]erhaps one of ordinary skill could discover this information, but this does not alter our conclusion that the description . . . just represent a wish or arguably a plan for future research") (internal quotation omitted).

We also recognize that there are no "bright-line rules governing . . . the number of species that must be disclosed to describe a genus claim, as this number necessarily changes with each invention." *Id.* at 1351. However, the evidence of record discussed above demonstrates activity in only a tiny fraction of the singly-substituted polypeptides in the genus of about 10^{59} to 10^{112} polypeptides claimed.

We find this is consistent with *AbbVie*, which required an inventor to show "that one has truly invented the genus, *i.e.*, that one has conceived and described sufficient representative species encompassing the breadth of the genus. Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus." *AbbVie*, 759 F.3d at 1300. Here, Patent Owner claims an immense number of mutations in the PH20 polypeptide, but provides insufficient guidance for a POSA as of 2012 to determine which, if any, of the untested multiple mutated forms will retain hyaluronidase activity.

In the recent case *Teva Pharmaceuticals International GmbH v. Eli Lilly & Co.*, 172 F.4th 1367 (Fed. Cir. 2026), the court distinguished "(1) claims to a method of using humanized anti-CGRP antagonist antibodies *to treat headache* and (2) claims to such antibodies themselves." *Teva*, 172 F.4th at 1378. The challenged claims here all fall into this second category because they are directed either to the "modified PH20

polypeptides" themselves or to a pharmaceutical composition comprising those "modified PH20 polypeptides." Ex. 1001, 309:19–312:7. With this understanding, the reasoning in *Ariad*, *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920 (Fed. Cir. 2004), *AbbVie*, and *Juno* support a finding that disclosure of the structure of a small number of species in an immense genus is insufficient to satisfy the written description requirement.

A preponderance of the evidence shows that the claims of the '758 patent fail to satisfy the written description requirement because they "recite a description of the problem to be solved while claiming all solutions to it and . . . cover any compound later actually invented and determined to fall within the claim's functional boundaries—leaving it to the pharmaceutical industry to complete an unfinished invention." *Ariad*, 598 F.3d at 1353.

Accordingly, we find that Petitioner has demonstrated by a preponderance of the evidence that challenged claims 1, 2, and 6–30 of the '758 patent do not comply with the written description requirement. Similarly, the current record does not appear to provide evidence of possession of the full scope of the claims of the '758 patent in any of the applications in the extensive priority chain, which all appear to have the same specification, including the '731 application, filed December 28, 2012, or in provisional application 61/631,313, filed December 30, 2011 or provisional application 61/796,208, filed November 1, 2012, for the reasons given above.

D. Ground II - Enablement

1. Principles of Law

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Trustees of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1362 (Fed. Cir. 2018) (bracketing in original; internal quotations omitted). That is, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill [in the art] how to make and how to use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991) (footnote omitted).

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

2. Petitioner's Position

Petitioner asserts that

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

Pet. 67 (citing Ex. 1003 ¶¶ 170–171, 190). Petitioner asserts that "the claims capture massive genera of modified PH20 polypeptides, most of which would have ***unknowable*** properties absent individual production and testing." *Id.* at 69 (citing Ex. 1003 ¶¶ 158). Petitioner asserts that the '758 patent

> provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement $PH20_{1-447}$ polypeptides, of which ~2500 were "active mutants." Those examples are a tiny fraction of the 10^{59} to 10^{112} 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.

Id. at 70–71 (citing Ex. 1003 ¶¶ 103, 155, 159, 167).

Petitioner asserts the common disclosure describes a process requiring "manually performing iterative rounds of ***randomized*** mutations (up to 41 rounds per starting molecule under the broadest claims) to ***discover*** which of the 10^{59}+ possible modified PH20 polypeptides having 2 to 41 replacements to any of 19 other amino acids in any of many, varying-length starting PH20 sequences might possess hyaluronidase activity." *Id.* at 71 (citing Ex. 1003 ¶¶ 188–190). Petitioner asserts that "[r]egardless whether individual rounds of 'iterative' production and testing might be considered 'routine," the process described in the common disclosure is indistinguishable from the '***iterative, trial-and-error process[es]***' that have consistently been found to not enable broad genus claims to modified proteins." *Id.* at 73 (quoting *Idenix Pharm. LLC v. Gilead Sci. Inc.*, 941 F.3d 1149, 1161–63 (Fed. Cir. 2019)).

Petitioner asserts "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." *Id.* at 74 (citing Ex. 1003 ¶¶ 158, 229). Petitioner asserts that the "cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design techniques to reliably predict the effects of each change on the protein's structure in 2011." *Id.* at 75 (citing Ex. 1003 ¶¶ 158, 190, 229; Ex. 1004 ¶¶ 158–159).

Petitioner asserts:

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

Id. at 76–77 (citing Ex. 1003 ¶¶ 158, 229).

3. Patent Owner's Response

Patent Owner asserts "[t]here is no dispute that POSAs could readily generate claimed PH20 variants with amino acid substitutions and test them for activity using routine molecular biology and biochemistry techniques." PO Resp. 63 (citing Pet. 35–38). Patent Owner asserts that

> POSAs would recognize, within this narrow genus, that the nine variants and their subvariants are structurally homogeneous in that they share at least 91% identical primary structure, the L317 mutation, and for those that are active, the same PH20 tertiary structure and several common structural features, such as the same common residues critical for catalysis; moreover, POSAs can distinguish actives from inactives by the absence of

> the common structural features in the inactives (e.g. changes to "scaffolding" such as disulfide bridges or modification of catalytic residues).

Id. at 63–64 (citing Ex. 2068 ¶¶ 287–293, 303, 316; Ex. 2070 ¶¶ 49–51, 53, 248–253, 325–342, 389–428). Patent Owner asserts "the patent provides extensive mutagenesis data across a full, mature, soluble PH20 sequence (SEQ ID NO: 3) that give POSAs predictive insight into which substitutions preserve activity and which abolish it." *Id.* at 64.

Patent Owner asserts that "[t]he invention is modified PH20 variants with a defined set of structures, which the inventors characterized via expansive disclosure in the specification regarding the tolerance of every position in a mature, soluble, active PH20 sequence to modification, making modification (and the nature of the invention) reasonably predictable." *Id.* at 67. Patent Owner asserts that POSAs

> possessed a high degree of skill and the tools and knowledge to model PH20 accurately, assess potential substitutions, and interpret their effects based on well-characterized structural and mechanistic features shared across hyaluronidases. Given this developed state of the art, the specification's disclosures provided more than sufficient guidance to enable the full scope of the claimed modified PH20 polypeptides without undue experimentation.

Id. at 69 (citing Ex. 2068 ¶¶ 362, 371; Ex. 2070 ¶¶ 52, 234, 262). Patent Owner asserts that "the specification supplies detailed instructions on how to make and used the claimed variants and sub-variants." *Id.* at 69 (citing Ex. 1001, 69:6–72:47, 73:5–13, Tables 5, 9–10; Ex. 2068 ¶¶ 372–377; Ex. 2070 ¶¶ 248–261).

Patent Owner asserts: "Dr. Petsko describes in detail how POSAs could use the functional data in connection with homology models" and also

"provided multiple examples of how POSAs could have used the data in connection with the homology model to make modified PH20s using routine methods and illustrating how a POSA would have predictably and easily used the data without trial-and-error experimentation." *Id.* at 71 (citing Ex. 2070 ¶¶ 297–342). Patent Owner asserts that "Petitioner's argument that POSAs would need to generate impossibly large libraries and screen them for activity to practice the claims is not credible." *Id.* at 72. Patent Owner contends that "[w]here, as here, the patent teaches POSAs a structure-function map of PH20, including which changes to make and which positions are generally tolerant to change, there is no reason to randomly screen to identify active PH20s with the L317 mutation." *Id.* Patent Owner asserts that

> by December 28, 2012, POSAs would have expected that PH20 polypeptides would be useful as contraceptive vaccines in humans and other mammals, particularly because it was widely known that PH20 plays a vital role in fertility and affects several stages of conception, including the critical final step of allowing the sperm to physically reach the egg.

Id. at 74 (citing Ex. 2072 ¶¶ 19–28).

Patent Owner asserts that

> Petitioner argues that "'inactive mutant' PH20 polypeptides would have no utility at all." Pet., 81. If true (it is not), those embodiments would simply be inoperative, and "[e]ven if some of the claimed combinations [are] inoperative, the claims are not necessarily invalid."

Id. at 79–80 (quoting *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984)) (alterations in original). Patent Owner asserts that "the specification, together with well-established tools in the art, provided the means to draw that distinction." *Id.* at 80.

4. Petitioner's Reply

Petitioner responds that

> When ***multiple*** mutations are made together, they affect a protein's structure, folding capacity and stability differently than how each does alone. Each can cause effects remote from the mutation that change how the protein reacts to subsequent changes. The unpredictable effects of combinations of mutations ("epistasis") prevent a POSA from predicting whether the vast majority of multiply-modified PH20s will "properly fold."

Reply 23–24 (citing Ex. 1003 ¶¶ 55–61, 156–159; Ex. 1133 ¶¶ 123, 125–126, 222, 232, 252–259, 262, 330; Ex. 1131, 79:15–22, 89:21–90:24; 270:9–17; Ex. 1160, 383–385). Petitioner asserts "[e]ven ***one*** mutation can prevent folding, cause misfolding or incomplete folding, or adoption of an unstable native fold that unfolds outside the cell and forms aggregates—Dr. Petsko's textbook illustrates this." *Id.* at 26 (citing Ex. 2164, 160; Ex. 1133 ¶¶ 73–76, 326; Ex. 1003 ¶ 54; Ex. 1131, 41:22–42:11).

Petitioner asserts that "[e]ven positions Dr. Petsko labeled as '100% tolerant' (the ***most*** predictable in his table) exhibit widely varying effects. That reflects that ***each*** substitution causes a ***unique*** effect on ***the entire*** PH20 protein structure not limited to its position." *Id.* at 28–29 (citing Ex. 1133 ¶¶ 264–269). Petitioner further asserts that, contrary to Patent Owner's assertion that the "α/β barrel motif in PH20s makes it possible to predict combinations of changes to them, . . . EX1144 reports an experiment where loops in a ***canonical*** α/β enzyme (PRAI) were replaced with loops from other α/β proteins with the ***same*** fold. Positions were chosen to increase odds of being tolerated." *Id.* at 31–32 (citing Ex. 2070 ¶¶ 52, 292; PO Resp. 49–51). Petitioner asserts that "[d]espite the constrained choices,

most α/β barrel mutants ***did not fold***." *Id.* at 33 (citing Ex. 1133 ¶¶ 177–182).

Petitioner asserts:

> Experimental design flaws and incomplete reporting of results independently render Dr. Petsko's ratings unreliable:
> - inadequate numerical, structural context, and physicochemical interrogation of positions prevent reliable ratings of tolerance;
> - no use of positive/negative controls in the primary assay, and no evidence of proteins in supernatants or their folded state;
> - no activities reported for inactives, precluding differentiation of non-secreted mutants from those with residual activity;
> - averaging of activities conceals inter-assay variability;
> - unusually high (~40%) assay variability (ordinarily ~10-15%) render classifications unreliable.
>
> Dr. Naismith showed that correcting for these limitations and problems paints very different pictures than Dr. Petsko presented.

Id. at 34 (citing Ex. 1003 ¶¶ 67–76, 96, 103–106; Ex. 1133 ¶¶ 175, 234–237, 239–242, 246–248, 250, 291–315, 304–305, 316–323, Appendix B (Ex. 1135)). Petitioner asserts that "the description does not propose selecting positions and substitutions based on ***a proportion*** of active mutants at a position. And where 'tolerance' is used to inform changes, the disclosure [simply] instructs POSAs to ***not include*** inactivating substitutions in active PH20s." *Id.* at 38 (citing Ex. 1026, 91:30–92:20; Ex. 1133 ¶¶ 206–207, 209).

Petitioner asserts that for several immunological reasons, "[c]ontraceptive utility was not a credible utility for any PH20 polypeptide in 2011-2012, it was just an invitation for further research." *Id.* at 43–44

(citing *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005); MPEP § 2107.01).

5. Patent Owner's Sur-Reply

Patent Owner asserts that "[t]he patent's disclosure provides a granular structure/function correlation that teaches, on a position-by-position basis, the effect on activity of substituting different amino acids into every position within the primary structure." PO Sur-reply 7. Patent Owner asserts:

> To evaluate written description and enablement, Drs. Petsko and Simpson used the same "visualization-based assessment" technique that Petitioner admits was "prevalent" in 2011 and "provid[es] a consistent, objective and unbiased evaluation of substitutions [throughout the protein]." Pet., 102-109. Indeed, Petitioner admits this method can be used to predict the effects of up to five modifications, ***without the patent data***.

Id. (citing Ex. 1003 ¶ 158; Ex. 1004 ¶ 159; Ex. 1133 ¶ 258 n.292). Patent Owner cites Dr. Petsko's testimony that "[a] POSA could select 23 residues to change and reasonably expect to obtain an active PH20 as those changes were based on the data in the patent." *Id.* at 10 (citing Ex. 2070 ¶ 359). Patent Owner asserts that "with the patent data in hand, the POSA can avoid the billions of PH20s that will be inactivated by changes identified in the patent." *Id.* at 12.

Patent Owner asserts: "here, the claim specifies a small range of sequences highly similar to mature PH20, and Petitioner's expert admitted that if active, ***they would fold to the PH20 alpha-beta barrel fold***." *Id.* at 14 (citing Ex. 2301, 213:10–18, 85:19–86:5; 95:9–20, 96:16–98:20, 99:13–18, 101:11–20, 159:13–25). Patent Owner asserts: "if the patent data were as useless as Petitioner claims, Petitioner should have easily been able [to]

show multiple examples of sequences within the scope of the claims that produced results that were not predicted by the patent's disclosure of tolerance data." *Id.* at 16. Patent Owner asserts "[t]hat guidance enables a POSA to identify tolerated substitutions and predictably make and use singly or multiply mutated PH20 variants without resorting to blind screening or undue experimentation." *Id.* at 17.

Patent Owner asserts that "POSAs would be able to practice the full scope of the claims despite Petitioner's 'sequence space': 'no POSA would start with the theoretical maximum number of potential sequence variants as a starting point for making a comparative analysis of what amino acids would retain activity in a PH20 polypeptide.'" *Id.* at 24–25 (citing Ex. 1130, 93:20–24). Patent Owner asserts that "Dr. Simpson, who has experience with the patent's assays, explained why variability does not undermine reliability and is consistent with a POSA's expectation." *Id.* at 26 (citing Ex. 2068 ¶¶ 202–203, 223–226, 182–183, 186).

Patent Owner asserts that "Petitioner's expert agrees that no known human contraceptives achieve 100% effectiveness and substantially lower efficacy would still 'have an important and valuable' application." *Id.* at 27 (citing Ex. 2302, 134:5–135:3).

6. Analysis

Petitioner has the burden to identify how the Specification allegedly fails to enable the claims. We address the *Wands* factors and the parties' respective arguments and evidence.

a) Breadth of Claims and Nature of the Invention

Dr. Park states, regarding the breadth of claim 1, that he "calculated the number of distinct polypeptides that exist that meet the specified criteria." Ex. 1004 ¶ 169. Dr. Park's table is reproduced below:

PH20 length	# Changes	Pos. 317 Choices	Add'l Changes	# Distinct Polypeptides
474	42	6	41	3.79×10^{112}
474	23	6	22	3.11×10^{66}
474	42	1	41	6.32×10^{111}
465	41	6	40	8.47×10^{109}
465	41	1	40	1.41×10^{109}
433	38	6	37	6.01×10^{101}
430	38	6	37	4.59×10^{101}
433	38	1	37	1.00×10^{101}
430	38	1	37	7.66×10^{100}
447	40	6	39	8.37×10^{106}
447	40	1	39	1.40×10^{106}
430	21	1	20	4.40×10^{59}
433	21	1	20	5.08×10^{59}

Dr. Park's table shows the different sequence lengths, their degree of sequence identity, and using the number of possible changes, provides a calculation for the number of distinct polypeptides, finding that the "number of distinct peptides is extremely large by all accounts, ranging from 10^{59} to 10^{112}." *Id.* Dr. Hecht agrees, stating the "sequence identity language causes

the claims to encompass an immense number of distinct PH20 polypeptides." Ex. 1003 ¶ 120. To illustrate how large a number like 10^{59} is, Dr. Hecht states that an "aggregate weight of the smallest set containing one molecule of each of the PH20 mutants would be . . . = 3.93 x 10^{40} kg. The weight of [the] Earth is 'only' ~ 5.97 x 10^{24} kg." *Id.* ¶ 123. That is, Dr. Hecht states that a complete set with one single molecule of protein comprising all possible mutations in PH20 as recited in claim 1 would weigh multiple fold more than the entire mass of planet Earth. *See id.*

In deposition, Dr. Hecht stated "my sense was that the . . . patent lists a minuscule and highly biased sample of what would be within that fence, in the sense that it only lists single amino acid substitutions while at the same time it's attempting to claim things that have 20 or more substitutions." Ex. 2076, 203:6–12. When asked if a sequence "gives you enough information to tell whether that amino acid sequence is 95 percent identical to SEQ ID NO. 3", Dr. Hecht answered "Yes, but that's all it tells you. It doesn't tell you anything about active, precipitated, aggregated, folded. It doesn't tell you anything." *Id.* at 204:11–19.

Dr. Simpson disagrees with Dr. Hecht and Dr. Park, stating "POSAs would not evaluate the scope of the claimed genus by calculating the total number of amino acid sequences that satisfy the 91% identity limitation. POSAs would evaluate the scope of the claims by considering the variation across the set of claimed proteins. And there is little variation across this set." Ex. 2068 ¶ 353. Dr. Simpson states that the "enzymatically active claimed variants and sub-variants share a common scaffold with common structures (*e.g.,* disulfide bonds) that enable them to fold into this common tertiary structure." *Id.* ¶ 356. Dr. Simpson states that the "enzymatically

active claimed variants and sub-variants share a common active site and common residues involved in facilitating the catalysis reaction." *Id.* ¶ 357.

Dr. Simpson states that

> [a]s to the nature of the invention, the claims cover modified PH20 variants and sub-variants. A POSA would have understood that predictably making and using the claimed PH20 variants and sub-variants required only routine molecular biology and protein biochemistry techniques, particularly in view of the extensive structure-function guidance provided in the '758 patent and the knowledge in the art.

Id. ¶ 360.

Dr. Petsko agrees with Dr. Simpson, stating that "POSAs think of the class of modified PH20 proteins sharing 91% of their sequence (including a change at position 317) as an extremely limited set of proteins. Those that fold are a limited set of structurally homogeneous proteins." Ex. 2070 ¶ 391. Dr. Petsko states that "[t]o further illustrate the common structural features shared by the claimed polypeptides, I generated models of several L317Q variant PH20s that satisfy the sequence identity requirements of claim 1." *Id.* ¶ 413. After showing images of one set of structures with particular variant PH20s, Dr. Petsko states that in this example, all share common structural features such as an alpha-beta barrel fold, common structure and interactions at position 317, and common active site residues in similar positions." *Id.* ¶ 429.

In deposition, despite acknowledging the accuracy of Dr. Park's calculation (*see* Ex. 1130, 90:14–16), Dr. Simpson stated "no POSA would start with the theoretical maximum number of potential sequence variants as a starting point for making a comparative analysis of what amino acids would retain activity in a PH20 polypeptide." *Id.* at 93:20–24. Dr. Simpson

also stated that a POSA "would have internal experimental criteria that they would be seeking to meet in generating a polypeptide that met the claims." *Id.* at 96:13–15.

Addressing the issue of the impact of mutations on the three dimensional structural integrity of the polypeptide, Dr. Petsko stated: "What I can say is, from years of experience in mutating enzymes and looking at them, just because a mutation has no activity or low activity doesn't mean it has disrupted the fold." Ex. 1131, 79:6–9. In response to being asked whether for "changes that cause a loss of activity . . . is it likely that individual residues have shifted in the spatial positioning of them relative to the native protein?", Dr. Petsko stated: "Maybe a few, but not many. And the alpha-beta barrel might be completely superimposed." *Id.* at 92:17–93:2. When asked about nonhuman proteins that would fall within the scope of the claims, Dr. Petsko acknowledged that the chimp, gibbon, and orangutan naturally-occurring sequences fall within the scope of claim 1. *Id.* at 84:10–24.

Dr. Naismith disagrees with Dr. Petsko's and Dr. Simpson's attempt to "portray the claims of the '758 Patent as covering a 'narrow' and 'structurally homogeneous' set of proteins,", stating

> If the set of polypeptides being claimed includes any polypeptide with an amino acid sequence that meets only [the sequence identity and substitution at position 317], it is both enormous and highly heterogeneous. Even if the set is restricted to enzymatically active modified PH20 polypeptides, a POSA would expect there to be variations in the structural features of that set of proteins, albeit in ways that [do not disrupt the spatial positioning of the catalytic machinery and/or substrate recognition motif]. Dr. Hecht illustrated these points in his declaration.

Ex. 1133 ¶ 40 (citing Ex. 2068 ¶¶ 44–46, 55-61, 156-159; Ex. 2068 ¶ 27, Ex. 2070 ¶ 49). Dr. Naismith notes that "Dr. Petsko said he uses enzymatic activity and the ability to be secreted as 'proxies' for PH20 proteins that have 'properly folded'." *Id.* ¶ 58. But "[w]hile enzymatic activity confirms that an enzyme has folded," Dr. Naismith states "there would need to be additional evidence to justify a conclusion that the folded enzyme is sufficiently stable to retain its folded state," and "a POSA would not believe an enzyme had 'properly folded' if it did not maintain activity over a meaningful period or if it formed aggregates within a short period." *Id.* ¶ 59.

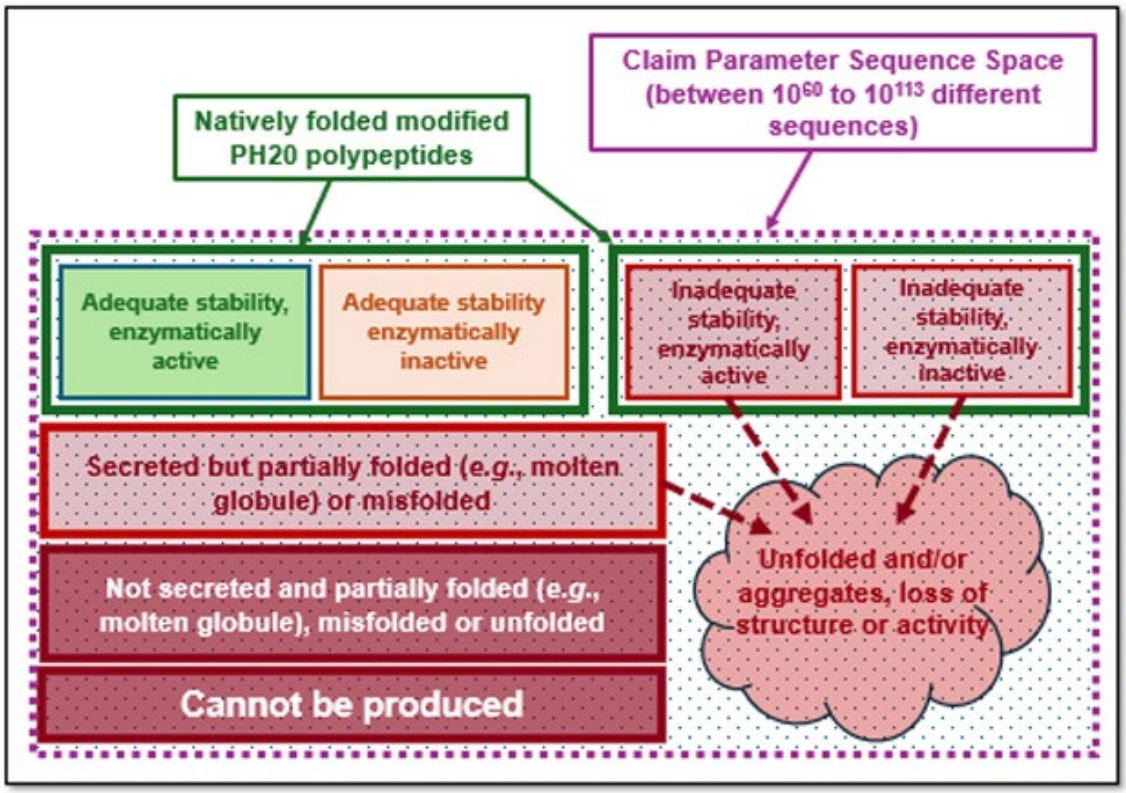
According to Dr. Naismith, sequences within the recited sequence space will adopt many different three-dimensional structures according to a complex folding process and that mutations to their amino acid sequence increase obstacles to them successfully folding to adopt their native (active) state. *See* Ex. 1133 ¶¶ 60–80. As evidence, Dr. Naismith cites "[a] series of articles by Dr. Christopher Dobson at Cambridge University before 2011" regarding "the complexity and challenges of protein folding, and the diversity of confirmations an amino acid sequence can adopt." *Id.* ¶ 62.

Dr. Naismith states that:

> As Dobson 2004a explains, native (not mutant) sequences have been specifically selected by evolution to fold. Of particular note is that only these "special" evolutionarily selected amino acid sequences will induce the "correct (native-like) interactions between different residues [that] are on average more stable than the incorrect (nonnative) ones." Mutated sequences do not benefit from this evolutionarily conferred advantage, which is why so many of them cannot find the pathway to the native state of the folded protein.

Id. ¶ 69 (citing Ex. 1136, 4). Dr. Naismith states that "[i]n the 2011-2012 timeframe, a POSA would not view the sequence space defined by the

sequence identity claim parameters as being structurally homogeneous. That is because it contains many unfolded sequences that can adopt an immense number of conformational states, all of which are different from the native fold" and impact activity. *Id.* ¶ 77. Dr. Naismith explains this will result in distinct sets of three-dimensional structures within the sequence space, providing the following figure to illustrate his point.



Id. ¶ 78. The figure above shows what Dr. Naismith describes as distinct "sets" or "categories" of sequences within the claimed sequence space (dotted line), including stable, active polypeptides (shown in green) and others that that suffer from various problems (shown in red). *See id.* ¶¶ 77–80. Dr. Naismith states that "[i]n the 2011-2012 timeframe, a POSA would have no reliable method of assigning sequences to the various categories [in the figure above] except by extensive experimentation." *Id.* ¶ 80.

Dr. Naismith states: "I do not agree that the 91% sequence identity requirement is a 'structural feature' of a modified PH20 polypeptide. It is a claim requirement that is determined mathematically." *Id.* ¶ 83. Dr. Naismith states that the percent identity "does not define any particular physical characteristic of a modified PH20 molecule. It functions solely to limit the size of the sequence space of the modified PH20 polypeptides." *Id.*

In deposition, Dr. Naismith agreed with Dr. Petsko that "what is really interesting . . . is despite the fact that they have the same fold, they actually have some differences in function, which shows you it is quite difficult to detect." Ex. 2301, 86:14–17.

Based on the evidence of record, we find that the breadth of claim 1 and the dependent claims is immense comprising a sequence space ranging from ranging from 10^{59} to 10^{112} distinct polypeptides. Ex, 1004 ¶ 179. We understand that the number of distinct polypeptides calculated by Petitioner's experts is larger than the genus recited in claims because that genus is limited to enzymatically active polypeptides. However, the number of active polypeptides encompassed by the challenged claims is still very large even though its precise breadth is unknown. *See, e.g.*, Ex. 1131, 61:19–64:11 (Dr. Petsko testifying that the number of properly folded proteins in the genus of claim 1 is large and that it would not be possible to calculate the number of such proteins that are not properly folded). Dr. Simpson acknowledged that a POSA would not expect the vast majority of the variants encompassed by claim 1 to be useful in an analysis. *See* Ex. 1130, 93:20–24.

We also disagree with Patent Owner's attempt, through its experts, to characterize the claim scope as "structurally homogenous." *See, e.g.*, PO

Resp. 63–67. In particular, we credit Dr. Naismith's testimony regarding a POSA's understanding of protein folding and the three-dimensional structure formed by enzymatically-active polypeptides. *See* Ex. 1133 ¶¶ 52–80. That testimony is well-supported by the references Dr. Naismith cites, including a textbook from Patent Owner's expert Dr. Petsko. *See id.* (citing Ex. 1136, 11; Ex. 1137, 888, Ex. 1138, 11; Ex. 1139, 351; Ex. 1140, 329 (Dobson articles); 1140, 329; Ex. 2164, 3, 160 (Petsko Textbook); Ex. 1014, 91–92).

We find Dr. Naismith's testimony in this regard to be more persuasive than the competing testimony offered by Dr. Simpson and Dr. Petsko to show that the claims are directed to a "limited set of structurally homogeneous proteins." *See, e.g.*, Ex. 2068 ¶¶ 287–293, 303, 315; Ex. 2070 ¶¶ 49–51, 53, 248–253, 325–342, 390–431. At most, their testimony shows that there may be some general structural features that at least some of the claimed polypeptides have in common, but Dr. Naismith shows that protein folding is extremely complex, resulting in many different subsets of polypeptides within the claims' immense sequence space (Ex. 1133 ¶ 78) and that even a single mutation can affect the net free energy such that the protein does not fold properly (*see, e.g., id.* ¶¶ 75–76).

We also agree with Dr. Naismith's criticism that Dr. Petsko's testimony regarding a common "alpha-beta barrel fold" exhibited by the recited polypeptides is imprecise and does not predict whether a particular amino acid sequence within the recited sequence space will possess that feature. *See, e.g.*, Ex. 1133 ¶¶ 152–163. Therefore, it cannot be said to be "a 'common structural feature' of the entire set of 10^{59} to 10^{112} polypeptides within the claim parameter sequence space" because, as Dr. Naismith

persuasively explains, within that "space will be many sequences that cannot be produced, will not properly fold, or will unfold because they are unstable" and without "a stable tertiary structure, they will not contain the 'PH20 α/ß barrel' motif present in the tertiary structure of the PH20 protein." *Id.* ¶ 170. We therefore agree with Petitioner, and Dr. Naismith, that the challenged claims are directed to very broad, "structurally heterogenous [genera]." *See* Reply 4–10; Ex. 1133 ¶ 80 (a POSA would recognize "there is an incredible amount of structural diversity" within the "claim parameter sequence space").

b) Skill in the Art

The parties both addressed the skill in the art as discussed above. *See supra* Section II.A. We find that the skill in the art is high, as indicated by both parties.

c) State of the Prior Art

Dr. Hecht acknowledges that protein expression is routine, stating that the "conventional procedures relating to production of the wild-type $PH20_{1-447}$ protein . . . could be applied to produce forms of $PH20_{1-447}$ that incorporate a single amino acid substitution (*e.g.*, the L317Q substitution . . .) with little effort." Ex. 1003 ¶ 203. Dr. Hecht further states that "[t]he first experimentally determined structure of a hyaluronidase was bvH, both alone and in complex with HA (published in 2007)" and that "Markovic-Housley identified the catalytic site and residues involved in catalytic activity using this structure." *Id.* ¶ 80 (citing Ex. 1033, 1028–31).

However, Dr. Hecht also states "[d]ata in the '429 Patent and a 2007 paper by Frost (EX1013) also showed that truncations of varying length at the C-terminus of PH20 caused significant variations in hyaluronidase

activity." *Id.* ¶ 90. Dr. Hecht states that the "Zhang paper reported that a truncation just upstream of the start of the Hyal-EGF domain in HYAL1 reduced its activity to ~6%." *Id.* ¶ 92. Dr. Hecht states that "[n]either the scientific literature existing by 2011 nor the common disclosure provides an explanation why these PH20 truncation mutations that differ by one residue (*i.e.*, $PH20_{1-446}$ vs. $PH20_{1-447}$ vs. $PH20_{1-448}$) exhibit variability in their activity." *Id.* ¶ 94.

Dr. Hecht states "[t]here were limits to using rational design techniques in the 2011-timeframe." *Id.* ¶ 50 (citing Ex. 1018, 378; Ex. 1059, 1225–26). "The complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational design." *Id.* ¶ 50 n.16 (quoting Ex. 1018, 378). Dr. Hecht states regarding another approach to protein modification, termed directed evolution, that the "challenge with directed evolution is scale. One has to identify the successful mutant out of an immense number of possibilities, which presents different kinds of challenges." *Id.* ¶ 52 (footnote omitted). Dr. Hecht states "changing many amino acids simultaneously risks disrupting the pattern necessary to induce formation of the original secondary structure . . . and [can] be highly destabilizing to the overall protein structure." *Id.* ¶ 55 (citing Ex. 1046, 2034; Ex. 1047, 6349, 6352). Dr. Hecht states that in a ten amino acid substitution situation, "[t]here are approximately 6×10^{12} different scenarios of 10 substitutions." *Id.* ¶ 58.

In deposition, Dr. Hecht stated: "Now AlphaFold is -- you know, it's an AI thing. People pop it in, and magic happens and something comes out. That's very different from what was going on 15 years ago." Ex. 2076, 33:19–22.

Dr. Simpson states that, as of 2012, the "crystal structures of bee venom hyaluronidase and human HYAL-1 had been solved" and that "made it possible to generate accurate homology models of PH20's tertiary structure." Ex. 2068 ¶¶ 366–367 (citing Ex. 1033; Ex. 1006). Dr. Simpson states "[m]utagenesis studies in both HYAL-1 and PH20 also had confirmed the importance of certain residues for enzymatic activity and structural stability." *Id.* ¶ 369 (citing Ex. 1010; Ex. 1011; Ex. 1033, 1029; Ex. 2070 ¶¶ 167–217). Dr. Simpson states that "as of December 28, 2012, a POSA would have had in-hand a PH20 homology model to evaluate potential substitutions." *Id.* ¶ 370.

In deposition, regarding the sequence alignment in Figure 3 of Chao (Ex. 1006), Dr. Simpson stated that

> a POSA would use the information about this structure, use the sequence alignment, and model PH20 according to this new structural information, and evaluate whether the blue invariant residues were located in a position of critical -- of a critical nature to the folded structure of PH20, and evaluate them individually, potentially, for their location in the structure, if they wanted absolute certainty about their role in maintaining the structure.

Ex. 1130, 121:8–17.

Dr. Petsko states that "PH20, Hyal-1 and bee venom hyaluronidase all achieve the function of cleaving HA using a common structure—the active site in all three proteins is a long groove and the same critical residues (oriented in about the same positions) catalyze the reaction in all three proteins." Ex. 2070 ¶ 139. Dr. Petsko states

> this common structural feature was recognized in the literature: Stern teaches that "HA-degrading enzymes" share a "common structural feature," which is an "elongated cleft for accommodating substrate" EX1008 (Stern), 833. Consistent

> with this, Marković-Housley reports that the "dominant feature of the [bee venom hyaluronidase] protein surface is a large groove" that forms the active site and "would be large enough to accommodate a hexasaccharide" of HA.

Id. ¶ 140 (citing Ex. 1033, 1028).

Dr. Cherr states that "by December 28, 2012, PH20 polypeptide vaccines had been successfully used for contraception in female guinea pigs." Ex. 2072 ¶ 35 (citing Ex. 2119; Ex. 1022; Ex. 2010; Ex. 1023). Dr. Moon states that "POSAs would have also known that 'intranasal immunization of various species, including humans, was efficient at inducing antigen-specific antibody responses in the *female* genital tract.'" Ex. 2074 ¶ 27 (quoting Ex. 2122, Abstract).

Dr. Naismith states: "By 2011-2012, it had been demonstrated that the five human hyaluronidase enzymes exhibit distinct profiles of biological activities and expression patterns." Ex. 1133 ¶ 183 (citing Ex. 1008, 825). Ex. 1008 states: "Hyal-2 of human origin degrades high molecular mass HA to an approximately 20 kDa product (~50 saccharide unites), whereas Hyal-1 can degrade high molecular weight HA to small oligomers, primarily to tetrasaccharides." Ex. 1008, 825. Dr. Naismith states that "[u]sing Dr. Petsko's high level perspective, all appear have the same 'alpha-beta barrel' motif. Despite this similarity, the five proteins exhibit subtle but meaningfully different substrate preferences and activity." Ex. 1133 ¶ 184. Dr. Naismith states that

> Dr. Simpson confirmed that her group used a Hyal-1 structural model to predict catalytic residues, then tested those predictions experimentally, with mixed results—for example, mutating Glu131 abolished activity, while mutating Asp129 did not. This reflects the understanding of a POSA in 2011-2012: that one could make a limited number of reasonable predictions

> using a homology or structural model but experimental confirmations are needed to test those predictions.

Id. ¶ 195 (citing Ex. 1130, 130:9–16; Ex. 1010, 9436–37). Exhibit 1010 (Zhang) states that "[a]nalogy to point mutations in both sperm hyaluronidase, PH-20, and bacterial *N*-acetylglucosaminidase H, further suggested Asp^{129} and Glu^{131} would be critical for catalytic activity of the enzyme. . . . Interestingly, Asp^{129} was not essential, because significant activity was retained." Ex. 1010, 9436–37.

In deposition, when asked, "Did you look at the experimentally determined PH20 structure?", Dr. Naismith stated: "I don't believe there is experimentally. There certainly wasn't one at 2011/2012." Ex. 2301, 87:19–23.

Based on the evidence of record, we find that simply making and expressing modified PH20 polypeptides was well within the state of the prior art. The evidence also shows that molecular modeling of a putative PH20 structure would have been routine as well, and that there was information about several amino acid locations within the protein that were involved in catalytic activity. Ex. 1033, 1028–31; Ex. 2070 ¶¶ 139–140. However, the evidence of record also demonstrates that it was known that mutations, whether conservative or non-conservative, may impact protein function and physical shape in unpredictable ways. *See, e.g.*, Ex. 1133 ¶ 76; 1003 ¶¶ 59–61. For example, this is evidenced by Zhang, which teaches that Asp^{129} was predicted to be critical for activity based on homology, but was determined experimentally by making and testing the modified PH20 polypeptide to not be essential. *See* Ex. 1010, 9436–37. A POSA would have understood this unpredictability was even more pronounced when multiple mutations were introduced. Ex. 1003 ¶¶ 54–61, 156; Ex. 1004

¶ 153; Ex. 1133 ¶¶ 252–259 (discussing epistasis and concurring with Petitioner's other experts "that after about 5 mutations, a POSA could no longer predict enzyme behavior by simple linear combinations of single site mutations").

Accordingly, the evidence of record demonstrates that methods of accurately identifying which of the 10^{59} to 10^{112} members of the potential PH20 polypeptide genus in the claims would either retain functional hyaluronidase activity (or otherwise be useful as antigens in contraceptive vaccines) aside from actually making and testing particular polypeptides was not known in the prior art as of the 2011–2012 time frame.

d) Presence of Working Examples

Dr. Hecht states that Table 8 of the common disclosure lists 6,753 $PH20_{1-447}$ mutants that were produced by substituting one amino acid from $PH20_{1-447}$, and the '758 patent "provides test results for 5,917 mutants." Ex. 1003 ¶ 103. Dr. Hecht states that there are 2,516 "active mutants" listed in Table 3, but "the number of 'inactive mutants' listed in Table 5 does not match the number of tested inactive mutants (<20% activity) listed in Table 10 (*i.e.*, 3,368 vs. 3,380)." *Id.* ¶ 104. Dr. Hecht calculates that based on the data in the '758 patent, "57.1% were inactive, and 29.4% others had activity <100%." *Id.* ¶ 105. Dr. Hecht states the '758 patent "does not identify any ***mutated*** PH20 polypeptides that were effective when used in a contraceptive vaccine." *Id.* ¶ 113 (emphasis added).

Dr. Petsko states that "[t]he '758 patent provides a comprehensive and systematic analysis of each position on PH20, achieved through large-scale

mutagenesis and enzymatic activity testing of thousands of variants, with up to 18 mutations per position." Ex. 2070 ¶ 44. Dr. Petsko states:

> The patent data show, for each of the 447 positions in SEQ ID NO: 3, the tolerance of each position to substitution. The data show which positions are critical to activity, which are generally intolerant in that they permit only very limited substitution, and which are generally tolerant in that they permit a broad range of substitutions. The data also identify tolerant positions that retain activity when different types of residues are substituted (*e.g.,* negatively charged, positively charged, large, small, hydrophobic, hydrophilic).

Id. ¶ 54. Dr. Petsko states "[i]n addition to providing data on 5847 single substitution variants, the patent also provides proof of principle for several multiply modified PH20s, including N47A/N131A, N47A/N219A, N131A/N219A and N47A/N131A/N219A, which were shown to be active." *Id.* ¶ 57.

Dr. Simpson states that the "patent provides a structure-function map of PH20 that informs a POSA, position by position, which residues are invariant, which tolerate little change, and which are amenable to substitution." Ex. 2068 ¶ 373 (citing Ex. 2070 (Petsko Decl.) ¶¶ 44, 54–56, 233–390). Dr. Simpson states:

> The inventors provide experimental data for exemplary L317A, L317I, L317K, L317M, L317Q, and L317R variants in the patent. . . . [T]he patent also teaches the activity levels for various PH20 polypeptide lengths (*i.e.*, C-terminal truncation variants) recited in the claims. Given the breadth of experimental data establishing a structure-function map of PH20, POSAs would not have required further working examples of every possible sub-variant to make and use the claimed sub-variants.

Id. ¶ 377.

Dr. Cherr and Dr. Moon identify no working examples of PH20 functioning as a contraceptive in the '758 patent. *See generally* Ex. 2072; Ex. 2074.

Based on the evidence of record, we find that the Specification of the '758 patent includes four working examples of "modified PH20 polypeptides" within the scope of the challenged claims, i.e., polypeptides corresponding to SEQ ID NOs: 3, 7, or 32–66 with a single substitution (A, I, K, M, Q, or R) at position 317. All six of those variants were shown to have hyaluronidase activity. Ex. 1001, 251:62–251:9 (entries in Table 9 disclosing active mutants with a L317 substitution).

The '758 patent also discloses data for most of the other modified polypeptides having a single substitution at one position in PH20,[19] classifying such mutants as either "inactive" or "active," and for the latter, disclosing data showing their activity relative to the unmodified protein. Ex. 1003 ¶¶ 103–105 (referring to Tables 8–10 in the '758 patent). This evidence shows that more than half of the single substitution variants tested

[19]Dr. Hecht observes that the '758 patent provides no data for 836 of the 6,753 possible single substitution mutants listed in Table 8. Ex. 1003 ¶ 103. Dr. Petsko does not disagree and apparently excluded them from his positional analysis. See Ex. 2070 ¶ 264 n.19 ("I understand there are additional substitutions in Table 8 that are not identified in Table 9 or 10 . . . it is not possible to tell why they were not included in either Table. Accordingly, I do not consider them in my analysis."). Accordingly, while it is true that the '758 patent provides data for most of these single substitution PH20 mutants, we disagree with Patent Owner to the extent its arguments suggest that data is "comprehensive" for all such mutants. See, e.g., PO Resp. 15 (characterizing the patent disclosure as "a comprehensive and systematic analysis of each and every position within the primary structure of PH20")).

in the '758 patent's working examples resulted in what the Specification describes as "inactive mutants." Ex. 1003 ¶ 105; *cf* Ex. 2070 ¶¶ 263–274 (Dr. Petsko tabulating data by position and noting by that measure "about 48% of positions in PH20 are generally intolerant of substitution"). This suggests there is substantial variability in the activity resulting from just a single modification to one of the residues in SEQ ID NO:3 (and SEQ ID Nos: 7 or 32–66). Patent Owner's experts also refer to a handful of examples of multiply-modified PH polypeptides disclosed in the '457 publication. *See, e.g.*, Ex. 2068 ¶¶ 189–192, 321. But none of these contain a substitution at position 317.

Finally, to the extent Patent Owner contends that a POSA could use the recited modified PH20 polypeptides as antigens in a contraceptive vaccine, we note that none of the working examples in the '758 patent relate to such a use. *See supra* Section II.C.6.b.2

e) Amount of Direction or Guidance Presented

The '758 patent states that "one or more modified PH20 polypeptides are tested for a desired activity or property, such as increased stability." Ex. 1001, 128:11–14. The '758 patent states regarding processes to make mutations in hyaluronidase enzymes such as PH20 that:

> Libraries or collections of modified hyaluronan-degrading enzymes can be screened. Hyaluronan-degrading enzymes can be modified by any process known to one of skill in the art that can alter the structure of a protein. Examples of modifications include replacement, addition, and deletion of one or more amino acids of the protein to form libraries or collections of modified hyaluronan-degrading enzymes. It is within the level of one of skill in the art to generate modified or variant proteins for use in the methods herein. Methods of

> mutagenesis are well known in the art . . . . The mutations can be made rationally or randomly.

Id. at 129:26–51. The '758 patent states regarding testing the resultant mutations that:

> For purposes of selecting or identifying a modified hyaluronan-degrading enzyme that exhibits stability or increased stability under the denaturation condition, activity can be compared to activity of the modified hyaluronan-degrading enzyme in the absence of the denaturation condition and/or activity of the corresponding unmodified hyaluronan-degrading enzyme in the presence of the denaturation condition.

Id. at 130:26–33. The '758 patent states "[c]ritical residues can be identified because, when mutated, a normal activity of the protein is ablated or reduced. For example, critical residues can be identified that, when mutated in a hyaluronan-degrading enzyme, exhibit reduced or ablated hyaluronidase activity." *Id.* at 135:14–18. The '758 patent states that "[p]roteins, such as modified PH20 polypeptides, can be purified using standard protein purification techniques known in the art." *Id.* at 145:18–20.

The '758 patent states: "[d]ue to the role of PH20 in fertilization, PH20 can be used as an antigen for immunocontraception." *Id.* at 72:63–65. The '758 patent states "[i]mmunization with PH20 has been shown to be an effective contraceptive in male guinea pigs . . . . It also has been shown to be an effective contraceptive in female guinea pigs." *Id.* at 187:51–55.

Dr. Hecht states that the '758 patent "uses the 40% activity threshold to classify a mutant as an 'active mutant'" and that "'inactive mutants' are mutants with 20% or less of the activity of unmodified PH20." Ex. 1003 ¶¶ 100–101. Dr. Hecht states that the data in the '758 patent shows "most of the single-replacement $PH20_{1-447}$ mutants [that were tested] exhibited less

activity than the unmodified $PH20_{1-447}$ (*i.e.*, 57.1% were inactive, and 29.4% others had activity <100%)." *Id.* ¶ 105.

Dr. Hecht states the '758 patent

> does not identify any ***mutated*** PH20 proteins that were shown to be effective in contraceptive vaccines. . . . It also does not provide guidance regarding how to identify candidate inactive PH20 mutants that may be useful as contraceptive vaccines (such as by identifying common structural or functional characteristics shared by such inactive mutants).

Id. ¶ 113 (emphasis added). Dr. Hecht states "the data for testing the 409 mutants reported in Tables 11 and 12 [of the '758 patent] does not provide any meaningful guidance to a skilled artisan about the types of mutations that would improve the stability of PH20 polypeptides generally, or for the $PH20_{1-447}$ form specifically." *Id.* ¶ 76. Dr. Hecht states that the '758 patent

> identifies no examples of PH20 polypeptides with multiple amino acid substitutions at different positions (*i.e.*, specific amino acids being inserted into two or more different positions of the same PH20 polypeptide) that rendered active proteins. This appears to be the case because no such multiply-modified PH20 polypeptides appear to have actually been made or tested.

Id. ¶ 172. Dr. Hecht characterizes the disclosure of the '758 patent as "best described as a research plan, as it generally outlines the types of steps one might take to carry out a mutagenesis and screening research program." *Id.* ¶ 173.

In deposition, Dr. Hecht stated: "if you're trying to take a protein -- this protein, PH20 -- and you're planning to make 10 mutations, in many cases even having the data here would not allow you to predict whether that protein would be active." Ex. 2076, 264:7–12. Dr. Hecht stated "the data in these tables is not going to always solve your problems if you're attempting to make 10 changes. You can get into a situation where two changes give

rise to a cooperative result, which means they're not just the additive sum of the two." *Id.* at 270:7–12.

Dr. Simpson states that the "specification provides the POSA detailed information for literally every position in the protein, so the POSA can proceed position by position, or region by region, making the desired changes, depending on the POSA's goals." Ex. 2068 ¶ 375.

In deposition, Dr. Simpson stated

> this patent discloses an enormous amount of data that help them beyond what was published in the literature at the time, which was the sequence, the sequence alignment to other hyaluronidases for PH20, as well as the knowledge of where it can be truncated to make it a soluble polypeptide, the fact that it retained activity as a soluble PH20 polypeptide.
>
> And now, in addition, mutagenesis at every single residue of the polypeptide that gives data on whether or not that single substitution remained active.

Ex. 1130, 97:16–98:2.

Dr. Petsko states "[w]ith the '758 patent in hand, the POSA knows what positions tolerate substitution and which do not. The POSA [is going to] use that information to obtain modified PH20 polypeptides with the desired properties. The POSA would then make and test the desired polypeptide." Ex. 2070 ¶ 348. Dr. Petsko states a "POSA seeking to make a modified PH20 with the '758 patent in hand would not make a randomly generated combinatorial library of billions of sequences that happen to be at least 91% identical to SEQ ID NO: 3 and then screen it for activity, because it makes no sense to do so." *Id.* ¶ 347. Dr. Petsko states that the

> patent provides valuable data for identifying potential rescue mutations. To determine likely candidates for rescue mutations, a POSA would have examined the PH20 model to determine why activity was lost for a particular substitution. If

> the interactions that were lost can be replaced by simultaneously making another substitution (*i.e.*, a "rescue mutation"), then activity may be restored.

Id. ¶ 376.

In deposition, when asked whether "the patent provides examples of particular combinations of mutations that are correlated to PH20 proteins with desired properties such as increased activity or increased stability?", Dr. Petsko stated:

> The main combinations referred to have to do with the glycosylation. I don't remember that any of those increased the activity. I don't know if the stability was measured. Solubility of those can [a]ffect -- I think that might have been looked at but I don't remember that either. So no, I don't think so.

Ex. 1131, 110:22–111:8.

Dr. Naismith states that

> the common disclosure does not explain how any of the experimental results reported in the common disclosure relate to any of the structural observations reported in the Stern, Markovic-Housley, Chao or Zhang publications. It also does not tell a POSA how to . . . use those findings in combination with the mutagenesis data when designing modified PH20 polypeptides to preserve the unique α/β barrel motif or other structural features in the tertiary structure of the wild-type PH20 protein.

Ex. 1133 ¶ 151. Dr. Naismith states: "Dr. Petsko's view of what a POSA would do directly contradicts the instructions of the common disclosure. The ***only*** description in the common disclosure for producing PH20 polypeptides with multiple substitutions is an iterative, directed evolution technique." *Id.* ¶ 204 (citing Ex. 1003 ¶¶ 173–178; Ex. 1026, 141:30–34, 150:1–26). Dr. Naismith states that "the common disclosure leaves POSAs no practical alternative to the iterative mutagenesis approach that Dr. Petsko

claims a POSA would avoid, notwithstanding that it necessarily entails generating and screening enormous numbers of largely nonfunctional variants." *Id.* ¶ 205 (citing Ex. 1003 ¶¶ 181–185).

Dr. Naismith states that there "is no technique or passage in the common disclosure that could provide a basis for Dr. Petsko's theory that a POSA could reliably identify rescue mutations to restore activity in inactive modified PH20 mutants." *Id.* ¶ 210.

In deposition, Dr. Naismith stated that "the data in the patent show that single site mutations are perturbing the active site. Most of them perturb the structure function relationship at the active site. So we know that they are having some, I think Dr. Petsko's phrase was, 'action at a distance.'" Ex. 2301, 110:8–14. Dr. Naismith states that the "patent doesn't give any teaching about combining multi-mutations at all." *Id.* at 133:8–9.

Based on the evidence of record, we find that a POSA would have significant guidance on synthesis and expression of modified PH20 polypeptides, including most (but not all) of the single substitution mutants within the native PH20 structure.

However, the evidence also shows that the '758 patent provides very limited guidance regarding effective methods to identify which of the immense number of distinct polynucleotides having both the recited position 317 substitution and other modifications (i.e., multiply-modified polypeptides) are likely to have activity other than actually making and testing them. Ex. 1003 ¶¶ 172–180; Ex. 1133 ¶¶ 203–204. To the extent computational tools and modeling might have been used, along with the data in the '758 patent, to help guide the discovery of specific multiply-modified polypeptides, we credit Petitioner's evidence that the tools available to a

POSA in the 2011–2012 timeframe did not allow for accurate predictions for 5 or more mutations. *See infra* Section II.D.6.g

Finally, to the extent Patent Owner contends the ability to provide a contraceptive effect is relevant, we find that there is essentially no guidance, either in the '758 patent or the prior art of record, demonstrating which, if any, of the possible modified polypeptides are useful for providing such an effect.

f) Quantity of Experimentation

Dr. Hecht states

> while the PH20 protein structure models Dr. Park used provided reliable insights when modeling the change of a single residue at a position where the model was, they cannot provide reliable insights when the modeled sequence incorporates many (*e.g.*, more than ~5) substitutions not found in a naturally occurring protein. That is because (i) if the modeled sequence incorporates multiple changes, it no longer has validity as a naturally occurring sequence, and (ii) the changes significantly diminish the reliability of other positions of the model used to assess the change because they are no longer based on the structural positioning of residues within the template structure used to generate the model. Thus, a skilled artisan would have had to discover which combinations of substitutions to the PH20 protein would result in mutants that do exhibit hyaluronidase activity by making and testing all of them, ***an impossibly large undertaking***.

Ex. 1003 ¶ 158 (emphasis added). Dr. Hecht states that "the single-replacement $PH20_{1-447}$ polypeptides reported in the common disclosure are not representative of all the types of mutated $PH20_{1-447}$ polypeptides that have sets a particular substitution at position 317 and sets of between 1 and 41 *additional* substitutions at any of hundreds of positions within the PH20 protein." *Id.* ¶ 159.

Dr. Hecht states that "[m]aking and identifying all of the multiple-modified PH20 polypeptides that are within the immense set of polypeptides (between 10^{59} and 10^{112} distinct mutants) defined by the claims' sequence identity parameters would require not only undue experimentation, it likely is impossible." *Id.* ¶ 170. Dr. Hecht states that the directed evolution methods of the '758 patent are "the quintessential 'make and test' trial and error technique. By definition, the scientist carrying out a directed evolution protocol does not know which of the potentially trillions of possible mutants might incorporate a substitution that causes the protein to exhibit an improved characteristic." *Id.* ¶ 186.

Dr. Simpson counters that "a POSA could have used the patent data to generate multiply modified PH20s with combinations of 5, 10, 15, or more substitutions. . . . The POSA would have expected those proteins to be active in view of the disclosure in the patent." Ex. 2068 ¶ 387. Dr. Simpson also states that a "POSA seeking to generate the claimed modified PH20 variants and sub-variants actually using the data in the patent (*i.e.*, without randomly screening large libraries) could have done so." *Id.* ¶ 389.

In deposition, in response to a question of "how would you identify which positions were important or necessary for folding of the protein?", Dr. Simpson explained that

> [b]y looking at the alignments, there are a number of invariant residues. A knowledge of which invariant residues are the active site residues allows us to exclude those from consideration as active site residues. There are a number of other invariant residues using the structure that can be deduced to be responsible for substrate docking. Those may or may not be folding determinants, but additional residues that don't appear to be directly in contact with the substrate and are not directly defined

> as active site residues within 5 angstroms of a docked substrate are likely candidates for structural determinants.

Ex. 1130, 76:19–77:18. When asked "[d]id you perform that analysis you just described of comparing the possible sequences to some smaller number of them that match the structure of the model of PH20?", Dr. Simpson stated: "I need to say that no POSA would start with the theoretical maximum number of potential sequence variants as a starting point for making a comparative analysis of what amino acids would retain activity in a PH20 polypeptide." *Id.* at 93:13–24.

Dr. Petsko stated that "[a]s of 2012, the structure for PH20 had not been solved. As Dr. Park explains in his Declaration, however, the 'absence of an experimentally determined structure for a protein does not preclude the use of structure-based modeling methods.' EX1004, ¶ 36. That is because the PH20 structure can be modeled." Ex. 2070 ¶ 117. Dr. Petsko states:

> A POSA seeking to make a modified PH20 with the '758 patent in hand would not make a randomly generated combinatorial library of billions of sequences that happen to be at least 91% identical to SEQ ID NO: 3 and then screen it for activity, because it makes no sense to do so. It is difficult to imagine why anyone would do such a thing. If the sequences truly are random, then it is likely that a substantial number would include substantial modifications to residues known to be invariant because they are involved in catalysis, the active site, or in protein structure. . . . [T]hanks to the '758 patent, the POSA has a much more sensible strategy.

Id. ¶ 347. However, Dr. Petsko does not identify any teaching in the '758 patent that suggests the use of molecular modeling. *See generally id.*

In deposition, when asked: "Is it possible to experimentally determine which ones are properly folded and enzymatically active in 2011 or 2012?", Dr. Petsko stated: "Not from experimenting on the entire ensemble."

Ex. 1131, 64:12–17. When asked whether "a person of ordinary skill in the art in the 2011-2012 timeframe would be able to predict the change to a protein's net free energy of stabilization associated with a set of 10 or 15 or 20 mutations?", Dr. Petsko answered "No. They would not be able to predict the number. They would be able to get a sense of whether those were likely to be destabilizing or not." *Id.* at 102:1–9.

Dr. Naismith states: "I agree with Dr. Hecht and Dr. Park that after about 5 mutations, a POSA could no longer predict enzyme behavior by simple linear combinations of single site mutations." Ex. 1133 ¶ 258. Dr. Naismith states "[t]hat is also the practical limit for screening enzyme libraries in the 2012 timeframe. Even using the most sophisticated screening technologies, the largest library that could be screened was around ~10^9 proteins." *Id.*

After reviewing the record, we find the evidence and expert testimony offered by Petitioner to be more persuasive than the competing evidence from Patent Owner and its experts. That is, the record shows that an ordinary artisan would have been able to align and computer model the PH20 sequence in combination with other known hyaluronidase sequences to identify amino acids implicated in structure and function. This could provide some measure of guidance to identify polypeptides having both multiple modifications and activity, but in the 2011–2012 timeframe, the computerized techniques for making such predictions quickly became unreliable as more modifications were introduced. Ex. 1004 ¶¶ 155–164; Ex. 1003 ¶¶ 49, 50, 217; Ex. 1133 ¶¶ 123–133, 260–263, 268, 270–274, 281–284.

The only "methods for identifying a modified or variant hyaluronan-degrading enzyme, such as a . . . modified PH20 polypeptide, that exhibits an altered activity of property compared to an unmodified hyaluronan-degrading enzyme" disclosed in the '758 patent follow directed evolution approaches. Ex. 1001, 126:59–63; Ex. 1003 ¶¶ 173–175. In such approaches, libraries of modified polypeptides are prepared by random or site-directed mutagenesis and screened for activity. Multiply-modified mutants can be identified by iterative screening, e.g., introducing single amino acid changes to create a first library, screening it to identify mutants that exhibit a particular property, and then introducing additional modifications to those mutants to create a second library for screening. Ex. 1001, 135:33–137:10; Ex. 1003 ¶¶ 174–178. As Petitioner's experts credibly explain, the problem with such approaches is scale—meaning it would require making and testing very large amounts of multiply-modified mutants to identify those within the recited sequence space that exhibit hyaluronidase activity. Ex. 1003 ¶¶ 179–189; *see* Ex. 1133 ¶¶ 204–205 ("the common disclosure leaves POSAs no practical alternative to the iterative mutagenesis approach that Dr. Petsko claims a POSA would avoid, notwithstanding that it necessarily entails generating and screening enormous numbers of largely nonfunctional variants").

The experts largely agree that it would not have been possible to make and test all of the polypeptides within the sequence space of the challenged claims for hyaluronidase activity. *See, e.g.*, Ex. 1003 ¶ 189. Both Dr. Simpson and Dr. Petsko acknowledge that an ordinary artisan would not consider it possible to perform testing on the complete claimed set of PH20 mutations recited in claim 1, suggesting that the quantity of experimentation

exceeded that feasible or possible at the time of invention. *See* Ex. 1130, 93:13–24; Ex. 1131, 64:12–17. And Dr. Naismith confirmed that neither the computer analysis nor screening technologies available in the 2012 timeframe would have been capable of testing the full scope of the challenged claims. Ex. 1133 ¶ 258.

We are unpersuaded by Patent Owner's attempt to sidestep the directed evolution experiments taught in the '758 patent through its expert's testimony that the experimental data in the Specification provides a "structure-function map of PH20" that teaches "which positions are tolerant and intolerant of substitution, including what types of changes are tolerated and not tolerated" such that a POSA could pick and choose modifications to combine with an expectation that the resulting polypeptide would have activity. *See, e.g.*, Ex. 2068 ¶¶ 379–384; PO Sur-reply 7–13 (urging the "patent's disclosure provides a granular structure/function correlation" a POSA could use to "visualize" multiply-modified species and predict activity). First, as Dr. Naismith explains, the predictive analyses and residue-selection strategies asserted by Patent Owner's experts are not taught, and in some respects run contrary to the teachings, in the '758 patent. Ex. 1133 ¶¶ 199–222. Second, Dr. Naismith also identifies a number of errors in Dr. Petsko's positional tolerance table that undermine the credibility of Patent Owner's experts' analysis in this regard. *Id.* ¶¶ 238–242.

Third, we credit Dr. Naismith's substantive criticisms of Dr. Petsko and Dr. Simpson's opinions that the '758 patent data provides a "functional

map"[20] that would allow a POSA to predict which multiply-modified mutants would have hyaluronidase activity without actually making and testing them. *See* Ex. 1133 ¶ 232 (summarizing points of disagreement). In particular, we credit Petitioner's showing that the effects observed from single amino acid modifications are not necessarily additive when combined in the same polypeptide and that a POSA could not reliably identify "rescue mutations" (i.e., mutations that restore activity lost from deleterious ones) from the data in the '758 patent. Ex. 1133 ¶¶ 210–211, 252–269; *see also* Ex. 1003 ¶¶ 55–61, 140–141; Ex. 1004 ¶¶ 168–169. Patent Owner suggests such evidence can be overlooked because instances of epistasis are "rare" and an inactive PH20 polypeptide "will stay inactive . . . absent intentional 'rescue' mutations." *See* PO Sur-reply 12–16. But the claims encompass far more than combinations of just two substitutions and even Dr. Petsko concedes there are "billions" of sequences within the recited sequence space that will not properly fold (Ex. 2070 ¶ 347). *See also* Ex. 1133 ¶ 236 ("While some [residues critical to protein structure] can be predicted (*e.g.*, highly conserved positions), many others cannot without experimentation"). "In other words, the functional and other characteristics of a PH20 protein that incorporates a first single amino acid substitution [from the '758 patent data] cannot be extrapolated to modified PH20 polypeptides that incorporate the myriad sets of combinations of multiple substitutions in addition to the first." Ex. 1003 ¶ 140. Accordingly, we find Petitioner's position more persuasive than Patent Owner's competing position and evidence.

[20] *See, e.g.*, Ex. 2070 ¶ 44.

We find the facts here similar to those in *Idenix Pharmaceuticals LLC*, 941 F.3d at 1156 where, in a genus of billions, the "key enablement question is whether a person of ordinary skill in the art would know, without undue experimentation, which [species] would be effective." *Idenix* states that because of the "many thousands of [species] which need to be screened for . . . efficacy, the quantity of experimentation needed is large and weighs in favor of non-enablement." *Id.* at 1159. Here, where the number is not thousands, but at least some representative number of the modified PH20 polypeptides within the potential genus of at least 10^{59} distinct polypeptides contemplated by the challenged claims, the quantity of experimentation would be many orders of magnitude more than that needed in *Idenix*.

We find the evidence demonstrates that a very large amount of experimentation would be necessary to enable the scope of the claims of the '758 patent.

g) Predictability of the Art

Dr. Hecht states that the

> effects caused by one substitution in a protein like PH20 thus cannot predict the effects on a modified form of that protein that incorporates 5, 10, 15 (or more) substitutions. A skilled artisan would not view the first, single amino acid substituted PH20 [as] representative of all modified PH20 proteins having that one substitution, along with 5, 10 or 15 or more additional substitutions.

Ex. 1003 ¶ 61. Dr. Hecht states, citing the '429 patent, that the "varying effects of changing residues in the Hyal-EGF region of PH20 show that a skilled artisan's belief that changes in this region would be unpredictable were warranted[,] and would be more so if multiple changes were made concurrently." *Id.* ¶ 96. Dr. Hecht states that the "effects of these myriad

sets of combinations of multiple substitutions within PH20 could not have been predicted by a skilled artisan in the 2011 timeframe using the tools that were available then." *Id.* ¶ 158. Dr. Hecht notes that "[a]nother problem caused by the use in the claims of sequence identity language to define the sets of proteins is that it captures many multiply-modified PH20 polypeptides with changes that common disclosures says are deleterious or eliminate hyaluronidase activity in PH20 enzymes." *Id.* ¶ 160.

Dr. Hecht states that the "skilled artisan also could not predict whether any combinations of up to 9 or up to 2 additional (or more) substitutions could be made anywhere in the $PH20_{1-419}$ sequence or comparably truncated PH20 polypeptide that would restore hyaluronidase activity to an inactive L317Q or L317K containing $PH20_{1-419}$ mutant." *Id.* ¶ 168. Dr. Hecht continues:

> In other words, the common disclosure not only does not help the skilled artisan identify which of the trillions of possible PH20 polypeptides of varying length with 2 to 42 substitutions have hyaluronidase activity; to practice the full scope of the claims it requires the skilled artisan to ignore what little guidance is in the specification about single-substitutions and truncations that render PH20 polypeptides inactive.

Id. ¶ 169. Dr. Hecht states that the artisan following the '758 patent's "iterative mutagenesis and screening research plan cannot know in advance of conducting multiple rounds of experiments, whether modified PH20 polypeptides will be produced that have sets of 5, 10, 15, or more substitutions and retain sufficient activity that will be selected for the next round of the process." *Id.* ¶ 184. Dr. Hecht's testimony as supported by record evidence demonstrates that it is highly unpredictable which

polypeptides would have hyaluronidase or contraceptive activity. *See, e.g.*, *id.* ¶¶ 140, 144, 155–172.

Dr. Park states:

> In 2011, a second or third substitution could possibly be considered, but modeling multiple substitutions is more challenging and predictions can quickly become unreliable. This is especially true if the mutated residues are close to each other, either in sequence or in space, so that they interact with each other. That is because one needs to model interaction between substituted residues as well as interaction between a substituted residue with constant neighbors. Because this is difficult to visualize, it becomes necessary to model individual combinations through homology modeling, which becomes combinatorial[ly] intractable.

Ex. 1004 ¶ 158. Dr. Park states "a skilled artisan in 2011 could not have used SWISS-MODEL to reliably predict the effects on the structure of a modified PH20 polypeptide of many substitutions (*e.g.*, 5 or more) in the PH20 sequence, if each position is allowed to vary independently to one of several amino acids." *Id.* ¶ 159.

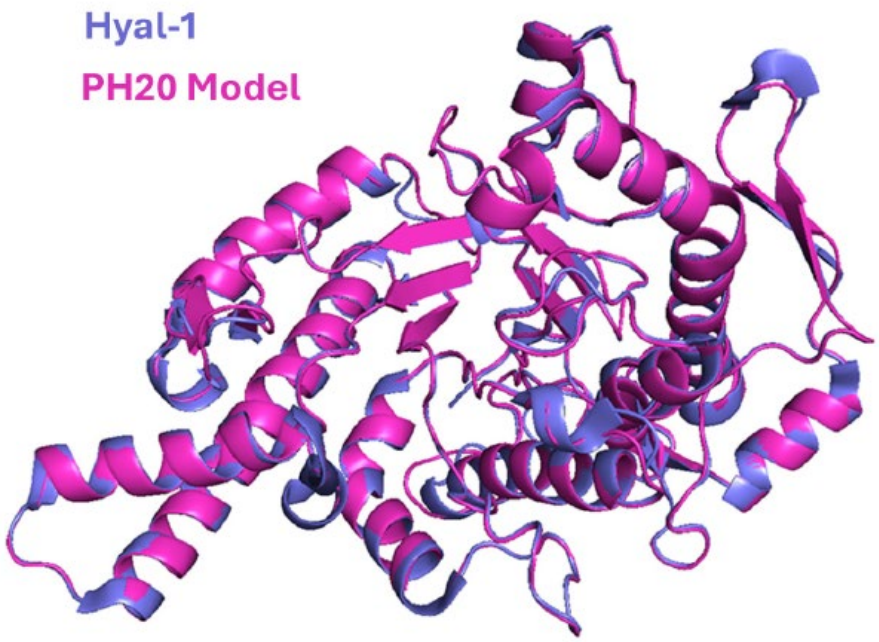
In deposition, Dr. Park, addressing single mutations, stated: "The problem is when you're looking at one substitution, there are only so many interactions that a single amino acid can make, and those are relatively straightforward to discern for an expert." Ex. 2077, 198:12–16. Dr. Park then stated that for multiple mutations, however,

> if those substitutions happen to be very close to each other, what happens is now suddenly you have to deal with many more possible changes in the interactions, because the individual substitutions would now alter their interactions with their neighbor, and there would be interactions between them as well. So now that results in both positive and negative interactions, all of which need to be tracked and estimated. Unfortunately, a person viewing the structure would not be able

> to differentiate many of these subtle changes, especially if there are multiple mutations nearby.

Id. at 199:7–19. Dr. Park stated regarding multiple mutations that "[a]s you introduce more and more mutations, the number of possible favorable and unfavorable interactions increases exponentially, and can quickly overwhelm a person's ability to evaluate them." *Id.* at 202:9–13. Dr. Park stated that "SWISS-MODEL doesn't put a number on – it doesn't tell you anything about the energetics of those substitutions. . . . It may be a horrendous combination of mutations. SWISS-MODEL would not know the difference between that and the best sequence." *Id.* at 204:19–205:5. Dr. Park stated that the inability to model multiple mutations "was not a solved problem back in 2011. I don't think it's a solved problem as of today." *Id.* at 212:17–19.

Dr. Petsko states that "Hyal-1 and PH20 also share a common alpha-beta barrel fold, with bee venom hyaluronidase adopting a similar fold. These three proteins are considered homologous with high sequence identity (30-40%)." Ex. 2070 ¶¶ 126–127. Dr. Petsko presents the figure reproduced below:



The figure above shows the PH20 model superimposed on the Hyal-1 structure. *Id.* ¶ 132. Dr. Petsko states: "When the PH20 model is superimposed on the Hyal-1 structure in PyMOL, as in the figure [above], it is evident that both proteins adopt essentially the same alpha-beta barrel fold." *Id.* Dr. Petsko states that "PH20, Hyal-1 and bee venom hyaluronidase share a common mechanism of action in that they all cleave HA through the same chemical reaction." *Id.* ¶ 135. Dr. Petsko states that another "common structural feature shared by Hyal-1 and PH20 is the EGF motif. . . . [T]he EGF region is required for enzymatic activity in both proteins" but also states that "bee venom hyaluronidase does not include an EGF domain at all." *Id.* ¶¶ 207, 210. Dr. Petsko states that "PH20, Hyal-1 and bee venom hyaluronidase all achieve the function of cleaving HA using a common structure—the active site in all three proteins is a long groove and the same critical residues (oriented in about the same positions) catalyze the reaction in all three proteins." *Id.* ¶ 139.

Dr. Petsko states that

> Zhang, on which Dr. Simpson is an author, contains mutagenesis data and provides insight regarding Hyal-1 residues required for activity. . . . Those data can be mapped onto the Hyal-1 structure and PH20 model. . . . And the POSA seeking to evaluate structure/function correlations and common structural features among enzymatically active hyaluronidases in 2012 would have performed this analysis.

Id. ¶ 167. Dr. Petsko states, as shown by his analysis, that

> POSAs expect that homologous proteins with high sequence similarity adopt the same fold because they share critical residues that adopt essentially the same positions and interactions (which in turn is what allows them to adopt the same fold). Because this principle holds for 40% identical homologous (but different) hyaluronidases, it certainly applies for 91% identical (properly folded) PH20 variants.

Id. ¶ 206.

In deposition, Dr. Petsko stated, "just because a mutation has no activity or low activity doesn't mean it has disrupted the fold." Ex. 1131, 79:7–9. Dr. Petsko stated that

> the most common things are more complicated and more subtle. They involve, for example, action at a distance. You could have a mutation that changes the electrostatic potential of the protein at the active site even though it's not in the active site, for example. But it would still have exactly the same fold.

Id. at 79:15–21. When asked whether a POSA in 2012 "would be able to predict the change to a protein's net free energy of stabilization associated with a set of 10 or 15 or 20 mutations?", Dr. Petsko answered "No. They would not be able to predict the number. They would be able to get a sense of whether those were likely to be destabilizing or not." *Id.* at 102:1–9. Despite that statement, when asked whether "you would be able to predict whether that mutated 15 or 20 residue-mutated PH20 will exhibit the activity

that you are hoping to get?", Dr. Petsko answered "My opinion is that you could do so." *Id.* at 111:9–16.

However, when asked "do you think that in 2011 or 2012, a POSA using only a homology model could have predicted the effect of making five changes that are close together in a -- in the PH20 protein?", Dr. Petsko stated: "I cannot answer that without knowing which five changes and where they are. . . . It will be context dependent to a large extent." *Id.* at 207:15–24.

Dr. Simpson states "in my opinion the specification gives a POSA the tools to make and use active (and inactive) PH20 variants and sub-variants and to distinguish between active and inactive PH20 variants using routine techniques." Ex. 2068 ¶ 378. Dr. Simpson states that the "patent data allows POSAs to reasonably predict what changes will maintain activity, abrogate activity, reduce activity, or improve activity." *Id.* ¶ 380 (citing Ex. 2070 ¶¶ 44, 54–56, 233–390). Dr. Simpson states that the "immense disclosure in the specification makes generating and using the modified PH20 variants and sub-variants in the claims predictable." *Id.* ¶ 384.

Dr. Simpson states that

> a POSA could have used the patent data to generate multiply modified PH20s with combinations of 5, 10, 15 or more substitutions. In fact, Dr. Petsko provided examples of such modified PH20s, including chimpanzee, gibbon and orangutan PH20s with the L317Q substitution. EX2070, ¶¶413-431. The POSA would have expected those proteins to be active in view of the disclosure in the patent.

Id. ¶ 387.

In deposition, Dr. Simpson states: "Given the amount of activity data and the amount of structural homology and the sequence information, you

would be able to predict the vast majority of activity structure, function relationships, for that family of modified PH20s." Ex. 1130, 100:5–9. But when asked about a specific mutation characterized in the Zhang paper (Ex. 1010), specifically, "is the result for the D129N mutation – that's not consistent with your hypothesis because it retained 5% of the activity. Right?", Dr. Simpson answered: "It isn't that it's inconsistent with our hypothesis. . . . But we did not actually expect, necessarily, that it would fully abolish activity." Ex. 1130, 130:23–131:20.

Dr. Naismith states:

> Dr. Petsko's textbook references Dr. Dobson's work and provides an illustration of the impact of even a single mutation to the structure and stability of a globular protein (*e.g.*, PH20). In this example, the single mutation does not prevent secretion of the globular protein but disrupts its stability to the degree that the original folded protein partially or completely unfolds in the extracellular environment.

Ex. 1133 ¶ 76 (citing Ex. 2164, 160 (Fig. 4-53)). Dr. Naismith states: "Dr. Petsko suggests a POSA would expect that if the L317Q substitution were introduced in three primate sequences, they would properly fold and be enzymatically active", however,

> [n]one of these proteins Dr. Petsko described were made or tested. It is important to note that they represent special cases. Dr. Petsko's experiment of introducing the L317Q change in chimp, orangutan or gibbon is simply introducing a single mutation into a naturally occurring sequence that has been shaped by evolution to stably fold and be active. Dr. Petsko's hypothetical mutants represent an infinitesimal portion of the patent's enclosed sequence space. There is no teaching in the patent or modelling software that would allow sets of 42 combined substitutions that differ by more than around five changes from a known stably folded active PH20 to be predictably active.

Id. ¶¶ 116–117 (citing Ex. 2070 ¶¶ 361–365, 413–421).

Dr. Naismith states: "Dr. Petsko's practical answer that a POSA would not have even tried to make modified PH20 polypeptides with more than about 5 modifications reflects the practical limitations of experimental and computational capabilities in the 2011-2012 timeframe for producing multiply modified PH20 polypeptides. I agree." *Id.* ¶ 124. Dr. Naismith states:

> If a POSA cannot accurately predict the effect of a set of mutations to a protein's free energy of stabilization (and particularly the overall magnitude of those effects), that person cannot predict whether that set of mutations will collectively increase, have no net effect on or decrease the stability of the folded protein (and if it folds). As Dr. Petsko's textbook explains, "the net free energy of stabilization of most folded proteins—the difference in free energy between the folded and unfolded states—is actually rather small, about 21-42 kJ/mole, or only about 10 times the average thermal energy available at physiological temperature." Changes that cause even modest reductions in the net free energy of stabilization of a modified PH20 polypeptide can slow or prevent folding or result in rapid unfolding of the protein after it has folded and/or been secreted.

Id. ¶ 129 (citing Ex. 2164, 26).

Dr. Naismith states that

> [t]he 2024 Chemistry Nobel Price Background paper that Dr. Hecht references in his declaration provides an accurate historical perspective on the capabilities of computational tools to accurately predict a protein's tertiary structure from its amino acid sequence. As that paper shows, those computational tools did not reach predictive accuracy levels comparable to experimental determination of structure until around 2019.

Id. ¶ 133 (citing Ex. 1027, 8).

Dr. Naismith states: "Many α/β barrel proteins are enzymes. In his textbook, Dr. Petsko estimated that ~10% of all enzymes share this protein

structural fold." *Id.* ¶ 139 (citing Ex. 2164, 38; Ex. 1143, 761). Dr. Naismith states that the "actual structural fold of each protein containing an α/β barrel motif may have considerably more structural size, diversity and complexity beyond what the term 'alpha-beta barrel' might suggest. Those structural differences also translate into functional diversity." *Id.* (citing Ex. 1142, 228).

Dr. Naismith states "[i]f Dr. Petsko is suggesting that positions 3 to 339 correspond to the α/β barrel motif in PH20, that would be misleading." *Id.* ¶ 162. Dr. Naismith states "[t]hat is because several loops in PH20 are much more extensive and contain additional and elongated secondary structural elements when compared to the canonical α/β barrel . . . . Similar observations were made by Chao (EX1006)." *Id.* (citing Ex. 1006, 6913).

Dr. Naismith states that "[s]everal individual mutants are classified as both 'active' and as 'inactive' mutants in the common disclosure (*e.g.*, mutants listed in both Tables 9 and 10)." *Id.* ¶ 239. Dr. Naismith states: "These double counted mutants create an ambiguity that cannot be resolved using the information only in the common disclosure. . . . A POSA would have found the classifications of these mutants to be unreliable and would not have used them in analyzing the tolerability of a position to change." *Id.* ¶ 241. Dr. Naismith states:

> The active/inactive classifications that are the foundation of Dr. Petsko's tolerance assessments do not differentiate reasons for loss of activity. For example, they do not differentiate between mutations that cause loss of activity between those that impair expression or secretion, induce aggregation, impair folding, or disrupt positioning of residues involved in catalysis, substrate binding or unknown biological functions. They also do not evaluate how the effects of individual substitutions change when combined—there is no investigation in the

> common disclosure of epistatic effects which manifest only when multiple residues are changed in one polypeptide. Narrowing the analysis to a smaller subset of positions that appear tolerant to single substitutions does not resolve these limitations.

Id. ¶ 276.

Based on the record as a whole, we again find the expert testimony and other evidence offered by Petitioner to be more persuasive than the competing evidence from Patent Owner and its experts. Patent Owner's experts identify four approaches that an ordinary artisan would have had available to identify PH20 polypeptides within the scope of claim 1 with hyaluronidase or contraceptive activity during the relevant time frame: sequence alignment, computer homology modeling, screening libraries both of randomly mutated PH20 polypeptides and site directed mutations of PH20 polypeptides. However, we are persuaded by Petitioner's experts and the other evidence Petitioner cites that none of these approaches individually or in combination would allow one to reasonably predict the effect of changes for the full scope of the challenged claims.

The '758 patent itself only discusses library screening and site directed mutation approaches. *See* Ex. 1001, 129:26–131:11. Both Petitioner's and Patent Owner's experts made statements that the library screening or site directed mutation at all positions would not be possible over the scope of claim 1. *See, e.g.*, Ex. 1003 ¶ 158; Ex. 1131, 64:12–17; Ex. 1133 ¶ 258. However, we are more persuaded by Petitioner's experts that none of the four approaches would reasonably address the full scope of claim 1. "[T]he specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023).

As to the use of computer homology modeling, we credit Petitioner's experts' testimony that, even with the data in the '758 patent in hand, the technology as of the 2011–2012 timeframe would not have been able to reliably predict the impact of more than about 5 changes to the PH20 protein on hyaluronidase activity. Ex. 1003 ¶¶ 159–160; Ex. 1004 ¶¶ 168–169; Ex. 1133 ¶¶ 125, 260–265, 323. That testimony is supported by the Scientific Background for the 2024 Chemistry Nobel Prize. *See, e.g.*, Ex. 1027, 7 ("Despite the progress outlined above, the average GDT score for the best *ab initio* predictions was stuck below 40% up until and including $CASP_{12}$ in 2016."); Ex. 1131, 207:15–24; Ex. 1003 ¶¶ 6, 58; Ex. 1004 ¶ 168. And even Dr. Petsko, when asked whether a homology model in 2012 could have predicted the effect of making five changes that are close together in the PH20 protein, was unable to refute Petitioner's experts' consistent testimony that such models at the time could not do so. *See* Ex. 1131, 207:15–24 ("I cannot answer that" because "[i]t will be context dependent to a large extent.").

As to sequence alignment, Chao provided an alignment of the human hyaluronidases that is reproduced below:

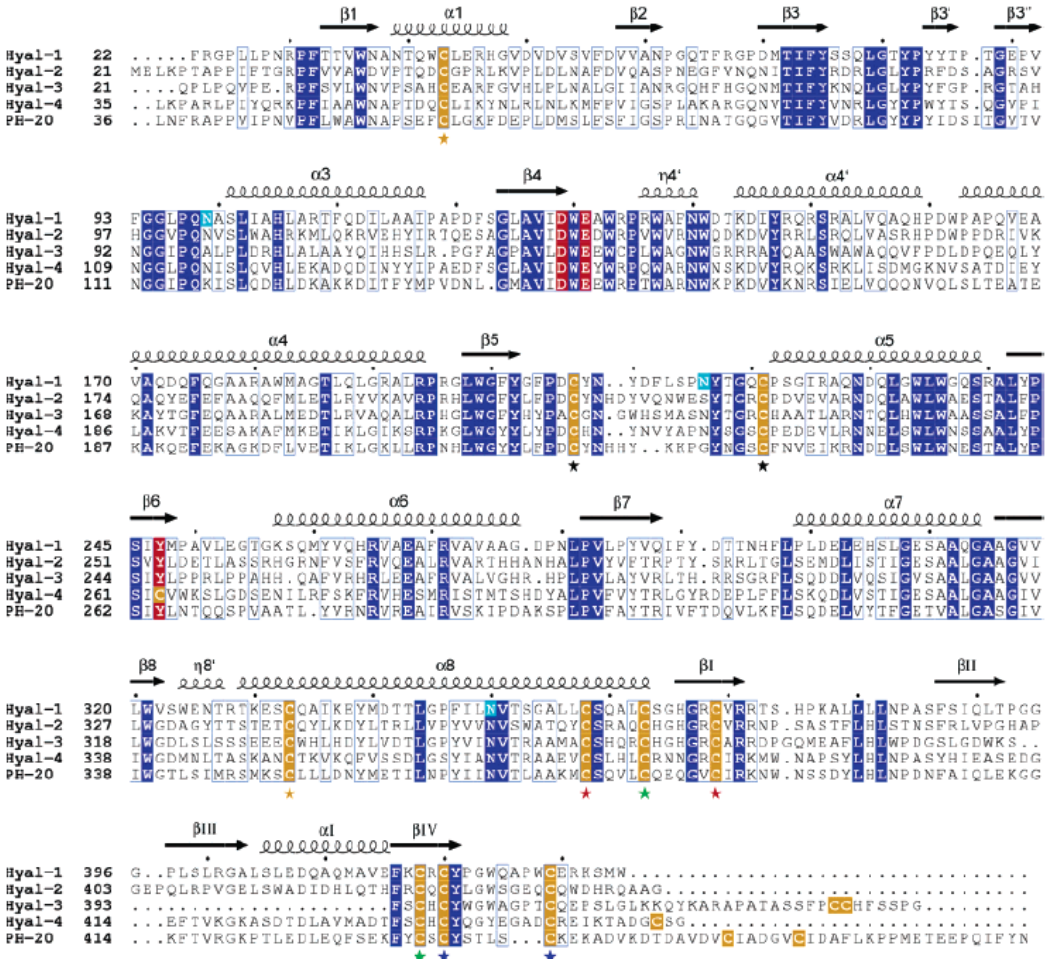


Figure 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagines residues are colored turquoise. Residues exhibiting conservative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

Ex. 1006, 6916. This alignment shows that only a small fraction of the alignment identifies amino acids that are invariant (in blue or red), and therefore the alignment information would not be sufficient to predictably identify which residues for the full scope of claim 1 would allow for mutation without loss of hyaluronidase or contraceptive activity.

Therefore, based on the evidence of record, we find that it is unpredictable which modified PH20 polypeptides within the scope of the claims of the '758 patent would retain hyaluronidase activity.

As for potential contraceptive use, nothing in the '758 patent nor the prior art suggests that it would have been predictable for a POSA to determine which, if any, of the modified PH20 polypeptides within the claimed sequence space might be useful for that purpose. *See supra* § II.C.6(2)(c).

7. Conclusion

We find that the balance of evidence supports a finding of undue experimentation. The claims are extremely broad and the "number of distinct peptides is extremely large by all accounts, ranging from 10^{59} to 10^{112}." Ex. 1004 ¶ 169. The skill in the art was relatively high. But while the prior art was developed in the field of hyaluronidases with alignments and projected three dimensional folding proposals (Ex. 1003 ¶ 81), the evidence also shows that structural modeling and other computational techniques were not yet reliable to predict the effect of multiple mutations. *See, e.g.*, Ex. 1027, 6–7. The '758 patent provides a significant number of working examples of single mutations, but provides essentially no examples of multiple mutations and no detailed approach to address how to reliably obtain multiply-mutated PH20 polypeptides having hyaluronidase activity. Ex. 1003 ¶¶ 103, 168–169.

The evidence discussed in our analysis of the quantity of experimentation and predictability factors demonstrates that undue experimentation would have been required to practice the full scope of the challenged claims. *See supra* Section II.D.6.f-g. Indeed, as noted above,

most of the experts acknowledge that actually making and testing the full scope of the potential genus of multiply-modified polypeptides would not be possible. *See, e.g.*, Ex. 1003 ¶¶ 186, 189; Ex. 1133 ¶ 258; Ex. 2070 ¶ 347; Ex. 1130, 93:13–24.

Lastly, while there appears to be some agreement that modeling might allow predictability for modifications with two or three amino acid changes, the record shows that the computational techniques available in December 2012, even when used in combination with the single substitution data in the '758 patent, could not be used to reasonably predict the effect of five or more amino acid changes on protein structure and activity. *See, e.g.*, Ex. 1003 ¶¶ 61, 140, 151–154, 158–164, 170; Ex. 1004 ¶¶ 168–169; Ex. 1133 ¶ 123.

To the extent Patent Owner contends the claims are not limited to polypeptides having hyaluronidase activity and that the recited polypeptides may also be used to provide a contraceptive effect, we find that identifying which, if any, modified polypeptides are useful for that purpose would also have required undue experimentation.[21] Again, while we acknowledge the expertise of Dr. Cherr and Dr. Moon, the only evidence of any efficacy of a PH20 polypeptide as a contraceptive vaccine was in guinea pigs and was an outlier from studies in other animals showing no such efficacy. *See supra* Section II.C.6.b.2. As explained above, a POSA at the time, would not have regarded the potential use of *modified* PH20 polypeptides as contraceptives to be a credible utility. *Id.* Even if the record did show that a *native* PH20

[21] To be clear, this is an alternative finding premised on Patent Owner's claim construction that we do not adopt because it is not supported by the intrinsic evidence. *See supra* Section II.B.

polypeptide could be used for this purpose, we credit Dr. Kelsoe's testimony explaining that a POSA would have needed to make and test *modified* PH20 polypeptides to determine if they could cause infertility over the competing testimony from Patent Owner's experts. *See* Ex. 1134 ¶¶ 70–118, 124. Thus, a POSA seeking to make and use the recited polypeptides as antigens in a contraceptive vaccine would still need to engage in undue experimentation to identify polypeptides suitable for that purpose.

Therefore, considering all of the *Wands* factors, we find that the totality of the evidence in the current record shows by a preponderance of the evidence that undue experimentation would have been required to enable the broad scope of the claims, and that the claims therefore fail to comply with the enablement requirement of 35 U.S.C. § 112(a).

E. Ground III - Obviousness

1. Principles of Law

The Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). In *KSR*, the Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art;[22] and (4) considering objective evidence indicating obviousness or non-obviousness. *KSR*, 550 U.S. at 406.

[22] *See supra* Section II.A.

2. Overview of the Asserted Prior Art

a) The '429 patent (Ex. 1005)

The '429 patent was filed on March 5, 2004, and issued on August 3, 2010. Ex. 1005, codes (22), (45). The '429 patent is drawn to "members of the soluble, neutral active Hyaluronidase Glycoprotein family, particularly the human soluble PH-20 Hyaluronidase Glycoproteins (also referred to herein as sHASEGPs)." *Id.* at 3:51–54.

The '429 patent teaches "a substantially purified glycoprotein including a sequence of amino acids that has at least . . . 95% . . . identity to the sHASEGP." *Id.* at 6:15–20. The '429 patent states:

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

Id. at 16:14–20. The '429 patent claims a specific truncated version of the hyaluronidase glycoprotein composed of positions 36–482 of SEQ ID NO: 1. *See id.* at 153:39.

b) Chao (Ex. 1006)

Chao is a publication in the journal Biochemistry that was published in 2007. Ex. 1006, 6911.

Chao states: "There are five homologous hyaluronidases encoded in the human genome: hHyal-1 through -4 and the sperm adhesion molecule 1 (termed PH-20)." *Id.* Chao states that "[i]n humans, eight alternative splice transcripts of *HYAL1* encode the full-length enzyme and five splice variants. Variants 1-5 (designated v1 through v5) are each truncated to a different

extent. They lack enzymatic activity." *Id.* at 6912 (citation omitted). Chao reports "the crystal structure of the enzyme showing that it contains an EGF-like domain not seen previously, and examine[s] the impact of alternative splicing on the enzyme structure and function." *Id.*

Chao states that "[h]uman hyaluronidases exhibit 33-42% sequence identities and even higher conservation of active site residues. Yet, the enzymes differ in their catalytic efficiencies and pH profiles." *Id.* at 6914. Figure 3 of Chao is reproduced below:

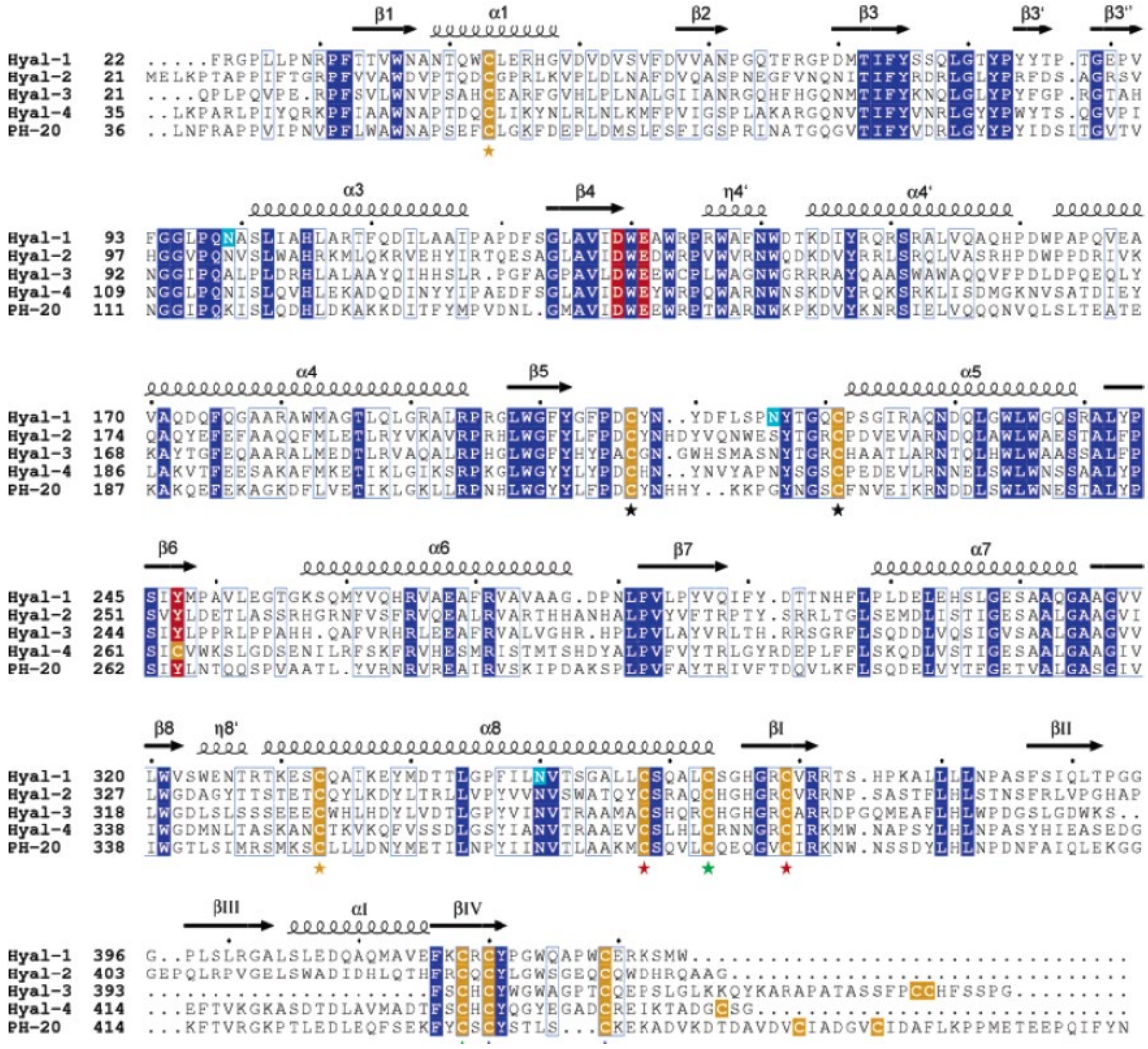


Figure 3 shows

> [s]tructure-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.

Id. at 6916.

3. Asserted Obviousness over the '429 Patent and Chao

a) Petitioner's Position

Petitioner asserts that the '429 patent "teaches making a ***particular*** type of modification (a single amino acid substitution) [at a] ***particular*** location (non-essential regions of PH20) in a ***particular*** PH20 sequence ($PH20_{1–447}$) to yield equivalents (of $PH20_{1–447}$) (*i.e.*, those that do not substantially alter the activity or function of $PH20_{1-447}$)." Pet. 87–88 (citing Ex. 1003 ¶ 206; Ex. 1004 ¶ 32). Petitioner asserts that Chao "identified a characteristic pattern for the Hyal-EGF domain, which in PH20 is at positions 337–409." *Id.* at 92 (citing Ex. 1006, 6911; Ex. 1004 ¶¶ 97–98; Ex. 1003 ¶¶ 84–85).

Petitioner asserts that a "skilled artisan would first identify the essential residues in PH20 by comparing proteins homologous to PH20 that were known in 2011. . . . A multiple-sequence alignment identifies non-essential regions in PH20—they are the sequences between essential residues and are positions at which variations occur at a frequency above ~5%." *Id.* at 92 (citing Ex. 1003 ¶¶ 212–214; Ex. 1004 ¶¶ 22, 25–32, Appx. D-2, Appx. D-3; Ex. 1006, 6916). Petitioner asserts that

> Dr. Park's sequence alignment also shows that many (11) different amino acids occur in homologous proteins at positions corresponding to position 317 in PH20. The diversity of characteristics of those amino acids at that position (e.g., polar vs. non-polar, small vs. large side chains, charged or uncharged residues, etc.), suggests that many different kinds of amino acids can be tolerated at this position in PH20.

Id. at 100 (citing Ex. 1004 ¶ 106; Ex. 1003 ¶ 219).

Petitioner asserts that "a skilled artisan would have reasonably expected the L317Q substitution to not substantially alter the biological activity (hyaluronidase activity) of $PH20_{1-447}$." *Id.* at 99 (citing Ex. 1003 ¶¶ 218–219; Ex. 1004 ¶¶ 106, 112).

Petitioner asserts that "[b]ased on the '429 Patent, Chao, and information available in 2011, the L317Q $PH20_{1-447}$ mutant polypeptide would have been obvious to a skilled artisan in 2011. And because claims 1-2, 6, 8, 10-16, and 25-26 each encompass one or more of these single-replacement mutants, each claim is unpatentable." *Id.* at 107.

b) Patent Owner's Response

Patent Owner asserts that "[b]ased on the teachings of Chao and the '429 patent, POSAs would not have had a reason to introduce substitutions at position 317." PO Resp. 86 (citing Ex. 2068 ¶¶ 405–416). Patent Owner asserts that while Chao provides insight into human hyaluronidase structures, "[n]one of these alleged 'insights' provides a reason to modify position 317 in PH20." *Id.* at 87 (citing Ex. 2068 ¶¶ 405–416).

Patent Owner asserts that "Petitioner's expert Dr. Park's analysis confirms that nothing in the art would have motivated POSAs to modify position 317. . . . Nothing in Dr. Park's results provides a reason to elevate L317 above the hundreds, if not thousands, of other substitutions he predicts

would have been tolerated." *Id.* at 88–90 (citing Ex. 2068 ¶¶ 404–416). Patent Owner asserts that "Petitioner provides no reason why POSAs, who have in hand a working enzyme, would tinker with that enzyme with the sole purpose of maintaining the same activity profile." *Id.* at 89.

Patent Owner asserts that "[n]one of the prior art offered any reason to pursue a substitution at L317, and Petitioner identifies none, except with the benefit of hindsight." *Id.*

c) Petitioner's Reply

Petitioner asserts "[w]ithout reviewing the disclosure, Dr. Park . . . identif[ied] L317Q as ***one of ~750 such substitutions*** suggested by the '429 Patent before 2011." Reply 44. Petitioner asserts that "Dr. Naismith found Dr. Park's analysis objective, rigorous, and unbiased. Thus, per *KSR*, the '429 Patent motivated POSAs to identify single substitutions in non-essential regions of $PH20_{1\text{-}447}$ that ***predictably*** retain activity." *Id.* at 45 (citing Ex. 1133 ¶¶ 333–343, 352–359; Ex. 1003 ¶ 216).

d) Patent Owner's Sur-Reply

Patent Owner asserts:

> Petitioner abandons any articulated motivation by asserting—without support—that all ~750 positions Dr. Park identifies for substitution would have been obvious candidates for substitution. But the claims require substitution ***at position 317***, and "there must be some reason to select a species from the genus." Petitioner offers none beyond impermissible, attorney-driven hindsight.

PO Sur-reply 29.

4. Analysis

Based on the evidence of record, we agree with Patent Owner that Petitioner has not provided any persuasive reason to particularly target the

leucine at position 317 of a PH20 polypeptide for modification as recited in claim 1 of the '758 patent. It is undisputed that neither of the cited prior art references, the '429 patent or Chao, specifically identifies or discusses position 317 of the PH20 polypeptide. *See, e.g.*, Pet. 88–109; PO Resp. 86–93.

We are not persuaded by Petitioner's argument that multiple sequence alignments identify amino acids that are tolerated at particular positions (*see* Pet. 99–109), because tolerance is not a positive reason to make a substitution. "It is not enough, even after *KSR*, to support a determination of obviousness that a reference includes a broad generic disclosure and a common utility to that in the claims and other prior art references—there must be some reason to select a species from the genus." *Knauf Insulation, Inc. v. Rockwool Int'l A/S*, 788 F. App'x 728, 733 (Fed. Cir. 2019).

Dr. Park identified 379 positions in PH20 (i.e., ~85% of the protein) with evolutionary variation, that is, where "homologous proteins have tolerated different amino acids at those positions." Ex. 1004 ¶ 31. Dr. Park distributes the twenty standard amino acids into four categories depending on their roles in forming secondary structure such as alpha helices or beta sheets, with each category having a minimum of six members. *See id.* ¶ 70. Nothing in the prior art or Dr. Park's analysis directs the ordinary artisan to position 317 itself.

Although Dr. Hecht asserts that the '429 patent suggests conservative mutations generally, Petitioner did not point us to any specific teaching or suggestion in the prior art cited by Dr. Hecht to modify position 317 of PH20. *See, e.g.*, Ex. 1003 ¶¶ 191–194. Petitioner did not point us to anything in Dr. Hecht's Declaration that explained why position 317 was of

interest in any way, versus position 316 or 318 or any other position within the PH20 polypeptide. It is Petitioner's "burden to show that the 'prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention.'" *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019) (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007)). Petitioner has not satisfied this burden of showing specific reasons to modify position 317 of the PH20 polypeptide.

We find that Petitioner has not shown by a preponderance of the evidence that the combination of the '429 patent and Chao with the knowledge and teaching described by Dr. Hecht and Dr. Park demonstrate obviousness for the claims of the '758 patent.

III. CONCLUSION

After considering the evidence and arguments presently before us on the complete trial record, we conclude that Petitioner has demonstrated, by a preponderance of the evidence, that challenged claims 1, 2, and 6–30 are unpatentable.[23]

[23] Should Patent Owner wish to pursue amendment of the Challenged Claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding, 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. §§ 42.8(a)(3), (b)(2).

In summary:

Claims	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not shown Unpatentable
1, 2, 6–30	112(a)	Written Description	1, 2, 6–30	
1, 2, 6–30	112(a)	Enablement	1, 2, 6–30	
1, 2, 6–30	103	The '429 patent, Chao		1, 2, 6–30
Overall Outcome			1, 2, 6–30	

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1, 2, and 6–30 of U.S. Patent 12,054,758 B2 are determined to be unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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