

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP and DOHME LLC,
Petitioner,

v.

HALOZYME, INC.,
Patent Owner.

PGR2025-00039
Patent 12,104,185 B2

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

VALEK, *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 1–4 and 7–11¹ of U.S. Patent No. 12,104,185 B2 (Ex. 1001, “the ’185 patent”). 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 1–4 and 7–11 are unpatentable.

A. Abbreviated Procedural History

Petitioner Merck Sharp & Dohme LLC filed a Petition requesting post grant review of all claims of the ’185 patent. *See* Paper 1 (“Pet.”). Patent Owner Halozyme, Inc. filed a Preliminary Response. Paper 17 (“Prelim. Resp.”).

Based on the preliminary record, we determined that the ’185 patent was eligible for post-grant review and that at least one of the challenged claims was more likely than not unpatentable. Paper 25 (“ID”). We instituted trial of claims 1–4 and 7–11 on October 1, 2025. *Id.*

After institution, Patent Owner filed a Response to the Petition (Paper 41, “Resp.”), Petitioner filed a Reply to Patent Owner’s Response

¹ Although the Petition was directed to claims 1–11 of the ’185 patent, Patent Owner filed a statutory disclaimer of claims 5 and 6 prior to institution, leaving just claims 1–4 and 7–11 at issue. *See* Ex. 2003.

(Paper 76, “Reply”), and Patent Owner filed a Sur-reply (Paper 93, “Sur-reply”).²

We held an oral hearing on June 23, 2026, a transcript of which is of record. Paper 98 (“Hr’g Tr.”).

B. Real Parties-In-Interest

Petitioner identifies Merck Sharp & Dohme LLC as the real party-in-interest. Pet. 7. Patent Owner identifies Halozyme, Inc. and Halozyme Therapeutics, Inc. as the real parties-in-interest. Paper 4, 1.

C. Related Matters

The ’152 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; 11,952,600; 12,018,298; 12,037,618; 12,054,758; 12,091,692; 12,104,185; 12,110,520; 12,152,262; 12,077,791; 12,195,773; and 12,264,345. Paper 96, 1; Paper 35, 1.

The ’185 patent is also related to a number of patents subject to post-grant review proceedings including those in the Table below:

² Patent Owner also filed a motion to terminate alleging that Petitioner failed to name its corporate parent as a real party-in-interest (RPI). Paper 49 (public version). That motion, along with related motions and briefing, were the subject of numerous papers in this proceeding. We denied Patent Owner’s motion to terminate. Paper 88 (public version). Patent Owner then requested Director Review of the Board’s order denying that motion. Paper 94 (public version). That request was not considered because the Board’s order denying the motion to terminate was “outside the scope of Director Review.” *See* Ex. 3101.

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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
12,054,758	PGR2025-00030	Feb. 4, 2025	Yes
12,049,652	PGR2025-00033	Mar. 7, 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 96, 1–2.

Patent Owner states that the '185 patent is related to the following pending U.S. Patent Applications:

U.S. Patent 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, 2026
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	June 25, 2026
19/720,766	June 25, 2026
19/722,345	June 26, 2026

U.S. Patent Application No.	Filed
19/722,335	June 26, 2026

Paper 96, 2–3.

D. The '185 Patent

The '185 patent issued October 1, 2024, from U.S. Application 18/599,428, filed March 8, 2024. Ex. 1001, codes (21), (22), (45). The '185 patent is a division of U.S. Application 18/338,189, filed on June 20, 2023, which is a division of U.S. Application 17/327,568, filed on May 21, 2021, which is a continuation in a lengthy set of applications claiming continuity to U.S. Application 13/694,731 (“the '731 application”), filed on December 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 December 30, 2011. *Id.*

The '185 patent is drawn to “[m]odified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity.” Ex. 1001, 4:16–18. The '185 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 '185 patent teaches that “since HA is a major component of the interstitial barrier, hyaluronan-degrading enzymes (e.g., hyaluronidase) increase tissue permeability and therefore can be used to increase the dispersion and delivery of therapeutic agents.” *Id.* at 4:37–40. According to the '185 patent, “[v]arious hyaluronidases have been used therapeutically . . . typically as dispersing and spreading agents in combination with other therapeutic agents,” but “[m]any of these are ovine

or bovine forms, which can be immunogenic for treatment of humans” and therefore “[i]mproved hyaluronan-degrading enzymes, such as hyaluronidases and compositions thereof that can be used for treatment are needed.” *Id.* at 4:41–50.

The ’185 patent purports to describe modified PH20 hyaluronidase polypeptides that have been modified with “amino acid replacement, deletion an/or insertions.” Ex. 1001, 4:56–58. For instance, the ’185 patent states as follows:

[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 ’185 patent states that the “modified PH20 polypeptides provided herein exhibit altered activities or properties compared to a wildtype, native or reference PH20 polypeptide.” Ex. 1001, 75:45–47. The ’185 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.

Id. at 75:47–56.

The '185 patent explains that modified PH20 polypeptides may be used as a spreading factor to increase the delivery of a therapeutic agent. For example, it states as follows:

Provided herein are methods and uses of any of the modified PH20 polypeptides provided herein that exhibit hyaluronidase activity based on its ability to degrade glycosaminoglycan(s) such as hyaluronan. Due to such activity, the modified PH20 polypeptides can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents.

Id. at 174:21–29; *see also id.* at 175:24–35 (explaining that drugs injected subcutaneously “spread very slowly” but “[c]o-injection with hyaluronidase . . . can cause rapid spreading”).

E. Illustrative Claims

Claim 1 is illustrative of the challenged claims in the '185 patent and is reproduced below.

1. A method for increasing delivery of a therapeutic agent to a subject, comprising administering to a subject a pharmaceutical composition comprising:
 - (a) a therapeutic agent; and
 - (b) a modified PH20 polypeptide comprising an amino acid sequence, wherein:
 - i. at least 95% of the residues of the amino acid sequence of the modified PH20 polypeptide are identical to the residues in an amino acid sequence selected from the group consisting of

SEQ ID NOs: 3 and 32-66 when the sequence of the modified PH20 polypeptide is aligned at positions corresponding to the sequence selected from the group consisting of SEQ ID NOs: 3 and 32-66 to maximize identical residues; and

ii. the amino acid sequence of the modified PH20 polypeptide comprises an amino acid modification at a position corresponding to position 320 with reference to amino acid positions set forth in SEQ ID NO: 3; and

iii. the modification at position 320 is a replacement selected from the group consisting of H, K, R and S.

Ex. 1001, 313:18–37.

F. Asserted Grounds of Unpatentability

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

Ground	Reference(s)/Basis	35 U.S.C. §	Claim(s) Challenged
1	Written Description	§ 112	1–4, 7–11
2	Enablement	§ 112	1–4, 7–11
3	'429 patent, ³ Chao ⁴	§ 103	1–4, 7–11

Pet. 7–8. Petitioner also relies on the Declarations of Michael Hecht, Ph.D., Sheldon Park, Ph.D., James Naismith, Ph.D., i.e., Exhibits 1003, 1004, and 1133, respectively. Patent Owner relies on the Declarations of Melanie Simpson, Ph.D. and Gregory Petsko, Ph.D., i.e., Exhibits 2068 and 2070, respectively.⁵

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* 6911–20 (2007) (“Chao”) (Ex. 1006).

⁵ Patent Owner withdrew the testimony of Dr. Triggs-Raine that it submitted prior to institution. Resp. 9 n. 6.

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 (“POSA”) as of the effective filing date of the challenged claims. Petitioner contends that a POSA

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

Pet. 16–17 (citing Ex. 1003 ¶ 13).

Patent Owner responds, observing “there is no significant difference between Petitioner’s POSA definition (Pet., 16-17; EX1003, ¶13) and Patentee’s, both of which were addressed in the Institution Decision (ID, 9-11).” Resp. 30. Patent Owner notes that “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.’” *Id.* (citing Ex. 2076, 63:8–64:2).

We find that Petitioner’s proposal is sufficiently comprehensive to encompass the prior art relevant to the ’185 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 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* Resp. 30, 60. We also 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 December 28, 2012 priority date Patent Owner asserts for the written description and enablement challenges. *See* Resp. 10 n.7 (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,” and “the December 30, 2011 priority date for purposes of responding to Petitioner’s obviousness challenge”). Patent Owner alleges that for its written description and enablement challenges, “Petitioner and its experts erroneously rely upon a December 30, 2011 date.” Resp. 36–37 n.12. However, as we explained in the Institution Decision, Petitioner “did not restrict the § 112(a) analysis to December 2011; rather, Petitioner stated that the claims are not entitled to the December 28, 2012 benefit date of the ’731 Application, while the obviousness ground[] use[s] the December 2011 priority date being claimed.” ID 36 n.14 (quotations omitted). Additionally, 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 interpreted the term “modified PH20 polypeptide” to require that the claimed polypeptide must have hyaluronidase activity. ID 15–21. We primarily relied upon the intrinsic evidence in a definitional passage in the 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 (emphasis added).

Based on the evidence of record at that time, we determined that the evidence of record shows the ’185 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, but *only* “so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.”

ID 17–18 (quoting Ex. 1001, 48:47–49); *see also* ID 21 (“adopt[ing]” the definition from the Specification). We also determined that the claim preamble is limiting, rejecting Patent Owner’s argument to the contrary in the Preliminary Response. ID 18–20 (citing Prelim. Resp. 27–30).⁶ We now address the parties’ contentions on the complete record.

1. Petitioner’s Position

Petitioner asserts that the terms used in the claims “are either expressly defined in the common disclosure^[7] or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition,” i.e., no construction is necessary beyond the definition provided in the Specification. Pet. 18. Petitioner further contends that the claims require use of active mutants because the preamble recites a method of “increasing delivery of a therapeutic agent” and the common disclosure teaches that “***at a minimum,*** to be used in the claimed methods, a modified PH20 polypeptide must be able to ***hydrolyze*** HA (*i.e.*, possess ‘hyaluronidase activity’).” *See id.* at 22–24. According to Petitioner, “the specification describes two distinct categories of modified PH20 polypeptides (‘active mutants’ vs. ‘inactive mutants’), each with distinct (alleged) utilities, but the claims are limited to

⁶ At trial, Patent Owner acknowledges, but does not dispute our preliminary determination that the preamble is limiting. *See* Resp 30. Accordingly, Patent Owner has waived any argument to the contrary.

⁷ Petitioner uses the term “common disclosure” to refer to the specifications of both “the ’185 patent and its ultimate parent ’731 Application,” i.e., the earliest non-provisional application in the chain of priority. *See* Pet. 2 (citing Ex. 1026); *see also id.* at 6, n. 6 (“‘[C]ommon disclosure’ refers to the shared disclosure of the ’185 Patent and the ’731 Application”).

methods that use only one of those categories of modified PH20 polypeptides one—“active mutants.”” *Id.* at 27. In addition to its argument based on the claim preamble, Petitioner identifies four other reasons the claims are limited to the active mutant category:

First, each [claim] requires modified PH20 polypeptides with one of four replacements at position 320 that yielded an “active mutant” as a single-replacement PH20₁₋₄₄₇ polypeptide (*i.e.*, D320H, D320K, D329R, or D320S). All four are identified as “Active Mutants” in Table 3 and have >100% activity per Table 9.

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

Third, the specification defines a “modified PH20 polypeptide” as “a PH20 polypeptide that contains at least one modification,” but can also “have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide *exhibits hyaluronidase activity*.” . . .

Fourth, claim 1 requires the modified PH20 polypeptide to be in a composition with a “therapeutic agent.” As the disclosure explains, such compositions can be formulated “so that the components, *particularly the PH20 . . . remain active* or are *stable*” “(*i.e.*, it [PH20] *retains* activity . . .).”

Id. at 29–31 (citing Ex. 1001, 32:25–40, 42:48–55, 48:38–53, 47:61–65, 76:5–8, 76:67–77:7, 81:1–82:10, 85 (Table 3), 97:34–46, 252 (Table 9); Ex. 1003 ¶¶ 133–136).

Petitioner also asserts that even if the claims were read to include inactive mutants, “every claim still necessarily includes (and thus must describe and enable) the full subgenus of ‘active mutants’ in claim 1 defined by claims 5 and 6.” Pet. 31

2. *Patent Owner's Response*

Patent Owner asserts that “the term ‘modified PH20 polypeptide’ as it is defined in the specification encompasses **both** enzymatically active and enzymatically inactive PH20s. However, in view of the ’185 claim language, Patentee does not dispute that the ’185 patent claims require modified PH20s with at least some hyaluronidase activity.” Resp. 30–31.

Regarding the definitional passage in the Specification (Ex. 1001, 48:38–46 quoted above), Patent Owner asserts that “the definition of ‘modified PH20 polypeptide’ is limited to the first sentence.” Resp. 32
According to Patent Owner,

The 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 33–34 (citing Ex. 1001, 43:50–44:53, 79:27–29, 115:41–44).

3. *Petitioner's Reply*

Petitioner responds, urging that Patent Owner “concedes the claims require the use of modified PH20 polypeptides that are enzymatically active.” *See* Reply 1. According to Petitioner, this concession renders “irrelevant [Patent Owner’s] comments about ‘inactive’ mutants, and their

reading of ‘modified PH20 polypeptide’ is legal error as it gives ‘PH20’ no weight.” *Id.* at 3 (citing Resp. 30–34; Ex. 1130, 55:23–56:7, 57:9–58:4).

In addition to its arguments regarding hyaluronidase activity, Petitioner asserts the claims require polypeptides that “cause increased diffusion (‘spreading’).” Reply 1. Petitioner contends that “‘spreading’ is a distinct activity [from hyaluronidase activity] identified using a different assay.” *Id.* at 1–2 (citing Pet. 22–25; Ex. 1026, 83:24–26, 194:35–195:3; Ex. 1003 ¶¶ 101–110, 180–183).

4. *Patent Owner’s Sur-Reply*

Patent Owner disagrees with Petitioner’s argument that “the claims require a different type of activity: a ‘spreading/diffusion’ activity.” Sur-reply 2. According to Patent Owner, “the specification teaches that spreading/diffusion **is the result** of PH20’s hyaluronidase activity; it is not a separate enzymatic function.” *Id.* (citing Ex. 1001, 174:22–28).

5. *Evidence and Analysis*

“[T]he 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). Unlike the related PGR proceedings, there is no dispute in this case that the challenged claims require the use of a modified PH20 polypeptide having hyaluronidase activity. Nevertheless, the parties disagree as to whether: (1) such hyaluronidase activity is required by the term “modified PH20 polypeptide” as defined in the Specification; and (2) the claims require the modified PH20 polypeptide to exhibit a second, distinct type of activity, i.e., “spreading” activity, in addition to hyaluronidase activity.

We address each of these issues in turn below, beginning with 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, 1315 (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).

- a) Whether “modified PH20 polypeptide” requires hyaluronidase activity

- (1) *Intrinsic evidence*

Claim 1 recites the administration of a composition comprising a therapeutic agent and a “modified PH20 polypeptide” with an amino acid sequence that is at least 95% identical to one of 36 SEQ ID NOs and that contains at least one modification comprising a H, K, R, or S substitution at position 320 of the reference sequence. The Specification of the ’185 patent has an extensive “Definitions” section (Ex. 1001, 44:53–68:39) that defines numerous terms, including “PH20” and “modified PH20 polypeptide.” The Specification states “[a]s used herein, PH20 refers to a type of hyaluronidase

that occurs in sperm and is neutral-active.”⁸ Ex. 1001, 45:55–56. The Specification further states 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 46:5–10. The Specification 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 46:14–17.

The Specification also defines the term “modified PH20 polypeptide,” stating:

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.

Ex. 1001, 48:38–53 (emphasis added).

⁸ “[N]eutral active” is defined as “the ability of a PH20 polypeptide to enzymatically catalyze the cleavage of hyaluronic acid at 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 also addresses a number of other terms that relate to the “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.

Ex. 1001, 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 50:18–29.

Other portions of the “Definitions” section also refer to the activity of the protein. For example, in its definition of a “denaturing condition” the Specification 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.”

Ex. 1001, 51:16–19. The Specification also states that the term

“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 terms “phenophile” and “thermophile” are both described as a “modified PH20 polypeptide” that

“exhibits 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” under certain conditions. *Id.* at 55:2–7; 55:18–23. The Specification further 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 57:57–60.

The “Definitions” section further 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.*” Ex. 1001, 63:37–44 (emphasis added).

In sum, considering the intrinsic evidence as a whole, the Specification supports that the term “modified PH20 polypeptide” requires hyaluronidase activity. Indeed, both the definition of “PH20” and “modified PH20 polypeptide” require hyaluronidase activity. Ex. 1001, 45:58–60, 50:43–46 (“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”); 48:46–49 (“A modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.”). And 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 63:37–44. In contrast, the

portions of the Specification that Patent Owner points to as using “‘modified PH20 polypeptide’ to refer to inactive polypeptides” (Resp. 33–34 (citing Ex. 1001, 43:50–44:53, 79:27–29, 115:41–44), are not part of the “Definitions” section of the ’185 patent. Accordingly, they do not modify the Specification’s definitions’ explicit requirement that “modified PH20 polypeptide” is limited to polypeptides having hyaluronidase activity. *See* Ex. 1001, 45:55–56, 48:38–53 (definitions of “PH20” and “modified PH20 polypeptide”).

(2) *Extrinsic evidence*

Both Petitioner and Patent Owner cite prior art references replete with disclosures demonstrating that “PH20” is ordinarily understood by those of skill in the art to refer to a polypeptide having hyaluronidase activity. We cite some examples of this evidence below.

“PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active.” Ex. 1007, 10:31–32; *see also* 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 (“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, 33655 (“PH20 (*i.e.*, testicular HAase [hyaluronidase]) is well characterized” and “is a sperm surface HAase that has a broad pH activity profile”); 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”).

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 be limited to enzymatically active mutants, i.e., modified PH20 polypeptides with hyaluronidase activity. Ex. 1003 ¶ 141 ("a skilled artisan would have understood the claims . . . cover modified PH20 polypeptides that are active mutant and would not view them as including inactive mutants"); Ex. 1133 ¶ 100 (agreeing with Dr. Hecht). 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]?", 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.

Ex. 2076, 181:9–18. When a further question asked, "the specification, in fact, uses the termed modified PH20 polypeptides to refer to inactives?", Dr. Hecht recognized a distinction in the Specification 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,⁹ Dr. Simpson, disagrees with Dr. Hecht. Dr. Simpson states, "[i]n my opinion, a POSA would have understood that the claims do not require hyaluronidase enzymatic activity, let alone $\geq 40\%$ hyaluronidase enzymatic activity." Ex. 2068 ¶ 256. Dr. Simpson relies on the first sentence in the Specification's definition of "modified PH20 polypeptide" and other statements discussing "inactive mutants" that were not found in the "Definitions" section to support the position that "a POSA would understand that modified PH20 polypeptides with a D320H, D320K, D320R, or D320S substitution are not always active." *Id.* ¶¶ 259–268, 271. 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 and is enzymatically active." *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.*

⁹ Patent Owner's expert Dr. Petsko did not independently analyze claim construction. He stated, "I have not been asked to opine regarding claim construction and do not do so in this declaration." Ex. 2070 ¶ 247.

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.

(3) *Analysis*

As discussed above, the definition of the term “PH20” in the Specification states that “PH20 refers to a type of hyaluronidase that occurs in sperm and is neutral-active”—meaning that it is understood to have hyaluronidase activity at neutral pH. Ex. 1001, 45:55–56, 50:39–42. And the second sentence of the definition of “modified PH20 polypeptide” in the ’185 patent allows for numerous amino acid modifications “*so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.*” *Id.* at 48:43–46 (emphasis added). We disagree with Patent Owner’s argument that this second sentence is not part of the definition. *See* Resp. 32–34. Contrary to Patent Owner’s argument, the phrase “so long as” is not permissive in nature such that it can be read to describe an exemplary, but not required, feature of the recited polypeptides. Ex. 1001, 48:43–46; *cf.* *Alnylam v. Moderna*, 138 F.4th 1326, 1333 (Fed. Cir. 2025) (distinguishing “non-limiting terms” such as “for example” and “include, but not limited to” that contrast with the patent specification’s definitional language).

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, she 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 ’185 patent, Patent Owner chose to inform the ordinary artisan that the claimed polypeptides would have the properties that the Specification expressly defines as part of a “PH20” polypeptide, including 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.

b) *Whether spreading/diffusion activity is a distinct functional requirement*

As before, we begin with the intrinsic record. Claim 1 recites a “method for increasing delivery of a therapeutic agent” by administering a composition comprising the therapeutic agent and a “modified PH20 polypeptide,” which as explained above requires a polypeptide with hyaluronidase activity. *See* Ex. 1001, 313:18–37.

The Specification explains the connection between hyaluronidase activity and increased delivery. It states:

By catalyzing the hydrolysis of hyaluronic acid, PH20 hyaluronidase lowers the viscosity of hyaluronic acid, thereby

increasing tissue permeability. Hence, soluble forms of PH20 are used as a spreading or dispersing agent in conjunction with other agents, drug and proteins to enhance their dispersion and delivery, and to improve the pharmacokinetic and pharmacodynamic profile of the coadministered agent, drug or protein.

Ex. 1001, 73:38–45 (citation omitted); *see also id.* at 175:24–33 (similar). Accordingly, '185 patent teaches that PH20 can be used as a spreading agent because it has hyaluronidase activity. *Id.* That teaching supports Patent Owner's position that spreading is *not* a distinct functional requirement of the claims, but rather is the result of the required hyaluronidase activity.

Indeed, Patent Owner cites the following passage (*see* Sur-reply 2), which makes this point even more clearly:

Provided herein are methods and uses of ***any*** of the modified PH20 polypeptides provided herein that exhibit hyaluronidase activity based on its ability to degrade glycosaminoglycan(s) such as hyaluronan. ***Due to such activity***, the modified PH20 polypeptides can be used as a spreading factor to increase the delivery and/or bioavailability of subcutaneously administered therapeutic agents.

Ex. 1001, 174:21–29 (emphases added). Here, the Specification teaches that: (1) modified PH20 polypeptides can be used as spreading factors “due” to their hyaluronidase activity, and (2) hyaluronidase activity and spreading agent functionality are coextensive in the sense that “any” modified PH20 polypeptide can be used for this purpose. *Id.*

The only intrinsic evidence Petitioner cites to support its position that spreading/diffusion is a distinct functional requirement of

the claims is the Specification's description of an in vivo assay to assess "[t]he ability of a [modified] PH20 polypeptide . . . to act as a spreading or diffusing agent" by injecting Trypan blue dye along with a PH20 polypeptide into nude mice. *See* Ex. 1001, 172:37–45. In isolation, this passage provides some support for Petitioner's position. But read in context of the entire Specification, we are not convinced that spreading is a distinct functional requirement for several reasons.

First, the mouse assay Petitioner relies upon is one of many assays described in the "Hyaluronidase Activity" subsection (*see* Ex. 1001, 171:21–172:45) of the Specification's larger description of "Methods of Assessing PH20 Activity and Stability." *Id.* at 170:63–64, 171:21. The fact that this mouse assay is included in the "Hyaluronidase Activity" subsection, as opposed to a separate section addressing a different functionality or property, suggests it is properly interpreted as a test for hyaluronidase activity. *Id.* at 171:21.

Second, as Petitioner conceded at the hearing, there is no evidence of any modified PH20 polypeptide that exhibits hyaluronidase (hyaluronic acid degrading) activity, but not spreading activity. *See* Hr'g Tr. 25:18–26:14. To the contrary, the Specification includes a single example assessing "Enzymatic Activity in an Intradermal Trypan Blue Dispersion Assay" of the unmodified, "wild-type" PH20 polypeptide and "the PH20 variant F204P." Ex. 1001, 308:29–41 (Example 14). According to that example, both of these PH20 polypeptides showed "substantially identical . . . dispersion activity," which is consistent Patent Owner's position that spreading/diffusion results from the polypeptide's enzymatic activity. *Id.* at 309:9–27. "While mechanisms of action may not always meet the most rigid

standards for inherency, they are still simply results that naturally flow from the administration of a given compound or mixture of compounds.” *In re Couvaras*, 70 F.4th 1374, 1380 (Fed. Cir. 2023).

Third, consistent with our findings above, Petitioner’s expert Dr. Hecht observes that the Specification “attributes the ability of both naturally occurring and modified PH20 polypeptides to increase delivery of another therapeutic agent to the PH20 protein having hyaluronidase enzymatic activity.” Ex. 1003 ¶¶ 131–132 (citing passages). To the extent Petitioner or its experts elsewhere attempt to characterize spreading as a separate functional requirement from hyaluronidase activity,¹⁰ we credit the intrinsic record’s teaching over that testimony. That is, the Specification teaches that “any” modified PH20 polypeptide that exhibits hyaluronidase activity can be used a spreading factor. Ex. 1001, 174:21–29.

In sum, we agree with Petitioner that the term “modified PH20 polypeptide,” as defined in the Specification, requires that the polypeptide has hyaluronidase activity. However, we disagree with Petitioner’s attempt to characterize spreading/diffusion activity as a

¹⁰ See Ex. 1003 ¶¶ 177–181 (“Other factors [besides hyaluronidase activity] may influence the ability of PH20 to act as a ‘spreading agent.’”).

separate functional requirement of that “modified PH20 polypeptide.”¹¹

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

¹¹ We note that even if we were to adopt the claim construction positions discussed but rejected above, it would not affect the ultimate outcome on the written description and enablement grounds. This is because it is undisputed that the claims recite a functionally-defined (i.e., peptides having hyaluronidase activity) genus and, as explained below, that requirement is central to the Section 112 arguments/analysis here.

establish by a preponderance of the evidence that the claims fail to comply with the written description requirement.

2. *Petitioner's Position*

Petitioner asserts “the claim language defines methods that encompass use of enormous genera of modified PH20 polypeptides: between 10^{49} and 10^{66} distinct polypeptides. . . . [T]esting every polypeptide within the claims’ scope in search of ‘active mutants’ is impossible—literally.” Pet. 31–32 (citing Ex. 1003 ¶¶ 125, 202). Petitioner asserts:

The genera of modified PH20 polypeptides that claims 1 to 4 specify use of are not only immense, but structurally and functionally diverse. They capture PH20 mutants with 2, 3, or more substitutions up to a number set by the sequence identity boundary (*i.e.*, 17 for the narrowest claims (*i.e.*, claim 3) to 23 for the broadest (*e.g.*, claim 1)). . . . Each claim also encompasses use of PH20 polypeptides having substitutions within C-terminally truncated forms of PH20 of varying lengths. Claim 1 does this explicitly, specifying 36 alternative sequences that terminate at positions 430 to 465.

Id. at 37–38 (citing Ex. 1003 ¶¶ 121–122).

Petitioner asserts that the ’185 patent “instructs the skilled artisan ‘to generate a modified PH20 polypeptide containing any one or more of the described mutation, and test each for a property or activity as described herein.’” Pet. 39 (citing Ex. 1001, 78:33–38; Ex. 1003 ¶ 206). Petitioner observes that the Specification identifies some changes to avoid in active mutants, *i.e.*, “(i) any substitution at 96 different positions in the PH20 sequence, and (ii) 313 specific amino acid substitutions listed in Tables 5 and 10 that are made at other positions,” but asserts that the “sequence identity claim parameters . . . capture such mutants.” *Id.* at 39–40 (citing Ex. 1001, 80:15–55; Ex. 1003 ¶¶ 155–158, 169).

Petitioner asserts that based on the prior art and the common disclosure, “a skilled artisan in 2011 would have believed that PH20 polypeptides that terminate before position 430 would be inactive (*e.g.*, at position 419, below),” even though the claims encompass “truncations down to and beyond position 419.” Pet. 43–44 (citing Ex. 1003 ¶¶ 95–96, 136, 170–172). According to Petitioner, the common disclosure “provides no examples of (or guidance concerning) PH20 mutants truncated below position 447 with one or more substitutions and that are enzymatically active,” and “thus ignores the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433.” *Id.* at 44 (citing Ex. 1003 ¶¶ 95–96, 98, 100).

Petitioner asserts that of approximately 5,917 single amino acid changes to the PH20₁₋₄₄₇ polypeptide that were tested in the common disclosure, “[m]ore than half (~57%)” were classified as “inactive mutants” and “~87% . . . had *less* activity than unmodified PH20₁₋₄₄₇.” Pet. 45–46 (citing Ex. 1003 ¶¶ 106–108). Petitioner asserts this data show the unpredictability of mutation where “even introducing different amino acids at the same position in PH20₁₋₄₄₇ resulted in (i) increased activity, (ii) decreased activity or (iii) inactive mutants.” *Id.* at 47 (citing data from Ex. 1001, Tables 3, 5, 9, 10). 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 provide no guidance to a skilled artisan

about which of the many possible PH20 mutants with different sets of 2-42^[12] substitutions will be enzymatically active. *Id.* at 48 (citing Ex. 1003 ¶¶ 147, 150, 168–169, 178, 183). Petitioner also asserts the common disclosure “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 49–50 (citing Ex. 1003 ¶¶ 75–76).

Petitioner asserts that the statements in the common disclosure fail to “identify **any** actual multiply-modified PH20 polypeptides (*i.e.*, PH20 polypeptide sequences with particular combinations of specific amino acid substitutions), much less provide results from testing any or indicat[e] which will increase delivery of therapeutic agents. They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides.” Pet. 52–53. According to Petitioner, the common disclosure merely outlines “a prophetic research plan requiring ‘iterative’ make-and-test experiments that **might discover** multiply-modified enzymatically active PH20 polypeptides,” but that “[t]his 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 53–54 (citing Ex. 1001, 135:4–16, 42:48–55, 44:1–2, 127:37–128:22, 128:25–130:3, 130:30–135:3; Ex. 1003 ¶¶ 185–189, 196–197, 200).

¹² Because Petitioner’s calculations show that the broadest challenged claims encompass a PH20 polypeptide with up to 23 modifications (*see* Pet. 37), we understand the reference to “42” here to be a typographical error. Dr. Hecht’s supporting testimony shows that the correct range should be “sets of between 2 and 23 substitutions.” Ex. 1003 ¶ 147.

Petitioner asserts that:

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

Pet. 56 (citing Ex. 1003 ¶¶ 146–147, 158).

Petitioner asserts the “single-replacement PH20₁₋₄₄₇ examples are not representative of the trillions and trillions of PH20₁₋₄₄₇ polypeptides having between **2 and 23 substitutions** at any of hundreds of positions within the protein.” Pet. 59 (citing Ex. 1003 ¶¶ 61, 150, 166). Petitioner asserts the “effects of numerous substitutions on the PH20 protein’s various secondary structures and structural motifs are not described or discussed in the common disclosure.” *Id.* (citing Ex. 1003 ¶¶ 164–165, 242).

Petitioner offers the figure below to illustrate “how **non-representative** the examples are: all of the examples of single-replacement PH20₁₋₄₄₇ mutants fit into one box of the array below:”

	Number of Changes																					
SEQ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
3																						
32																						
33																						
34																						
35																						
36																						
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Pet. 62–63. The figure above depicts a 22 x 36 array representing the scope of the challenged claims, which Petitioner contends is limited to the recited replacement at position 320 and anywhere from 1 to 22¹³ additional changes within 36 different unmodified PH20 sequences. *Id.* at 62. Petitioner uses the single shaded red box in the top left corner of its figure to represent that only

¹³ This is for the broadest claims. Petitioner asserts that claims 3 and 4 are limited to as many as 16 and 20 additional changes respectively. Pet. 62.

single amino acid changes in only one sequence (SEQ ID NO: 3) were tested in the working examples of the common disclosure. *Id.*

Petitioner asserts that “[t]he common disclosure attributes a PH20 protein’s capacity to ‘increase delivery’ capability to its ability to cause ‘spreading’ or ‘diffusion,’” which “at a minimum” requires “a PH20 with hyaluronidase activity.” Pet. 65 (citing Ex. 1001, 174:19–28, 175:23–35, 73:22–47). According to Petitioner, the common disclosure does “not identify which of the trillions of modified PH20 polypeptides within claim 1’s genus have hyaluronidase activity,” nor does it identify which of those trillions “also possess ‘spreading’ / ‘diffusion’ activity—it identifies only one (F204P PH20₁₋₄₄₇).” *Id.* at 65–66 (citing Ex. 1001, 308:29–31:16).

Petitioner asserts that all of the other challenged claims lack written description support for the same or substantially similar reasons. *See* Pet. 67–69.

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 four D320 variants and 95% identical subvariants.” 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 95% identical subvariant polypeptides as of December 28, 2012. *Id.* at 36 (citing Ex. 2068 ¶¶ 277–342, 419).

Patent Owner asserts that “[t]he specification describes and characterizes the common structural features of the four D320 variants recited in the claims (D320K, D320R, D320H and D320S) and their 95% identical subvariants.” Resp. 37. 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.* Patent Owner asserts that its expert

Dr. Petsko generated homology models of multiply-modified PH20s identified in the patent with the claimed 320D mutation, including chimpanzee PH20, gibbon PH20, orangutan PH20. EX2070, ¶¶411–424. 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^[14] teaches is active). In other words, they are multiply mutated.

Id. at 37–38. According to Patent Owner, the Specification identifies specific amino acids necessary for enzymatic activity, amino acids involved in disulfide bridges, and sites involved in substrate binding. *Id.* at 40 (citing Ex. 1001, 70:46–54, 70:14–26, 70:34–41; Ex. 2068 ¶ 303). Patent Owner asserts “because the specification discloses the structural features necessary for activity, POSAs would have understood them as common to active D320

¹⁴ The “’457 publication” is U.S. Patent Application Publication No. 2010/0143457 A1 to Wei et al., published June 10, 2010. It is referenced in the ’185 patent. *See, e.g.*, Ex. 1001, 70:6–8.

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 40–41.

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.

Resp. 42 (citing Ex. 2070 ¶¶ 44–54; Ex. 2068 ¶¶ 305–306). Patent Owner asserts that “[t]hese data collectively would have provided more than sufficient blaze marks for POSAs to visualize or recognize all the members of the claimed genus, reliably distinguishing actives from inactives.” *Id.* at 44 (citing Ex. 2068 ¶ 311). Patent Owner asserts that unlike the situations in *Ariad* and *AbbVie*,¹⁵ 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 D320 mutation and 95% identity—to be covered. And, as the inventors identified by sequence and structure-function mapping the full scope of the narrow set of claimed D320 variants and subvariants, they in fact possessed the full scope of the genus.

Id. at 45.

Patent Owner asserts that “Dr. Petsko’s and Dr. Simpson[’s] analyses show that in fact the claimed subvariants are structurally homogeneous.

¹⁵ *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

And the large number of inactivating mutations are not evidence of unpredictability.” Resp. 8 (citing Ex. 2068 ¶¶ 379–380). Patent Owner asserts “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.* (citing Ex. 2070 ¶¶ 353–365; Ex. 2068 ¶¶ 316–323).

Patent Owner asserts, as to C-terminal truncations, that the ’457 publication shows 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 provides activity data for all of the SEQ IDs 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 ’185 claims.

Id. at 50 (citing Ex. 2068 ¶¶ 324–335; Ex. 2070 ¶¶ 226–230).

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 320) were active.” Resp. 53 (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 four variants and their 95% identical sub-variants. Moreover, the working examples comprehensively characterize the structure-function of PH20 (SEQ ID NO: 3) through the mutagenesis data.

Id. at 53–54.

4. *Petitioner's Reply*

Petitioner responds, urging its “description of the claims’ ‘sequence space’ [of the claims] is not a ‘parlor trick’— Halozyme’s experts **confirmed** it was correct ($\sim 10^{49}$ to $\sim 10^{66}$ sequences).^[16] 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.” Reply 4 (citing Ex. 1003 ¶¶ 121–124; Ex. 1004 ¶¶ 168–171; 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 “[p]roperly folded PH20s are the only PH20s in the sequence space that could have a common set of structural features, yet the disclosure entirely fails to identify what those common features are and which of the $10^{49}+$ sequences will fold to have them.” Reply 13. Petitioner asserts that “[a]s a **claim element**, the 95% 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 13–14.

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.

¹⁶ 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 95% sequence identity to one of SEQ ID NOS: 3 and 32–66, and one position 320 change to H, K, R or S).” Ex. 1133 ¶ 48 (citing Ex. 1003 ¶¶ 118–127). We use that term in the same way herein.

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.

Reply 16 (citing Ex. 1133 ¶¶ 153, 167–172). 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 17–18 (citing Ex. 1133 ¶¶ 137–141, 152–154; Ex. 2070 ¶ 52). Petitioner asserts that the common “disclosure’s reference to a ‘common core hyaluronidase domain’ shared by PH20s (3-339 of PH20) does not identify the Hyal-EGF domain—it terminates 4-5 residues into it[.]. That ‘domain’ also is not a ‘common structural feature’ of active PH20s—mutants truncated at position 340 do not ‘properly fold’ and lack activity.” *Id.* at 20 (citing Ex. 1011, 813–814; Ex. 1026, 79:20–31; Ex. 1133 ¶¶ 163–165, 194–195).

Petitioner asserts that Patent Owner’s argument that singly-substituted PH20s provide structure/function correlations for multiply-modified PH20s is incorrect for several 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, much less which combinations of changes maintain that structure.
Reply 22–23 (citing Ex. 1003 ¶¶ 54–61, 67–76, 105–106, 14, 147–150; Ex. 1133 ¶¶ 115–116, 153, 234–235, 248–261, 266–271, 309–311).

Petitioner asserts that Patent Owner “points to 7 supposed ‘examples’ of ‘D320 modified PH20s.’ None are described in its disclosure or were actually made.” Reply 23 (citing Ex. 1133 ¶¶ 115–120). According to Petitioner, “[n]one address the unpredictability of making 5+ changes to a *native* PH20 sequence.” *Id.* (citing Ex. 1133 ¶¶ 115–120; Ex. 1003 ¶¶ 55–59).

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 4. Patent Owner asserts “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 (citing Pet. 12–16, 79, 103–110; Ex. 1004 ¶¶ 36, 104–167; Ex. 2077, 176:2–5; Ex. 1130, 97:14–99:10; Ex. 2070 ¶¶ 112–230, 343–428; 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.” Sur-reply 6. 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 in the protein using the data in the ’185 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 9 (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 10 (citing Ex. 2070 ¶¶ 61–67, 343–428). 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 11.

Patent Owner notes that “Petitioner insists that introducing multiple mutations into PH20 is unpredictable, raising on Reply various theoretical problems concerning protein folding, aggregation and the specter of ‘epistasis.’” Sur-reply 12. According to Patent Owner, “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 13. Patent Owner asserts that Petitioner “identifies no prior art or post-filing 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 15. 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 17–18.

Patent Owner asserts that

the specification discloses the common structural features based on that primary structure and the related mutagenesis data:

- 95% sequence identity to the primary structure of the recited SEQ IDs;
- The D320H, D320K, D320R, and D320S mutations;
- And for actives:
 - o A PH20 alpha-beta barrel fold, with known catalytic and binding sites.
 - o Lack of the inactivating changes identified in the disclosure.

Sur-reply 19–20. Patent Owner asserts “[t]here is no dispute that there are several highly active representative species disclosed in the specification. Moreover, Petitioner’s new expert 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 22 (citing Ex. 2301, 213:10–18, 85:19–99:18, 101:11–20, 159:13–25).

6. *Evidence and Analysis*

a) Description in the '185 patent

Our review begins with the claims and Specification of the '185 patent.¹⁷ Claim 1 recites a method “for increasing the delivery of a therapeutic agent” by administering a composition containing the therapeutic agent and a “modified PH20 polypeptide.” Ex. 1001, 313:18–23. The claim further recites that the sequence of the modified PH20 polypeptide is 95% identical to one of the 36 recited SEQ ID NOs and there must be a H, K, R, or S substitution at position 320. *See id.* at 313:24–37. In addition to these structural requirements, the claims include a functional limitation in that the modified PH20 polypeptide must exhibit hyaluronidase activity. *See supra* Section II.B (interpreting “modified PH20 polypeptide” to require hyaluronidase activity based on the definition in the Specification).

Indeed, this functional requirement is integral to the method recited in the challenged claims. The Specification teaches that “[d]ue” to their hyaluronidase activity “modified PH20 polypeptides can be used as a spreading factor to increase the delivery . . . of subcutaneously administered therapeutic agents.” Ex. 1001, 174:22–28; *see also id.* at 4:37–40 (“since [hyaluronan] is a major component of the interstitial barrier, hyaluronan-degrading enzymes (ie.g., hyaluronidase) . . . can be used to increase the dispersion and delivery of therapeutic agents”). In other words, the

¹⁷ Because there is no dispute that the specifications of the '185 patent and the '731 application contain the same relevant disclosure, for expediency herein we refer to the Specification of the '185 patent with the understanding that the same disclosures appear in the “common disclosure.”

description in the '185 patent indicates that enzymatically inactive PH20 polypeptides would not be useful in the claimed method.

The '185 patent generally describes PH20 polypeptides with “at least one amino acid replacement” 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 73:2–10. Significantly, the '185 patent discloses examples of mutants having single amino acid substitutions at every position of the mature, soluble PH20 polypeptide with analysis for most (but not all) those mutants showing whether the modification impacted hyaluronidase activity. *Id.* at 193:35–223:46 (Example 2), 227:5–273:24 (Example 4); *see also infra* § II.D.6.d (analyzing examples provided in the Specification).

The '185 patent also references the '457 publication, which discloses three double mutations and a single example of a triple mutation in the PH20 hyaluronidase enzyme. *See* Ex. 2068 ¶¶ 338–340; Ex. 2165, Table 16. These four multiple mutation examples are described as having activity, but none has a replacement at position 320 as recited in the challenged claims. *See* Ex. 2068 ¶¶ 338–340.

The '185 patent does not provide any other information regarding modified PH20 polypeptides with more than one mutation, nor does it provide any information regarding the three-dimensional structure of any PH20 or other hyaluronidase enzyme. *See generally* Ex. 1001; Ex. 1003 ¶¶ 106, 138 (“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”), 181 (same), 242 (protein structural models available to a POSA in 2011 such as a “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 or more concurrent changes.”).

b) Expert testimony

There is agreement amongst the experts, and we find, that the claims encompass the use of PH20 polypeptides with (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 four recited substitutions at position 320, and (ii) a number of additional modifications, including substitutions, deletions, and additions, that varies based on the particular sequence identity and SEQ ID NOs recited in the claim. Ex. 1003 ¶¶ 118–122; *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 23 changes that could be substitutions, deletions, or additions). There is also agreement, and we find, that these modifications result in approximately 10^{66} different polypeptide sequences within the sequence space of the broadest claims (e.g., permutations based on as many as 23 changes to the longest of the PH20 backbones in the recited SEQ ID NOs in claim 1) and approximately 10^{49} for the narrowest claim (i.e., permutations based on as many as 17 changes to SEQ ID NO:35 in claim 3). Ex. 1003 ¶ 124; Ex. 1004 ¶¶ 169–171; Ex. 1133 ¶¶ 48–49, 112; *see* Ex. 1130, 90:1–16 (“I don’t disagree with the method [Dr. Hecht and Dr. Park] used to calculate the theoretical maximum in the number of variants.”); Ex. 1131, 60:24–61:8 (similar).

The parties disagree, however, on the scope of the impact of the claimed $\sim 10^{49}$ to 10^{66} different polypeptide sequences on the protein's structure and resulting hyaluronidase activity.

(1) *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” and that “the single-replacement PH20₁₋₄₄₇ polypeptides reported in the common disclosure are not representative of all of the types of mutated PH20₁₋₄₄₇ polypeptides that have a particular substitution at position 320 and sets of between 1 and 22 *additional* substitutions at any of hundreds of positions within the PH20 protein.” Ex. 1003 ¶¶ 165–166.

Dr. Naismith concurs with Dr. Hecht, stating that “[t]here is no teaching in the patent or modelling software that would allow sets of 17^[18] combined substitutions that differ by more than around five changes from a known stably folded active PH20 to be predictably active.” Ex. 1133 ¶¶ 114–118; *see also id.* ¶¶ 258–260 (discussing and agreeing with Dr. Hecht's testimony). Dr. Naismith continues, stating that other than offering a relatively small number of “hypothetical” examples, “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.* ¶ 120.

¹⁸ As explained below, 17 is the maximum number of changes allowed by the narrowest of the challenged claims. *Infra* § II.D.6.a.; Ex. 1003 ¶ 124.

Dr. Hecht notes that claim language does not require “changes (besides the position 320 change) to be restricted to any region of the polypeptide” and these “changes can be additions, deletions or replacements, and for replacements, can be at any position in the sequence and to any other amino acid (*i.e.*, 19 alternatives).” Ex. 1003 ¶ 121. As discussed above, this results in a potential genus or sequence space of between about 10^{66} polypeptides for the broadest claims and 10^{49} for the narrowest. *Id.* ¶ 124; Ex. 1004 ¶¶ 169–171. Dr. Hecht characterizes even the minimum number of $\sim 10^{49}$ possible polypeptides as “astronomical in size.” Ex. 1003 ¶ 127.

Regarding structural 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 ¶ 159; *see also* Ex. 1133 ¶¶ 23–24 (agreeing). 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 especially true if the mutated residues are close to each other, either in sequence or in space, so that they interact with each other.” Ex. 1004 ¶ 161. Dr. Park cites Zhang (Ex. 1010), which states, “analysis of Hyal1¹⁹ point mutants highlights the importance of specific conserved

¹⁹ Hyal1 (also referred to in the record as “HYAL1” or “Hyal-1”) is one of the five homologous hyaluronidases, which also include PH20, encoded in the human genome. Ex. 1006, 6911. In the 2011–2012 timeframe, Hyal1 was the only human hyaluronidase for which the crystal structure had been solved. Ex. 2070 ¶ 121 n. 10. The parties’ experts agree it would have been the best template for structural modeling and analysis of PH20 that would have been available to a POSA at that time. *Id.* ¶¶ 118–120; *see also* Ex. 1004 ¶¶ 150–151 (Dr. Park stating that he used Hyal1 for his structural

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 Exhibit 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 [sequence identity and position 320 substitution] requirements, it is both enormous and highly heterogeneous” and “[e]ven 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 permit substrate recognition and catalysis.” Ex. 1133 ¶ 40.

Dr. Naismith states:

analysis and he “expected that a PH20 structure modeled on the HYAL1 template would be a reliable PH20 model given the high degree of sequence identity.”); Ex. 1003 ¶ 22 (agreeing).

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 (Fig. 4-53); 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 (Fig. 4-53) (alteration in original)). Dr. Naismith states "[l]arge numbers of those amino acid sequences [falling within the sequence space of the challenge claims] 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).

Dr. Naismith states:

I do not agree [with Dr. Petsko] that the 95% 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.

Ex. 1133 ¶ 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” and are “not representative of the breadth of modified PH20 polypeptides within the scope of the claims.” Ex. 1133 ¶¶ 115–116. 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.* ¶ 125.

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.” Ex. 1133 ¶ 130 (citing Ex. 1003 ¶¶ 49–50; Ex. 1004 ¶ 162).

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 a “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 the use of structural modeling to characterize 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.

Ex. 2077, 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 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." Ex. 2077, 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 between Hyal1 and PH20 would impact protein folding, stating: "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 "epistasis," i.e., the "non-additivity of single site 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." Ex. 2301, 106:10–22.

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 three dimensions] remained low for many years, until CASP12^[20] 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 CASP₁₄, 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 AlphaFold2 (AF2) program.” *Id.* at 9 (footnotes omitted). Dr. Naismith explains that the Scientific Background presents “an accurate historical perspective on the capabilities of computational tools to accurately predict a protein’s tertiary structure from its amino acid sequence” and shows those “tools did not reach predictive accuracy level comparable to experimental determination of structure until around 2019.” Ex. 1133 ¶ 135.

(2) *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

²⁰ 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.

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.

Id. ¶¶ 126–127. Dr. Petsko states: “a POSA would have expected that a folded modified PH20 that is 95% 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:

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 “in the experiments in the patent, the inventors changed each position in the protein to, on average, 13 other amino acids” and that the data from those experiments “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.” Ex. 1131, 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^[21] associated with a set of 10 or 15 or 20 mutations?”, Dr. Petsko answered: “No. They would not be able to

²¹ “[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 (and usually will) 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.

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 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 [a modified PH20 polypeptide’s] 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.

(3) *Review*

As to hyaluronidase activity, we credit Petitioner’s evidence showing that a POSA, in the 2011–2012 timeframe, would not have been capable of predictably determining the full scope of PH20 polypeptides having multiple modifications, i.e., changes in addition to the recited replacement at position 320 (i.e., H, K, R, or S), that would have retained hyaluronidase activity over the competing evidence offered by Patent Owner. As Dr. Park explained, SWISS-MODEL (and other then-available computational modeling techniques) would not reliably provide such information. Ex. 1004 ¶¶ 160–161; *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"). That testimony 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 experimental and computational techniques in view of the written description in the '185 patent could not have determined which of the many multiply-modified PH20 polypeptides within the scope of the challenged claims would retain hyaluronidase activity and which would not, and therefore the written description does not reasonably convey to the ordinarily-skilled artisan that the inventors had possession of the full scope of the claimed subject matter. Ex. 1003 ¶¶ 49–52, 164–165, 173–175; Ex. 1004 ¶¶ 62, 160; Ex. 1133 ¶¶ 121, 124–135 (explaining that while individual assessment can be made the breadth of the claims is such that "[i]t would require an impossible amount of time and effort to do that individualized assessment of the . . . possible combinations of mutation in the claim parameter sequence space"); *see also* Ex. 1131, 102:1–14 (Dr. Petsko conceding a POSA could not "predict the change to a protein's net free energy of stabilization associated with a set of 10 or 15 or 20 mutations" and could only "possibly" get a sense of whether those mutations would be destabilizing to the point of causing unfolding).

Patent Owner's evidence does not undermine 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 ¶¶ 264–274 (color-coding positions based on this data). More importantly, the data in the common disclosure do not show results for polypeptides having multiple modifications, which can greatly complicate the interactions involved undermining predictability. *See, e.g.*, Ex. 1003 ¶¶ 138, 165–166; Ex. 1133 ¶¶ 116, 131; Ex. 2077, 198:12–199:19, 202:9–206:3, 212:16–18; Ex. 2301, 106:17–108:15. This unpredictability is further evidenced by Dr. Naismith’s testimony, referring to Dr. Petsko’s textbook as illustrating an example in which 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 (Fig. 4-53); Ex. 1140, 329 (Fig. 1)). 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., as Dr. Simpson herself puts it, merely a “tool to engage in further modification”²²) 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

²² Ex. 2068 ¶ 157.

structural connections and three-dimensional modeling Patent Owner's experts attempt to make (*see, e.g.*, Ex. 2070 ¶¶ 126–213, 297–342; Ex. 2068 ¶¶ 123–125, 245, 294–313, 318) 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 ¶¶ 112–232 (identifying problems with the approaches proposed by Patent Owner's experts).

For these reasons, we find that a preponderance of the evidence 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 in the '185 patent.

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 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, 1335 (Fed. Cir. 2021) (quoting *Ariad*, 598 F.3d at 1349).

As explained above, the challenged claims are limited to the use of modified PH20 polypeptides having hyaluronidase activity. *See supra* Section II.B. Moreover, the claims recite a broad swath of sequence space, i.e., modified PH20 polypeptides comprising a H, K, R, or S substitution at position 320 in the reference sequence and for the narrowest claims as many as 16 additional modifications. However, the common disclosure only provides examples having single amino acid substitutions as position 320—there are no examples of multiply-modified PH20 polypeptides having the recited replacement at position 320 as well as other modifications and hyaluronidase activity. *See* Ex. 1133 ¶ 116 (summarizing deficiencies in the common disclosure).

Based on this limited disclosure and our claim interpretation, we find the evidence in this case is closer to *Juno* than *Capon*, and that the written description in the ’185 patent does not disclose sufficient structural features in the PH20 sequences associated with hyaluronidase activity to allow an ordinary artisan to distinguish which multiply mutated sequences will result in enzymatically-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 on the entire claim. *See* Ex. 1131, 64:12–17. And then-available computational modeling techniques would have only allowed a POSA to reasonably predict the effect of, at most, five substitutions on the resulting protein’s structure. Ex. 1004 ¶¶ 160–162; Ex. 1003 ¶ 239; Ex. 1133 ¶¶ 128–129, 133, 260–263, 268, 270–274, 281–284.

While *Capon* allows some reliance on the prior art for written description (*see Capon*, 418 F.3d at 1357–58), Patent Owner is trying to extend that to include that which is at most obvious to a POSA in view of the prior art, as opposed to what is actually described. That is, it may have been obvious to a POSA to align PH20 sequences with the sequences of other known hyaluronidase enzymes and obvious to use the crystal structure of a different hyaluronidase (Hyal-1) in SWISS-MODEL to generate a three-dimensional structure, but none of that is described in the common disclosure itself. “[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 the genus of multiply-modified PH20 polypeptides recited in the challenged claims, the four corners of the written description here do not demonstrate the inventors were in possession of such. *See id.* at 1356–57 (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.” *Ariad*, 598 F.3d at 1351. However, the evidence of record discussed above demonstrates possession of only a tiny fraction of species, i.e., four single-substituted (H, K, R, and S at position 320) PH20 polypeptides, out of a sequence space of $\sim 10^{112}$ modified PH20 polypeptides for the broadest claims and $\sim 10^{59}$ for the narrowest. The actual genus encompassed by the challenged claims is

smaller than the outer boundaries of their sequence space because the claims are limited to polypeptides having hyaluronidase activity. But that distinction highlights what is a salient point for our written description analysis—an ordinarily-skilled artisan in 2012 would not have been able to determine the set, or any significant portion of, the set of modified PH20 polypeptides having such activity from the description in the common disclosure. Instead of demonstrating the inventors were in possession of that genus, the written description leaves the POSA to experiment to try to find representative multiply-modified PH20 polypeptides having the required activity.

As our reviewing court explained in *AbbVie*, in instances such as these the written description must 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 possible mutations to various PH20 polypeptide sequences, but provides insufficient guidance for a POSA as of 2012 to determine which, if any, of the untested multiply-mutated forms will retain hyaluronidase activity.

Patent Owner contends the claims of the ’185 patent have a “narrower claim scope because you’re limited to this method for increasing delivery,” as opposed to claims for the “modified PH20 polypeptide” itself, and this distinction may distinguish the analysis in this case from that in the related

PGR proceedings.²³ *See* Hr’g Tr. 43:1–47:2. At the hearing, Patent Owner pointed to two cases: (1) *Teva Pharm. Int’l GmbH v. Eli Lilly & Co.*, 172 F.4th 1367 (Fed. Cir. 2026); and (2) *Ajinomoto Co., Inc. v. Int’l Trade Comm’n*, 932 F.3d 1342 (Fed. Cir. 2019) for its position. *Id.* We address both cases below.

In *Teva*, the Federal Circuit distinguished between “(1) claims to a method of using humanized anti-CGRP antagonist antibodies *to treat headache* and (2) claims to such antibodies themselves.” 172 F.4th at 1378. The court determined that “[t]he headache patents [i.e., the patents claiming the methods of use] make clear that their invention is the use of anti-CGRP antagonist antibodies, or humanized versions thereof, *to treat headache*—not such antibodies themselves.” *Id.* at 1377. Moreover, “a reasonable jury could have found that, by the priority date, (1) anti-CGRP antagonist antibodies and methods of making them were well known, and (2) humanization was a routine procedure.” *Id.* The court held that “[t]aken together, these fact findings . . . along with the specification’s disclosures” of “several examples of murine anti-CGRP antagonist antibodies and prior-art methods of humanization” were sufficient to support the jury’s rejection of the written description challenge. *Id.* at 1376–77.

Ajinomoto is one of the cases the Federal Circuit relied on in *Teva*. *See Teva*, 172 F.4th at 1374–75 (describing *Ajinomoto* as “particularly instructive for analyzing written description in circumstances like those here—where the claim pertains to a well-known genus that is not, itself, the

²³ *See, e.g.*, PGR2025-00003, Paper 128 (Final decision finding composition claims reciting the same genus of modified PH20 polypeptides unpatentable for lack of written description and enablement.).

invention”). The patent in *Ajinomoto* identified a specific gene in *E. coli* (the yddG gene) encoding a protein, which when enhanced to produce more of that protein yielded bacteria with improved properties. 932 F.3d at 1346. The claims recited a recombinant bacterium with its yddG gene activity enhanced by replacing the native promoter on the bacterial chromosome with “a more potent promoter.” *Id.* at 1347. The patent challenger argued there was not enough written description to support the genus of “more potent promoters.” *Id.* at 1358–59. But the Federal Circuit disagreed, observing that the patent described several examples of more potent promoters and the record supported a finding that enhancing promoter activity was well-known in the art. *Id.* at 1359. The court explained that the patent “makes clear that its invention was identifying the yddG gene . . . and discovering that the gene conferred on a microorganism” certain improved properties when the gene was enhanced, “not the well-known techniques for performing the amplification or expression enhancement.” *Id.* (internal quotations omitted).

Both *Teva* and *Ajinomoto* are readily distinguishable from this case. First, unlike the antibodies in *Teva* and the promoters in *Ajinomoto*, the claimed “modified PH20 polypeptides” in this case (i.e., those with the recited substitutions at position 320 and other modifications) are not well-known or otherwise described in the prior art. Instead, the claims are drawn to the use of an allegedly novel genus of modified PH20 polypeptides with one of four substitutions at position 320, as many as 22 additional modifications, and hyaluronidase activity sufficient to increase delivery of a co-administered therapeutic. As explained herein, the ’185 patent discloses four representative species, i.e., PH20 polypeptides corresponding to SEQ

ID NO:3 with a single substitution (H, K, R, or S) at position 320. *See infra* § II.D.6.d. But the claims encompass an immense genus of multiply-modified PH20 polypeptides and we credit Petitioner’s showing that, even with the patent data in hand, a POSA could not reliably predict whether any particular multiply-modified polypeptide having 5 or more changes would exhibit hyaluronidase activity such that it could be used to increase delivery of the therapeutic agent according to the method in the challenged claims. *See, e.g.*, Ex. 1003 ¶¶ 165–166; Ex. 1133 ¶¶ 116–118, 258–260.

Second, unlike *Teva* and *Ajinomoto*, the ’185 patent makes clear that the invention here is the modified PH20 polypeptides themselves—not the use of such hyaluronidases to increase delivery of a therapeutic agent. The Specification and various other references evidence that the use of PH20 and other hyaluronidases as spreading factors to increase delivery of a therapeutic agent was already known in the art. *See* Ex. 1001, 4:41–46 (“Various hyaluronidases have been used therapeutically (e.g., hyaluronidase sold under the trademarks Hydase® (bovine testicular hyaluronidase), Vitrase® (ovine hyaluronidase), and Wydase® (bovine hyaluronidase), typically as dispersing agents and spreading agents in combination with other therapeutic agents.”); 73:22–47 (“The hyaluronidase activity of PH20 accounts for the spreading activity observed in animal testes extracts that have been used clinically for decades to increase dispersion and absorption of drugs.”); *see* Ex. 1013, 430 (“The discovery of the human PH20 gene and its subsequent identification as a hyaluronidase opened the possibility of producing a recombinant version of the testes-sourced hyaluronidase enzymes that had been used commercially as spreading factors for > 50 years.”); Ex. 1080, 230–231 (same). The

challenged claims recite the same, long-established use of this class of enzymes as a spreading factor. This fact distinguishes *Teva* where the method claim was drawn to a **new** use (treating headache) of “a well-known genus [anti-CGRP antibodies] that is not, itself, the invention.” 172 F.4th at 1377. Here, the claims are drawn to an **old** use—meaning the invention, if any, is the recited genus of modified PH20 polypeptides itself.²⁴

With this understanding, the reasoning in *Ariad*, *Rochester*, *AbbVie*, and *Juno* all support a finding that disclosure of only a few species within the immense functionally-defined genus of “modified PH20 polypeptides” having the recited position 320 substitution as well as additional modifications up to the limits of the recited sequence identity requirements is insufficient to satisfy the written description requirement. Put differently, the written description of the ’185 patent is insufficient because it and the challenged claims merely “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.

For these reasons, we find that Petitioner has demonstrated by a preponderance of the evidence that for challenged claims 1–4 and 7–11 the ’185 patent does not comply with the written description requirement.

²⁴ In this regard, the challenged claims are more similar to the method claims found invalid in *Rochester* and *Ariad* than the claims in *Teva*. See *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 918 (Fed. Cir. 2004); *Ariad*, 598 F.3d at 1340–41 (finding claims to methods reciting the use of a functionally-defined genus of compounds invalid for lack of written description).

Similarly, for the reasons stated above, the written description does not demonstrate possession of the full scope of the claims of the '185 patent in any of the applications in the extensive priority chain, which all appear to have the same relevant disclosure, 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.

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 specified in the claimed methods to increase delivery of another therapeutic agent. Using that disclosure and knowledge in the prior art, the skilled artisan would have to perform undue experimentation to identify which of the $10^{49}+$ PH20 polypeptides having multiple amino acid replacements and/or truncations are “active mutant” PH20 polypeptides that can be used in the claimed methods of increasing delivery of a therapeutic agent.

Pet. 70–71 (citing Ex. 1003 ¶¶ 182–184, 203). Petitioner asserts that the “claims capture massive genera of modified PH20 polypeptides, most of which would have unknowable properties (particularly with respect to their ability to increase delivery of other therapeutic agents) absent individual production and testing.” *Id.* at 72–73 (citing Ex. 1003 ¶¶ 163–165).

Petitioner asserts that the '185 patent “provides an extremely narrow set of working examples: ~5,917 randomly generated single-replacement PH20₁₋₄₄₇ polypeptides, of which ~2500 were ‘active mutants.’” Pet. 74 (citing Ex. 1003 ¶¶ 106–107). According to Petitioner,

[t]hose examples are a tiny fraction of the 10^{49} to 10^{66} modified PH20 polypeptides whose use in the increased delivery method is covered by the claims, and provide no guidance that would help a skilled artisan navigate the ‘trial-and-error methodology the common disclosure describes using to make and identify modified PH20 polypeptides that can be used to increase delivery of another therapeutic agent.

Id. (citing Ex. 1003 ¶¶ 162–166, 173).

Petitioner asserts that the “prospective research plan requires a skilled artisan to engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of *randomized*

mutations” and “[s]econd, it provides no meaningful guidance about producing ‘active mutant’ modified PH20 polypeptides.” Pet. 75 (citing Ex. 1003 ¶¶ 151, 165, 185, 191–193, 196–197; Ex. 1018, 382). Petitioner asserts that 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 78 (quoting *Idenix Pharm. LLC v. Gilead Sci. Inc.*, 941 F.3d 1149, 1161–63 (Fed. Cir. 2019)) (alteration in original).

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.” Pet. 79 (citing Ex. 1003 ¶¶ 165, 242). Petitioner asserts that the “cumulative effects of multiple changes would also have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein’s structure.” *Id.* at 80. 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 ranges 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 81–82 (citing Ex. 1003 ¶¶ 165, 242).

3. Patent Owner’s Response

Patent Owner asserts “there 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.”

Resp. 54–55 (citing Pet. 41). Patent Owner asserts that

POSAs would recognize, within this narrow genus, that the four variants and their subvariants are structurally homogeneous in that they share at least 95% identical primary structure, the D320 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 55 (citing Ex. 2068 ¶¶ 287–293, 303, 316; Ex. 2070 ¶¶ 49–51, 53).

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 56.

Patent Owner asserts that the claims are drawn to “a method of use comprising 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.” Resp. 59. 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 61 (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 in the claimed method.” *Id.* (citing Ex. 1001, 69:13–71:48, 73:2–10, 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 the ’185 patent] in connection with homology models known in the art to make active subvariants” 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.” Resp. 63 (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” because “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 D320 mutation.” *Id.* at 64.

4. *Petitioner’s Reply*

Petitioner responds that

When **multiple** mutations are made together they affect a protein’s structure, capacity to fold, and stability differently than how each does alone. Combinations can disrupt or alter secondary and higher order structures, change their relative positioning, and even form new motifs. Combinations also can affect the folding process, cause remote effects not observed with individual changes (“epistasis”), and alter how the protein reacts to subsequent changes. The unpredictable effects of combinations of mutations prevent a POSA from being able to

predict whether the vast majority of multiply-modified PH20s in the sequence space will “properly fold,” exhibit activity much less increase delivery of therapeutic agents.

Reply 25–26 (citing Ex. 1003 ¶¶ 55–61, 149, 163–166; Ex. 1133 ¶¶ 97, 125, 127–128, 131, 224, 234, 254–261, 264, 332; Ex. 1131, 79:15–22, 89:21–90:24; 270:9–17; Ex. 1160, 383–85). Petitioner asserts “[e]ven *one* mutation can prevent folding, cause misfolding or incomplete folding, or instability that causes the PH20 to unfold outside the cell and form aggregates, as Dr. Petsko’s textbook illustrates.” *Id.* at 29 (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—*each* substitution causes a *unique* effect on *the entire* PH20 protein structure, rather than being limited to its position.” Reply 31 (citing Ex. 1133 ¶¶ 266–271).

Petitioner further asserts that, contrary to Patent Owner’s assertion that “the α/β barrel motif in PH20s makes it possible to predict how combinations of changes with impact the structure and functions of PH20s,” a “2009 paper (EX1144) demonstrates the contrary.” Reply 33. According to Petitioner, “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” and the “mutations involve *4-17* residues—comparable to the changes permitted by the claims” *Id.* at 34. Petitioner asserts that “[d]espite the constrained choices, most mutants *did not fold*.” *Id.* at 35 (citing Ex. 1133 ¶¶ 179–184).

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.

Reply 36–37 (citing Ex. 1003 ¶¶ 72, 76, 99; Ex. 1133 ¶¶ 237–238, 240–244, 248–250, 252, 291–325, Appendix B (Ex. 1135)). Petitioner asserts, “the description does not propose to do what Dr. Petsko did—select positions and substitutions based on *a proportion* of active mutants at a position. Where tolerance is used to inform changes, the disclosure instructs POSAs to generally not make inactivating substitutions in active PH20s.” *Id.* at 40 (citing Ex. 1026, 91:30–92:20; Ex. 1133 ¶¶ 206–209, 211) (internal quotations omitted).

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.” Sur-reply 6. Patent Owner asserts:

To evaluate written description and enablement, Drs. Petsko and Simpson used the same “visualization-based assessment”

technique that Petitioner admits was “a prevalent technique” in 2011 and “provid[es] a consistent, objective and unbiased evaluation of substitutions.” Indeed, Petitioner admits this method can be used to predict the effects of up to five modifications, *without the patent data*.

Id. (citing Pet. 102–110; Ex. 1003 ¶ 165; Ex. 1004 ¶ 162; Ex. 1133 ¶ 260 n.296) (alteration in original). Patent Owner cites Dr. Petsko’s testimony that in his opinion “a POSA could use the data from testing single mutants in the patent to select 15 or 20 substitutions in the PH20 sequences” and “they would be able to predict beforehand what that variant might do with a – in many cases, on a high degree of confidence.” *Id.* at 8–9 (citing Ex. 1131, 111:9–19, 114:5–16; Ex. 2070 ¶ 355). 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 11.

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*.” Sur-reply 13 (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 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,” but they did not. *Id.* at 15. According to Patent Owner, “A POSA armed with the patent’s data does not guess; the POSA predicts, then confirms.” *Id.* at 16.

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.” Sur-reply 24 (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).

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. Hecht relies on Dr. Park’s calculations to determine the number of distinct polypeptides within the sequence space of the challenged claims. Ex. 1003 ¶ 124 (citing Ex. 1004 ¶¶ 168–171, App’x F-1, F-2). Dr. Hecht’s table is reproduced below:

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

Id. Dr. Hecht’s table shows that the “sequence identity language causes the claims to encompass use of an immense number of distinct PH20 polypeptides,” ranging from $\sim 10^{49}$ for the narrowest claim to 10^{66} for the

broadest. Ex. 1003 ¶¶ 122, 124; *see also* Ex. 1004 ¶ 171 (“The number of distinct polypeptides is extremely large by all accounts, ranging from 10^{49} to 10^{66} .”). To illustrate how large these numbers are Dr. Hecht states that an “aggregate weight of the smallest set containing one molecule of each of the PH20 mutants would be . . . = 1.37×10^{27} kg. The weight of the Earth is ‘only’ $\sim 5.97 \times 10^{24}$ kg.” Ex. 1003 ¶ 125. That is, the set containing just one molecule of each polypeptide within the sequence space recited for even the narrowest of the challenged claims would weigh many orders of magnitude times more than the entire mass of planet Earth. *See also* Ex. 1133 ¶ 48 (confirming Dr. Hecht’s description of the sequence space).

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 Petitioner’s focus on “the absolute number of possible sequences that meet the 95% sequence identity limitation in the claims,” stating that “POSAs would not evaluate the scope of the claimed genus by calculating the total number of amino acid sequences that satisfy the 95% identify 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” and “a glycosylation site at (mature) position 333, because glycosylation at that site is required for activity.” *Id.* ¶ 357.

Dr. Simpson states:

[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 '185 patent and the knowledge in the art.

Ex. 2068 ¶ 360.

Dr. Petsko states that “POSAs think of the class of modified PH20 proteins sharing 95% of their sequence (including the recited change at position 320) as an extremely limited set of proteins. Those that fold are a limited set of structurally homogeneous proteins.” Ex. 2070 ¶ 391.

Dr. Petsko states:

To further illustrate the common structural features shared by the claimed polypeptides, I generated models of several D320K variant PH20s that satisfy the sequence identity requirements of claim 1. Specifically, I generated models for the following multiply modified PH20s:

- D320K Chimpanzee PH20
- D320K Gibbon PH20
- D320K Orangutan PH20
- N47A/N131A/D320K PH20
- N47A/N219A/D320K PH20

- N131A/N219A/D320K PH20
- N47A/N219A/N131A/D320K PH20

Id. ¶ 410. Dr. Petsko states that “all of the D320K models share a common structural feature in that they all have an interaction between K320 and E324. The D320S models share a common feature in that S320 does not interact with E324.” *Id.* ¶¶ 415–416.

In deposition, Dr. Simpson acknowledged the accuracy of Dr. Park’s sequence space calculations. *See* Ex. 1130, 90:1–16. However, 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 in his deposition: “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 . . . if you position that changed protein . . . and overlaid it on the structure of the human PH20 protein, 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, apart from position 320, 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 ’185 Patent as covering a ‘narrow’ and ‘structurally homogeneous’ set of proteins,” stating

If the set of administered polypeptides being claimed includes any polypeptide with an amino acid sequence that meets only the above two claim requirements [i.e., the sequence identity and substitution at position 320 limitations], 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 permit substrate recognition and catalysis. Dr. Hecht illustrated these points in his declaration.

Ex. 1133 ¶ 40 (citing Ex. 1003 ¶¶ 44–46, 55–61, 163–166). Dr. Naismith explains that Dr. Petsko uses “enzymatic activity and the ability to be secreted as ‘proxies’ for PH20 proteins that have ‘properly folded.’” *Id.* ¶ 58 (citing Ex. 2070 ¶ 128 n.12; Ex. 1131, 74:18–75:12, 86:17–87:14). 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.

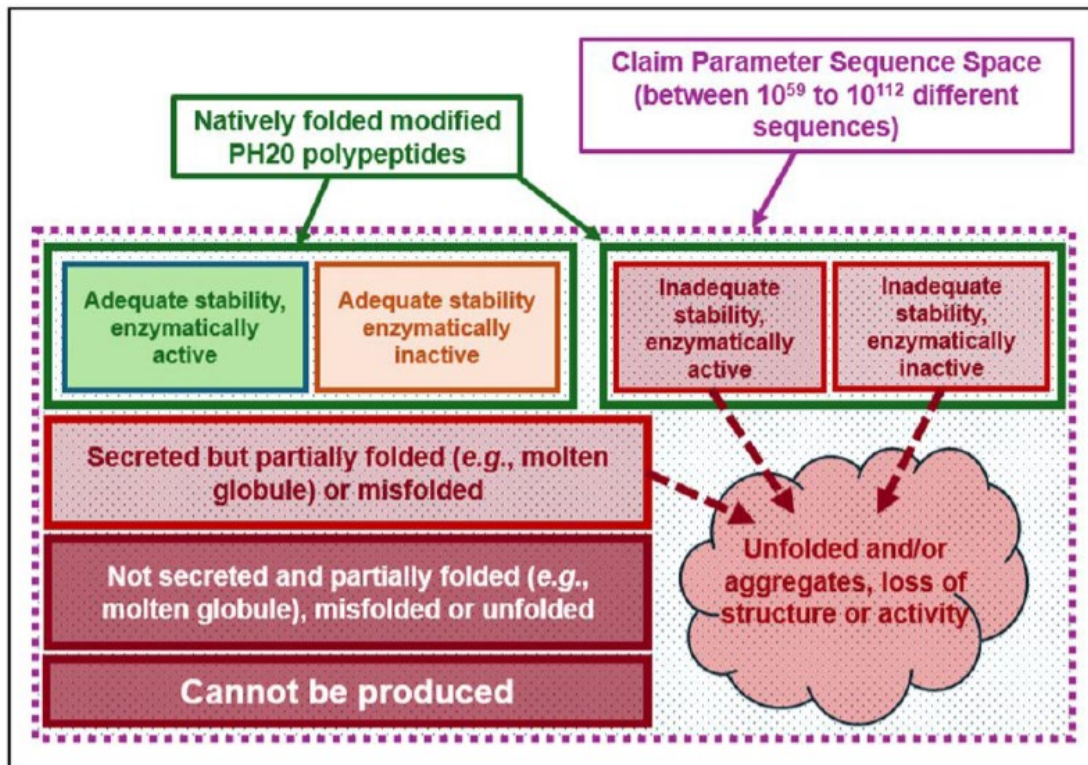
According to Dr. Naismith, sequences within the recited sequence space will adopt many different three-dimensional structures according to a complex folding process and that mutations to their amino acid sequence

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 (Dobson 2004a), 4). Dr. Naismith states that “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.” *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 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 [Patent Owner’s experts] that the 95% sequence identity requirement is a ‘structural feature’ of a modified PH20 polypeptide. It is a claim requirement that is determined mathematically.” Ex. 1133 ¶ 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 observed with respect to the structural comparisons of Hyal1 and PH20 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, 85:19–86:17.

Based on the evidence of record, we find that the breadth of the challenged claims is immense, comprising a sequence space ranging from $\sim 10^{49}$ distinct polypeptides for the narrowest claims to $\sim 10^{66}$ for the broadest. Ex. 1003 ¶¶ 123, 125; Ex. 1004 ¶ 171. 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, 61:19–64:17 (Dr. Petsko testifying there are a “large number” of properly folded, enzymatically active PH20 polypeptides within the sequence space and it would not have been possible to calculate or experimentally determine the number of such proteins).

We also disagree with Patent Owner’s attempt, through its experts, to characterize the scope of the recited PH20 polypeptides as “structurally homogenous.” *See, e.g.*, Resp. 55–59. 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); 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 ¶¶ 33, 317, 354–359; Ex. 2070 ¶ 58, 391–423. At most, their testimony shows that there may be some broad 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 ¶¶ 155–165. Therefore, it cannot be said to be “a ‘common structural feature’ of the entire set of 10^{49} to 10^{66} 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/β barrel’ motif present in the tertiary structure of the PH20 protein.” *Id.* ¶ 172. We therefore agree with Petitioner, and Dr. Naismith, that the challenged claims are directed to very broad, “structurally

heterogenous genera.” *See* Reply 4–6; 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 PH20₁₋₄₄₇ protein . . . could be applied to produce forms of PH20₁₋₄₄₇ that incorporate a single amino acid substitution (*e.g.*, the D320K or D320S substitutions . . .) with little effort.” Ex. 1003 ¶ 216. Dr. Hecht further states that “[t]he first experimentally determined structure of a hyaluronidase was [bee venom hyaluronidase], 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). Moreover, Dr. Hecht states that the Chao paper published in 2007 reported the structure for Hyal-1 and compared it to bee venom hyaluronidase, observing that they had “extensive overall structural similarity” including at their catalytic sites. *Id.* ¶¶ 81–82.

However, Dr. Hecht 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.” Ex. 1003 ¶ 93. Dr. Hecht also states that the “Zhang paper [Ex. 1010] reported that a truncation just upstream of the start of the Hyal-EGF domain

in HYAL1 reduced its activity to ~6%.” *Id.* ¶ 95. 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., PH20₁₋₄₄₆ vs. PH20₁₋₄₄₇ vs. PH20₁₋₄₄₈) exhibit variability in their activity.” *Id.* ¶ 97.

Dr. Hecht states “[t]here were limits to using rational design techniques^[25] in the 2011-timeframe.” Ex. 1003 ¶ 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.* at n.16 (quoting Ex. 1018, 378). Regarding directed evolution approaches, Dr. Hecht states that the “challenge . . . is scale. One has to identify the successful mutant out of an immense number of possibilities, which presents different kinds of challenges” such as the need for “sophisticated methods for generating mutations likely to yield beneficial changes, highly efficient, rapid and accurate screening methods that identify mutants which have desired properties (and which avoid those that do not) and efficient recovery and characterization techniques.” *Id.* ¶ 52 (citing Ex. 1018, 378; Ex. 1059, 1226–1227).

²⁵ “At a conceptual level, there are two approaches for creating engineered proteins, referred to as ‘rational design’ and ‘directed evolution.’” Ex. 1003 ¶ 47 (citing Ex. 1059, 1225–1227; Ex. 1018, 378–379; Ex. 1017, 223). “‘Rational design’ involves an in-depth study of the structural features of a protein and their contribution to stability and function” using computational tools, e.g., sequence alignments and structural modeling such as SWISS-MODEL. *Id.* ¶¶ 48–49 (citing Ex. 1017, 224–228; Ex. 1018, 378). “In ‘directed evolution,’ one generates large libraries of mutant proteins with randomly distributed mutations” and “then screens those libraries to find mutants having the desired properties.” *Id.* ¶ 51 (citing Ex. 1059, 1225–1226).

Regarding multiple mutations, Dr. Hecht states “[b]ecause so many secondary structures are dependent on particular patterns of amino acids . . . 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.” Ex. 1003 ¶ 55. Dr. Hecht states that even in just a ten amino acid substitution situation, “[t]here are approximately 6×10^{12} different scenarios of 10 substitutions.” *Id.* ¶ 58.

In deposition, Dr. Hecht referred to differences in present day computational modeling tools such as AlphaFold as compared to the tools available to a POSA in the 2011–2012 timeframe, explaining: “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 the 2011–2012 timeframe, 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. 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. It's also my opinion, though, that if I have this information about invariant residues in an alignment and about functional data that implicates certain of those invariant residues in maintaining enzymatic activity of the enzyme, that a POSA would avoid residues that are invariant if they wish to maintain activity of the polypeptide.

Ex. 1130, 121:8–24.

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.” 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. 1008, 833; Ex. 1033, 1028) (alteration in original).

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 ¶ 185 (citing Ex. 1008, 825).

For example, Stern (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 [five human hyaluronidases] appear [to] have the same ‘alpha-beta barrel’ motif. Despite this similarity, the five proteins exhibit subtle but meaningfully different substrate preferences and activity.” Ex. 1133 ¶ 186.

Dr. Naismith states that Zhang (Ex. 1010), a paper co-authored by Dr. Simpson, “highlights the limits of homology models in predicting mutation effects.” Ex. 1133 ¶ 197. Dr. Naismith states:

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. (citing Ex. 1130, 130:9–16; Ex. 1010, 9436–9437). Indeed, Zhang itself states that “[a]nalogy to point mutations in both sperm hyaluronidase, PH-20 (25), and bacterial *N*-acetylglucosaminidase H (20), further suggested Asp¹²⁹ and Glu¹³¹ would be critical for catalytic activity of the enzyme. . . .

Interestingly, Asp¹²⁹ 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; *see also* Ex. 2070 ¶ 121 n.10 (“In 2012, Hyal-1 was the only human hyaluronidase for which a crystal structure had been solved.”).

Based on the evidence of record, we find that simply making and expressing a modified PH20 polypeptide having one of the recited substitutions at position 320 was well within the state of the prior art. The evidence also shows that molecular modeling of a putative PH20 structure, using a then-available tool such as SWISS MODEL, would have been routine as well, and that there was information about several amino acid locations within PH20 and related hyaluronidases that were involved in catalytic activity. *See, e.g.*, Ex. 1033, 1028–31; Ex. 2070 ¶¶ 139–140.

However, the evidence of record also demonstrates that it was known that mutations, even those predicted to be conservative or non-conservative ones, may impact protein function and physical shape in unpredictable ways. *See, e.g.*, Ex. 1003 ¶¶ 81–100 (discussing references showing disparate effects from modifying hyaluronidases and evidencing uncertainty regarding the effect of changes, particularly to certain regions of PH20, e.g., changes to the Hyal-EGF domain); Ex. 1133 ¶¶ 185–197, 223–224 (similar). This is further evidenced for example by Zhang, which teaches that Asp¹²⁹ 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 to the protein’s hyaluronidase activity. *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,

161; Ex. 1004 ¶ 161–162; Ex. 1133 ¶¶ 254–261 (discussing epistasis²⁶ 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^{49} to 10^{66} members of the challenged claims’ sequence space would retain functional hyaluronidase activity aside from actually making and testing particular polypeptides was not known in the prior art as of the 2011–2012 timeframe.

d) Presence of Working Examples

Dr. Hecht states that the ’185 patent “provides a compilation of all the mutants that apparently were produced by the inventors in Table 8. There are 6,753 entries in this table. These are all mutants generated by substituting one amino acid from PH20₁₋₄₄₇.” Ex. 1003 ¶ 106. Other tables (e.g., Tables 3, 5, 9, and 10) identify the number of “active” and “inactive” mutants, albeit with some unexplained discrepancies. *Id.* ¶¶ 106–107. Dr. Hecht calculates that based on the data in the ’185 patent “57.1% were inactive, and 29.4% others had activity <100%.” *Id.* ¶ 108.

Dr. Petsko states that “[t]he ’185 patent provides a comprehensive and systematic analysis of each position on PH20, achieved through large-scale

²⁶ Dr. Naismith explains that “epistasis refers to a non-additive interaction of an additional mutation, where the functional effect of the functional mutation is context-dependent,” meaning that when combined two singly beneficial mutations may be deleterious. Ex. 1133 ¶¶ 255–256 (citing Ex. 1160, 383–385).

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. Dr. Simpson states:

The inventors provide experimental data for the D320H, D320K, D320R, and D320S 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.

Based on the evidence of record, we find that the Specification of the ’185 patent includes four working examples of “modified PH20

polypeptides” within the scope of the challenged claims, i.e., polypeptides corresponding to SEQ ID NO:3 with a single substitution (H, K, R, or S) at position 320. All four of those variants were shown to have hyaluronidase activity. Ex. 1001, 252:32–41 (entries in Table 10 disclosing active mutants with a D320 substitution).

The ’185 patent also discloses data for most of the other modified polypeptides having a single substitution at one position in PH20,²⁷ classifying such mutants as either “inactive” or “active” and for the latter disclosing data showing their activity relative to the unmodified protein. Ex. 1003 ¶¶ 106–108 (referring to Tables 8–10 in the ’185 patent). This evidence shows that more than half of the single substitution variants tested in the ’185 patent’s working examples resulted in what the Specification describes as “inactive mutants,” which presumably could not be used in the claimed method.²⁸ *Id.* ¶ 108; *cf* Ex. 2070 ¶¶ 263–274 (Dr. Petsko tabulating

²⁷ Dr. Hecht observes that the ’185 patent provides no data for 836 of the 6,753 possible single substitution mutants listed in Table 8. Ex. 1003 ¶ 106. 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 ’185 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.,* Resp. 13–14 (characterizing the patent disclosure as “a comprehensive and systematic analysis of each and every position within the primary structure of PH20”)).

²⁸ As noted above, Example 14 shows the “PH20 variant F204P” had dispersion activity similar to unmodified PH20. Ex. 1001, 308:29–41. This is consistent both with the Specification’s identification of that variant as

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. 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 320.

e) Amount of Direction or Guidance Presented

The ’185 patent states that “one or more modified PH20 polypeptides are tested for a desired activity or property, such as increased stability.” Ex. 1001, 129:28–30. The ’185 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 129:45–130:3. The ’185 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

one of the “active mutants” in Table 9 (*id.* at 244:51) and the fact that F204P is not one of the F204 variants identified as “inactive mutants” in Table 10. *See id.* at 265.

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 130:45–52. The '185 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 under a normal or control assay condition.” *Id.* at 135:31–35. The '185 patent states that “[p]roteins, such as modified PH20 polypeptides, can be purified using standard protein purification techniques known in the art.” *Id.* at 145:33–35.

Dr. Hecht states that the '185 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 ¶¶ 103–104. Dr. Hecht states that the data in the '185 patent shows “most of the single-replacement PH20₁₋₄₄₇ mutants that were tested exhibited less activity than the unmodified PH20₁₋₄₄₇ (*i.e.*, 57.1% were inactive, and 29.4% others had activity <100%).” *Id.* ¶ 108.

Dr. Hecht further states “the data for testing the 409 mutants reported in Tables 11 and 12 [of the '185 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 PH20₁₋₄₄₇ form specifically.” Ex. 1003 ¶ 76.

Regarding multiply-modified peptides, Dr. Hecht states:

Unlike its description of single-replacement PH20₁₋₄₄₇ mutants, the common disclosure 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.

Ex. 1003 ¶ 184. Dr. Hecht characterizes the '185 patent's disclosure of "how to make modified PH20 polypeptides, including those with more than one amino acid substitution" 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.* ¶ 185.

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 [the '185 patent's] 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.

Patent Owner's experts characterize the '185 patent's disclosure differently. For example, 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, make the desired changes, depending on the POSA's goals." Ex. 2068 ¶ 375.

Similarly, 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 ’185 patent in hand, the POSA knows what positions tolerate substitution and which do not. The POSA would 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 that “with the ’185 patent in hand [a POSA] would not make a randomly generated combinatorial library of billions of sequences that happen to be at least 95% identical to SEQ ID NO: 3 and then screen it for activity, because it makes no sense to do so.” *Id.* ¶

347. Dr. Petsko also 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. ¶ 374.

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 responds to Dr. Simpson's and Dr. Petsko's characterization of the common disclosure, stating that it

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 ¶ 153.

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." Ex. 1133 ¶ 206 (citing Ex. 1003 ¶¶ 182–187; 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.* ¶ 207 (citing Ex. 1003 ¶¶ 193–197).

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" and "there was no reliable way to predict in advance which, if any, additional mutations would restore activity in a given

protein, or PH20” particularly since “such mutations are often distributed throughout a protein and act through indirect effects on stability or dynamics, rather than through obvious local structural corrections.”

Ex. 1133 ¶¶ 212–213.

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 substitutions within the native PH20 structure.

However, the evidence also shows that the ’185 patent provides very limited guidance regarding effective methods to identify which of the immense number of distinct polynucleotides having both the recited position 320 substitution and other modifications (i.e., multiply-modified polypeptides) are likely to have activity other than actually making and testing them. *See* Ex. 1003 ¶¶ 186–192; Ex. 1133 ¶¶ 206–207. To the extent computational tools and modeling might have been used, along with the data in the ’185 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.

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 ¶ 165 (emphasis added). Dr. Hecht states that “the single-replacement PH20₁₋₄₄₇ polypeptides reported in the common disclosure are not representative of all the types of mutated PH20₁₋₄₄₇ polypeptides that have a particular substitution at position 320 and sets of between 1 and 22 *additional* substitutions at any of hundreds of positions within the PH20 protein.” *Id.* ¶ 166.

Dr. Hecht states that “[m]aking and identifying all of the multiply-modified PH20 polypeptides that are within the immense set of polypeptides . . . defined by the claims’ sequence identity parameters would require not only an undue amount of experimentation, it likely is impossible.” Ex. 1003 ¶ 182. Dr. Hecht states that the directed evolution methods of the ’185 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. ¶ 199.

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.* ¶ 391.

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.’ That is because the PH20 structure can be modeled.” Ex. 2070 ¶ 117 (quoting Ex. 1004 ¶ 36).

Dr. Petsko states:

A POSA seeking to make a modified PH20 with the ’185 patent in hand would not make a randomly generated combinatorial library of billions of sequences that happen to be at least 95% 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 ’185 patent, the POSA has a much more sensible strategy.

Id. ¶ 347. However, Dr. Petsko does not identify any teaching in the ’185 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 ¶ 260.

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 $\sim 10^9$ proteins.” *Id.*

After reviewing the record, we find the evidence and expert testimony offered by Petitioner 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 ¶¶ 160–162; Ex. 1003 ¶ 242; Ex. 1133 ¶¶ 130–135, 262–265, 272–276, 283–286.

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 ’185 patent follow directed evolution approaches. Ex. 1001, 127:8–12; Ex. 1003 ¶¶ 185–190. In such approaches, libraries of modified polypeptides are prepared by random or site-directed mutagenesis and screened for activity. Ex. 1001, 127:37–42. 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, 128:17–22, 135:5–13; Ex. 1003 ¶¶ 188–190. 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 ¶¶ 193, 196–197; *see* Ex. 1133 ¶¶ 206–207 (“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 polypeptides within the sequence space of the challenged claims for hyaluronidase activity. *See, e.g.*, Ex. 1003 ¶¶ 182, 199–203. 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 2011–2012 timeframe would have been capable of testing the full scope of the challenged claims. Ex. 1133 ¶ 260.

We are unpersuaded by Patent Owner’s attempt to sidestep the directed evolution experiments taught in the ’185 patent though 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 ¶¶ 377, 379; Sur-reply 6–9 (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 ’185 patent. Ex. 1133 ¶¶ 204–224. Second, Dr. Naismith identifies a number of errors in Dr. Petsko’s positional tolerance table that generally undermine the credibility of Patent Owner’s experts’ analysis in this regard. *Id.* ¶¶ 240–244.

Third, we credit Dr. Naismith’s substantive criticisms of Dr. Petsko and Dr. Simpson’s opinions that the ’185 patent data provides a “functional map”²⁹ that would allow a POSA to predict which multiply-modified mutants would have hyaluronidase activity without actually making and testing them. *See* Ex. 1133 ¶ 234 (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 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 ’185 patent. *Id.* ¶¶ 212–213; 254–271; *see also* Ex. 1003 ¶¶ 58–61, 147; Ex. 1004 ¶¶ 160–162. Patent Owner suggests such evidence

²⁹ *See, e.g.*, Ex. 2070 ¶ 44.

can be overlooked because instances of epistasis are “rare” and an inactive PH20 polypeptide “will stay inactive . . . absent intentional ‘rescue’ mutations.” *See* Sur-reply 10–13. 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. *See* Ex. 2070 ¶ 347; *see also* Ex. 1133 ¶ 239 (“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 ’185 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 ¶ 147; *see also* Ex. 1133 ¶ 278 (explaining how even with the patent data in hand “an immense sequence space remains for which the dataset provides no predictive insight, meaning the individual combinations would need to be produced and experimentally investigated”). Accordingly, we find Petitioner’s position more persuasive than Patent Owner’s competing position and evidence.

Indeed, the facts at issue in this case are similar to those in *Idenix*, 941 F.3d at 1156 where, in a genus of billions, the Federal Circuit explained that 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 multiply-modified PH20 polypeptides within the 10^{49-66} sequence space sufficient to enable the full scope of the challenged claims, the quantity of experimentation would likely be many orders of magnitude more than that needed in *Idenix*.

For these reasons, we find that a very large amount of experimentation would be necessary to enable the full scope of the challenged claims.

g) Predictability of the Art

Dr. Hecht states:

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 to . . . be 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.* ¶ 99. 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.* ¶ 165.

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.” Ex. 1003 ¶ 167. For example, Dr. Hecht explains that

“the sequence identity language causes the claims to capture multiply-mutated PH20 polypeptides with C-terminal truncations that truncate the sequence below position 429.” *Id.* ¶ 170. Dr. Hecht observes that the common disclosure “describes no multiply-modified ‘active mutant’ PH20 polypeptides” much less “those having fewer than 447 residues and provides no guidance about making enzymatically active mutants based on PH20 sequences ending before position 447 [i.e., truncated sequences] and containing 2 or more substitutions.” *Id.* ¶ 173.

Dr. Hecht continues:

In other words, the common disclosure also does not help the skilled artisan identify which of the trillions of possible PH20 polypeptides of varying length with 2 to 23 substitutions have hyaluronidase activity and would be useful in a method for increasing delivery of a therapeutic agent to a subject; 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.

Ex. 1003 ¶ 175. Dr. Hecht states that a POSA following the ’185 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.* ¶ 196. Dr. Hecht’s testimony, as further supported by record evidence, demonstrates that it is highly unpredictable which polypeptides would have hyaluronidase activity. *See, e.g., id.* ¶¶ 147, 159–181.

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 intractable.

Ex. 1004 ¶ 161. 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.* ¶ 162.

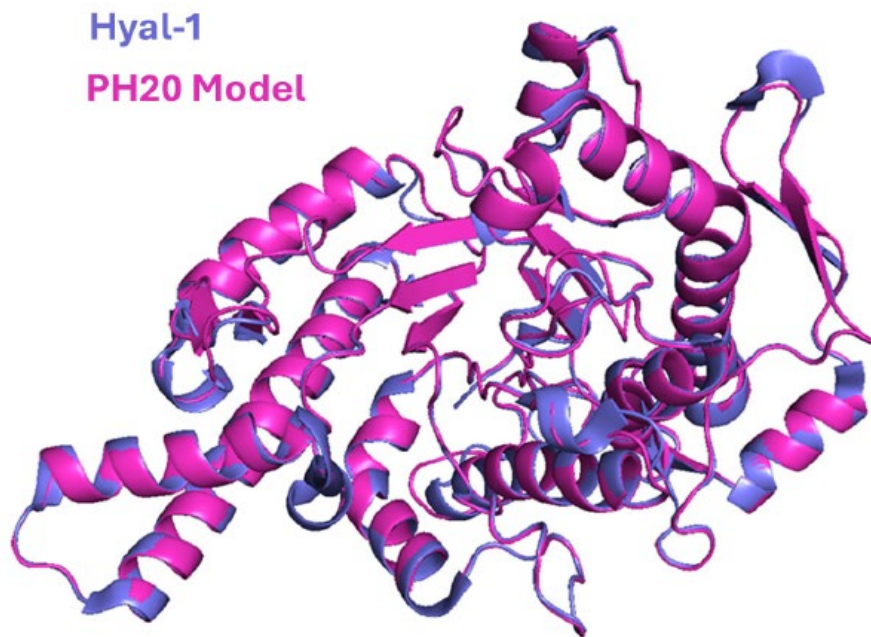
In deposition, Dr. Park, addressing single mutations, stated: “The problem is when you’re looking at one substitution, there are only so many interactions that a single amino acid can make, and those are relatively straightforward to discern for an expert.” Ex. 2077, 198:12–16. Dr. Park then stated that this was not the case for multiple mutations because:

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 (citing Ex. 1006, 6912; Ex. 1008, 826). Dr. Petsko presents the figure reproduced below:



Id. ¶ 132. The figure above shows the PH20 model superimposed on the Hyal-1 structure. *Id.* 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 “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 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

Zhang [Ex. 1010], on which Dr. Simpson is an author, contains mutagenesis data and provides insight regarding Hyal-1 residues required for activity. Arming [Ex. 1011] reports the results of mutagenesis experiments with PH20. 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.

Ex. 2070 ¶ 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 95% 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, 233–389). 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 D320K substitution. The POSA would have expected those proteins to be active in view of the disclosure in the patent.

Ex. 2068 ¶ 387 (citing Ex. 2070 ¶¶ 413–434).

In deposition, Dr. Simpson stated, “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 D320K substitution was introduced in three primate sequences, they would properly fold and be enzymatically active”, however,

[n]one of these proteins that Dr. Petsko described were made or tested. It is important to note that they represent special cases. Dr. Petsko’s experiment of introducing the D320K 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 17 combined substitutions that differ by more than around five changes from a known stably folded active PH20 to be predictably active, or soluble or exhibit the ability to increase delivery of a therapeutic.

Id. ¶¶ 117–118 (citing Ex. 2070 ¶¶ 361–366, 410–418).

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.”

Ex. 1133 ¶ 125. 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. ¶ 131 (citing Ex. 2164, 26).

Dr. Naismith states that

[t]he [Scientific 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.

Ex. 1133 ¶ 135 (citing Ex. 1027, 8).

According to Dr. Naismith the alpha-beta barrel motif that Patent Owner's experts point to in PH20 is a common motif. *See* Ex. 1133 ¶ 139. 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 classification." *Id.* ¶ 141. 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.*

Dr. Naismith explains that "the phrase 'PH20 alpha-beta barrel fold' as it is being used by Drs. Petsko and Simpson" is not a precise description nor does it identify the structural features shared by enzymatically active forms of the PH20 protein. *See* Ex. 1133 ¶¶ 154–165. 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.* ¶ 164. 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 notes discrepancies in the patent data and Dr. Petsko’s positional analysis thereof. *See* Ex. 1133 ¶¶ 240–253. For example, he 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.* ¶ 241; *see also id.* ¶ 242 (identifying 50 such double counted mutants). 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.* ¶ 243. Dr. Naismith further identifies flaws in the hyaluronidase assay design and reporting in the ’185 patent that limit the information a POSA can draw from it. *Id.* ¶¶ 250–253. 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, because the data still provides no reliable basis for predicting how multiple substitutions distributed across the

protein will interact to affect folding, stability, solubility or activity. Thus, an immense sequence space remains for which the dataset provides no predictive insight, meaning the individual combinations would need to be produced and experimentally investigated.

Id. ¶ 278.

Based on the record as a whole, we again find the expert testimony and other evidence offered by Petitioner 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 considered to identify modified PH20 polypeptides with hyaluronidase activity that could be used in the claimed methods during the 2011–2012 relevant timeframe: 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.

As explained above, the '185 patent itself only discusses directed evolution approaches involving library screening of random and site directed mutations. *See* Ex. 1001, 127:4–135:42; Ex. 1003 ¶¶ 185–190. Both Petitioner's and Patent Owner's experts testified that library screening and site directed mutation at all positions would not be possible for the full scope of claim 1. *See, e.g.,* Ex. 1003 ¶¶ 199–202; Ex. 1131, 64:12–17; Ex. 1133 ¶¶ 124, 260.

As to the use of homology modeling, we credit Petitioner's experts' testimony that, even with the '185 patent data in hand, the technology available in the 2011–2012 timeframe would not have been able to

reasonably predict the impact of more than about five changes to the PH20 protein on hyaluronidase activity. Ex. 1003 ¶¶ 165, 183; Ex. 1004 ¶¶ 160–162; Ex. 1133 ¶¶ 118, 125, 259–265, 323. That testimony is supported by the Scientific Background for the 2024 Chemistry Nobel Prize. *See* 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 CASP12 in 2016.”); Ex. 1133 ¶ 135. 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 provides an alignment of the human hyaluronidases that is reproduced below:

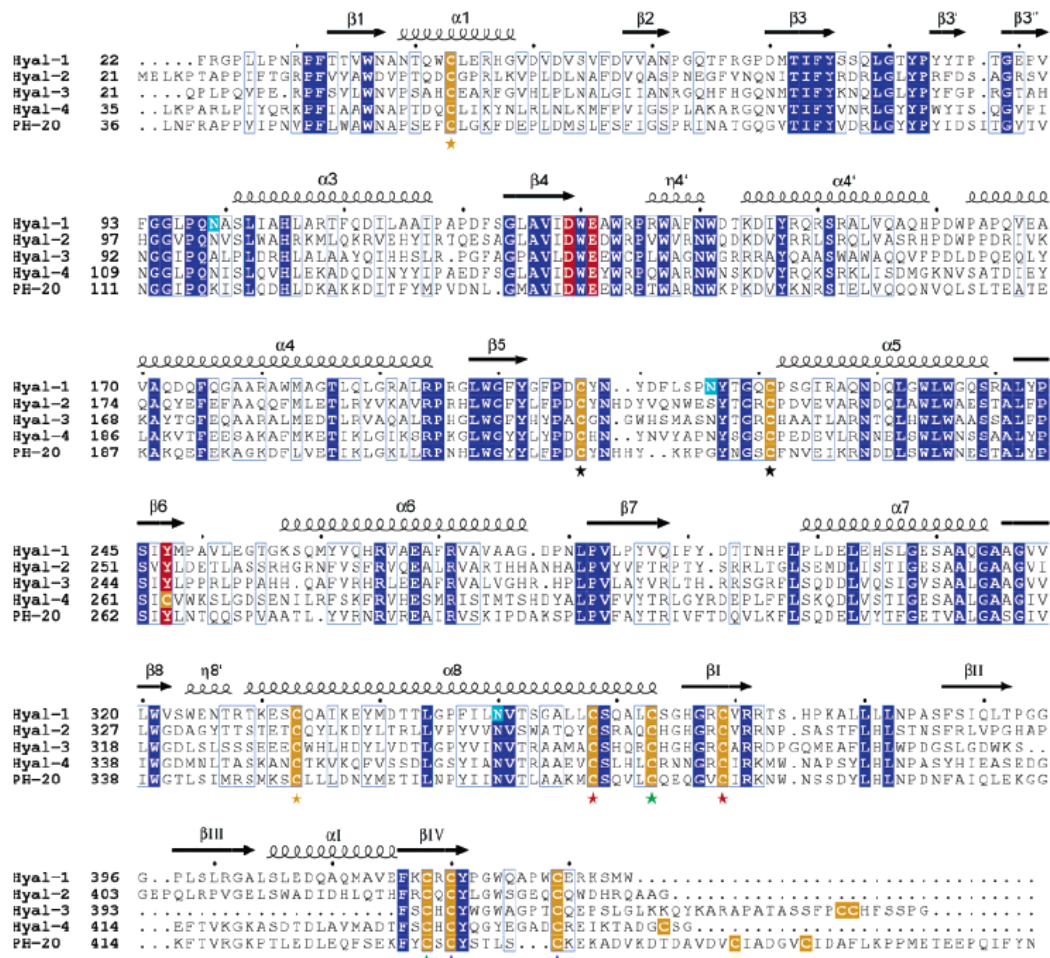


Figure 3: Structure-based sequence alignment of human hyaluronidases. Invariant residues are shown in blue except for three key catalytic residues that are colored red. Cysteine residues are colored yellow. The hHyal-1 N-glycosylated asparagine[] residues are colored turquoise. Residues exhibiting conservative 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 amino acids are invariant (in blue or red). This sequence alignment information would, therefore, not be sufficient to predictably identify which residues for the full scope of challenged claims would allow for mutation without loss of hyaluronidase activity.

Therefore, based on the evidence of record, we find that it is unpredictable which modified PH20 polypeptides within the full scope of the challenged claims of the '185 patent would retain hyaluronidase activity sufficient for their use in the methods of the challenged claims.

7. Conclusion

Based on our review of the *Wands* factors in view of the record as a whole, we find that undue experimentation would have been required to practice the full scope of the challenged claims. The claims are extremely broad, encompassing the use of modified polypeptides having as many as 23 amino acid modifications in some instances, such that the “number of distinct polypeptides [within the sequence space of the challenged claims] is extremely large by all accounts, ranging from 10^{49} to 10^{66} .” Ex. 1004 ¶ 171; *see also* Ex. 1003 ¶¶ 124–125. The level of 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 (*see* Ex. 1003 ¶ 80), the evidence also shows that structural modeling and other computational techniques were not yet reliable to predict the effect of multiple mutations. *E.g.*, Ex. 1004 ¶¶ 160–162. The '185 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. *See, e.g.*, Ex. 1003 ¶¶ 138, 147–150.

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, both

sides' experts acknowledge that actually making and testing the full scope of the potential genus of multiply-modified polypeptides would not be possible. Ex. 1003 ¶¶ 182, 199–203; Ex. 1133 ¶ 260; *see also* Ex. 1130, 93:13–24; Ex. 1131, 64:12–17. 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 as of December 2012, even when used in combination with the single substitution data in the '185 patent, could not be used to reasonably predict the effect of more than about five amino acid changes on protein structure and activity. *See, e.g.*, Ex. 1003 ¶¶ 61, 147–148, 165, 183; Ex. 1004 ¶¶ 160–162; Ex. 1133 ¶¶ 118, 125, 259–265, 323.

Therefore, considering all of the *Wands* factors and the totality of the record, we find by a preponderance of the evidence that undue experimentation would have been required to enable the full scope of the challenged claims. The challenged 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; and

(4) considering objective evidence indicating obviousness or non-obviousness. *KSR*, 550 U.S. at 406.

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.” Ex. 1005, 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).” Ex. 1006, 6911 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.” Ex. 1006, 6914. Figure 3 of Chao is reproduced below:

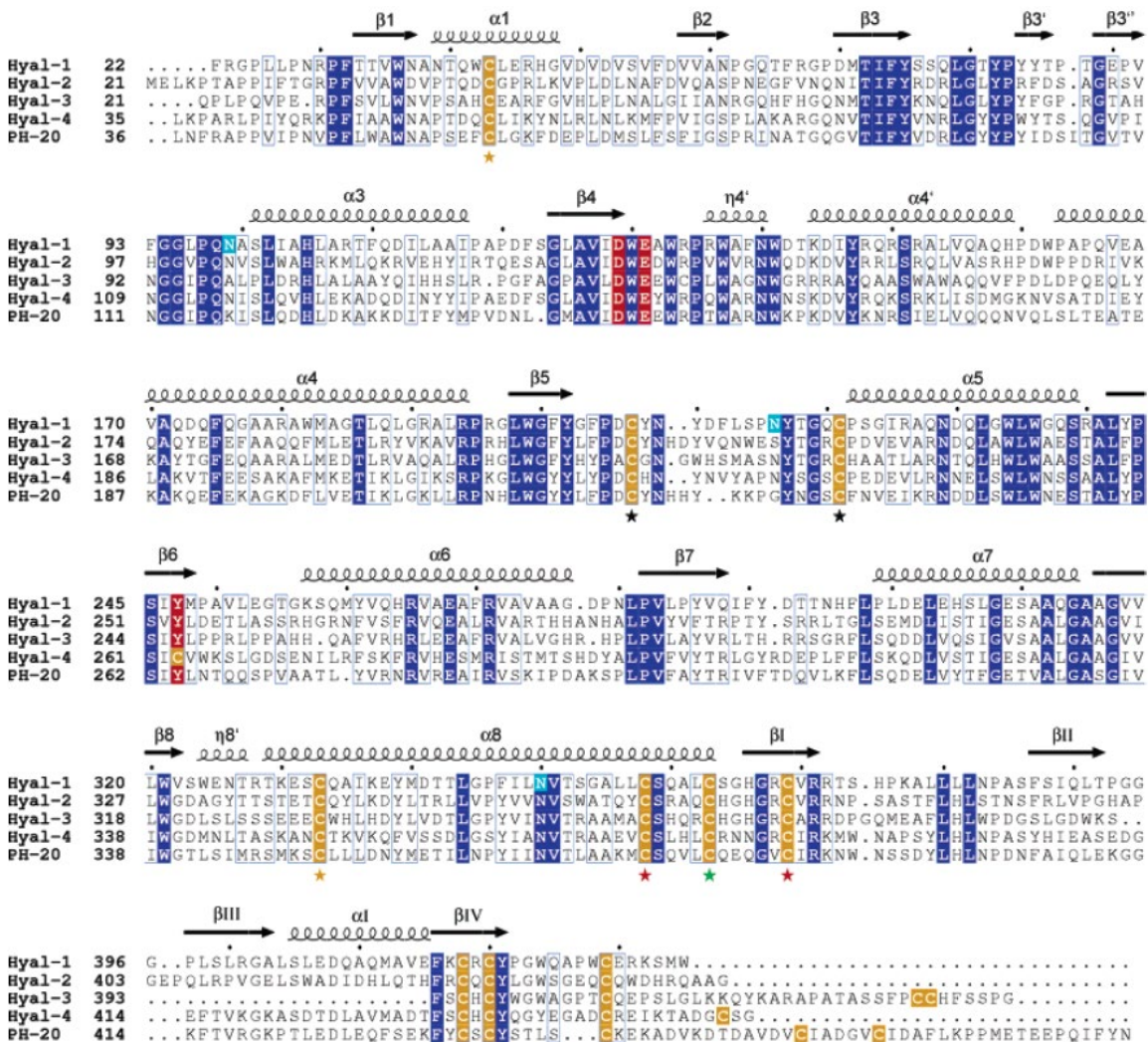


Figure 3 shows

[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 asparagine[] 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.

Ex. 1006, 6916.

3. *Asserted Obviousness over the '429 Patent and Chao*

a) Petitioner's Position

Petitioner contends that claims 1–4 and 7–11 would have been obvious over the '429 patent in view of Chao. Pet. 88. Petitioner asserts that the '429 patent “teaches making a *particular* type of modification (a single amino acid substitution) in 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}).” *Id.* at 90–91 (citing Ex. 1003 ¶ 219; Ex. 1004 ¶ 32). Petitioner also asserts that the '429 patent teaches the use of modified PH20 polypeptides to increase spreading and delivery of other agents. *Id.* at 91–93.

Petitioner asserts that Chao showed that “hyaluronidases share a highly conserved active site;” “predicted secondary structures,” “invariant conserved positions, and “residues involved in catalysis;” and “identified a characteristic pattern for the Hyal-EGF domain in PH20 at positions 337–409.” Pet. 94–96 (citing Ex. 1006, 6911, 6916–6917 (Fig. 4A); Ex. 1003 ¶¶ 81–84, 87, 224; Ex. 1004 ¶¶ 89–92, 97–98).

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.” Pet. 96 (citing Ex. 1003 ¶¶ 225–227; Ex. 1004 ¶¶ 22, 25–30, Appx. D-3). Petitioner asserts by performing this analysis, as Dr. Park did, “a skilled artisan would have identified position 320 as a position in a non-essential region [of] PH20₁₋₄₄₇.” *Id.* at 98 (citing Ex. 1003 ¶ 234; Ex. 1004 ¶¶ 31–32, 104, Appx. D-2; Ex. 1005, 16:14–22, 16:24–36; Ex. 1006, 6916).

Petitioner asserts that the “skilled artisan also would have selected lysine (K) for . . . a single substitution at position 320 in PH20₁₋₄₄₇.” Pet. 100 (citing Ex. 1003 ¶¶ 234–235; Ex. 1004 ¶¶ 41–42, 106, 116). Petitioner asserts “[f]irst, lysine is the most prevalent amino acid at positions corresponding to 320 in PH20.” *Id.* (citing Ex. 1003 ¶¶ 231, 234; Ex. 1004 ¶¶ 43, 106, 116). Petitioner asserts second, “lysine was known to be favored in sequences that form α -helix secondary structures due to its high helix propensity . . . and position 320 is within the α 8 helix sequence in PH20.” *Id.* at 100–101 (citing Ex. 1003 ¶¶ 205, 233; Ex. 1004 ¶¶ 32, 69–70, 108; Ex. 1006, 6916, Fig. 3; Ex. 1050, 422–24, Table 2).

Petitioner asserts that Patent Owner “relied on [the ’429 patent’s] statements that a skilled artisan would have expected **any** single amino acid substitution in **any** non-essential position of PH20₁₋₄₄₇ to not substantially affect the activity of the enzyme.” Pet. 102. Petitioner also asserts “[p]atentee should not be permitted to now contend that a skilled artisan would not have reasonably expected that the D320K substitution in PH20₁₋₄₄₇ would yield an enzyme with substantially the same activity as unmodified PH20₁₋₄₄₇.” *Id.*

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 320.” Resp. 72 (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 320 in PH20.” *Id.* at 73 (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 320 Nothing in Dr. Park’s results provides a reason to elevate D320 above the hundreds, if not thousands, of other substitutions he predicts would have been tolerated.” Resp. 74–75 (citing Ex. 2068 ¶¶ 404–416). Patent Owner asserts that “Petitioner has not provided any reason why POSAs, who had in hand a working enzyme, would tinker with that enzyme with the sole purpose of maintaining the same activity profile.” *Id.* at 75.

Patent Owner asserts that “[e]ven if position 320 were somehow selected (it would not be), there is no reason POSAs would have substituted aspartic acid (D) with lysine (K).” Resp. 76 (citing Ex. 2068 ¶¶ 417–418). According to Patent Owner, “[n]either Chao nor the ’429 patent suggests replacing D320 with lysine or serine.” *Id.*

c) Petitioner's Reply

Petitioner asserts Dr. Park “identif[ie]d D320K as *one of ~750 such substitutions* suggested by the ’429 Patent before 2011.” Reply 43 (citing Ex. 1133 ¶¶ 346; Ex. 1003 ¶¶ 245–247; Ex. 2176). Petitioner asserts that “per *KSR*, the ’429 Patent motivated POSAs to identify single substitutions

in non-essential regions of PH20₁₋₄₄₇ that ***predictably*** retain activity, and to use them to increase spreading.” *Id.*

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 320***, and “there must be some reason to select a species from the genus.” Petitioner offers none beyond impermissible, attorney-driven hindsight.

Sur-reply 26.

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 residue at position 320 of a PH20 polypeptide for modification with one of “H, K, R, and S” as required by the challenged claims. It is undisputed that neither of the cited prior art references, the ’429 patent or Chao, specifically identifies or discusses position 320 of the PH20 polypeptide. *See generally* Pet. 96–98; Reply 42–47; Resp. 72–76.

We are not persuaded by Petitioner’s argument that multiple sequence alignments identify amino acids that are tolerated at particular positions (*see* Pet. 96–98), because tolerance alone 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 “PH20₁₋₄₄₇ other than the 68 essential residues” (i.e., ~85% of the protein) with evolutionary variation, meaning that “homologous proteins have tolerated different amino acids at those positions.” Ex. 1004 ¶ 31. Dr. Park also evaluated the “compatibility with the predicted secondary structure” for the possible substitutions at those positions by categorizing 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.* ¶¶ 69–70. But nothing in the prior art or Dr. Park’s analysis directs the ordinary artisan to position 320 itself. And while Dr. Hecht asserts that the ’429 patent suggests conservative mutations generally, Petitioner does not point to any specific teaching or suggestion in the prior art cited by Dr. Hecht to modify position 320. *See id.* ¶¶ 220–221 (asserting a POSA would expect that “a single amino acid substitution in a non-essential region would retain much of its activity”).³⁰ Petitioner did not point us to anything in Dr. Hecht’s Declaration that explained why position 320 was of interest in any way, versus other positions within the PH20 polypeptide.

We also are not persuaded by Petitioner’s arguments that lysine (K) would have been a logical option to incorporate as a substitution for aspartic acid (D) at position 320 in the α 8 helix region of in PH20₁₋₄₄₇. *See* Pet. 100–

³⁰ Indeed, in support of his testimony that a POSA would not be able to predict the effects of multiple modification, Dr. Hecht observes that position 320 is located within the ‘ α 8’ α -helix structure in PH20” and “[i]ntroducing random amino acids could disrupt that pattern, which could have a range of effects in this region of the helical structure.” Ex. 1003 ¶ 205. This seems to contradict aspects of Dr. Hecht and Dr. Park’s obviousness analysis.

101. For example, Petitioner asserts that lysine “was known to be favored in sequences that form α -helix secondary structures.” *Id.* But Dr. Park identified seven different amino acids that favor alpha helix formation. *See* Ex. 1004 ¶ 70. Moreover, Figure 3 of Chao shows a number of different alpha helical regions, $\alpha 1$, $\alpha 3$, $\eta 4'$, $\alpha 4'$, $\alpha 4$, $\alpha 5$, $\alpha 6$, $\alpha 7$, and $\alpha 8$, each composed of multiple amino acids, many of which appear to be non-conserved. *See* Ex. 1006, 6916 Fig. 3. Each of these amino acids found within alpha helices might be subject to substitution by one of the seven preferred amino acids identified by Park, but 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’s other rationale for substituting lysine at position 320 is that those residues are found at the corresponding position in some homologous hyaluronidase sequences. *See* Pet. 98–99. But that rationale assumes that an ordinarily-skilled artisan would have already had a reason to target position 320 and Petitioner offers no reason to do so other than Dr. Park’s observation that it is amongst the overwhelming majority (~85%) of positions in PH20 that are apparently in non-essential regions of the protein. *See* Ex. 1004 ¶ 31.

In sum, 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 challenged claims of the ’185 patent.

III. CONCLUSION

After considering the evidence and arguments presently before us in the complete trial record, we conclude that Petitioner has demonstrated, by a preponderance of the evidence, that challenged claims 1–4 and 7–11 are unpatentable.³¹

In summary:

Claims	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not shown Unpatentable
1, 2, 6–29	112(a)	Written Description	1–4, 7–11	
1, 2, 6–29	112(a)	Enablement	1–4, 7–11	
1, 2, 6–29	103	'429 patent, Chao		1–4, 7–11
Overall Outcome			1–4, 7–11	

³¹ 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).

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–4 and 7–11 of U.S. Patent 12,104,185 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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