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BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner

v.

HALOZYME INC.,
Patent Owner

Case PGR2025-00003
U.S. Patent No. 11,952,600

PATENT OWNER RESPONSE
UNDER 37 C.F.R. § 42.120

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Halozyme EX2033
Merck v. Halozyme
IPR2026-00313

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PATENT OWNER'S UPDATED EXHIBIT LIST

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2002	*Curriculum Vitae* of Barbara Triggs-Raine, Ph.D.
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2070	Declaration of Gregory A. Petsko, Ph.D. in Support of Patent Owner's Response
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2072	Declaration of Gary N. Cherr, Ph.D. in Support of Patent Owner's Response
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2174	Errata from Park Deposition (introduced during Park deposition and marked by court reporter as "Park 2068")
2175	Mutational Analysis Table, 2024-11-7, Native Excel File (introduced during Park deposition and marked by court reporter as "Park 2069")
2176	Mutational Analysis Table, 2024-11-7, PDF File (introduced during Park deposition and marked by court reporter as "Park 2070")
2177	E-mail Correspondence dated August 14, 2025
2178	1LOH pdb file
2179	1FCV pdb file
2180	2PE4 pdb file
2181	8SMN pdb file
2182	D320H Swiss Model
2183	D320K Swiss Model
2184	D320R Swiss Model
2185	D320S Swiss Model
2186	N47_N219A_D320K Swiss Model
2187	N47A_N131A_D320K Swiss Model
2188	N47A_N131A_N219A_D320K Swiss Model
2189	N131A_N219A_D320K Swiss Model
2190	Orangutan_D320K Swiss Model
2191	PH20 Swiss Model

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I. INTRODUCTION

U.S. Patent No. 11,952,600 (the '600 patent)[1] is directed to a "modified PH20 polypeptide" with a substitution at one specific position in the amino acid sequence of PH20—position 320. Position 320 is an aspartic acid ("D") in the unmodified sequence, and thus the substitution at 320 is referred to as the "D320 mutation" herein. EX1001, cl.1. The claimed substitution must consist of one of four amino acids—H, K, R, or S. *Id*. All four of the recited amino acid substitutions at position 320 improve the activity of the modified PH20 compared to wildtype, with one substitution (K) increasing activity by over 600%. EX1001, Table 9. It is undisputed that these mutations were not known in the art.

The '600 inventors discovered the D320 mutation through an unprecedented comprehensive, and systematic analysis of PH20's structure. The inventors performed this analysis through large-scale mutagenesis and enzymatic activity testing of thousands of variants. EX2068, ¶158; EX2070, ¶44, 233-34. Specifically, among its teachings regarding PH20, the '600 patent provides the results of a mutagenesis experiment in which ***every single position*** in a mature, soluble, active PH20 (SEQ ID No: 3) was mutated with up to 18 different amino acids and then

[1] Petitioner challenges patentability of claims 1-4 and 8-21 of the '600 patent. Dependent claims 5-7 have been statutorily disclaimed. EX2003.

tested for activity and compared to wildtype. *Id*.

The results of this study detail the common structural elements of active PH20s and their correlation to hyaluronidase function. EX2068, ¶¶157-164; EX2070, ¶¶51-58. Specifically, for the mature, soluble PH20 polypeptide, the study identifies which positions and regions tolerate substitutions and which do not, which types of residues at each position are likely to be successful in terms of maintaining activity,[2] and which positions in particular could be targeted to maintain or improve activity. *Id*. As the '600 patent[3] states, the "[d]etailed structure/function of virtually each amino acid in a PH20 polypeptide is provided herein" along with "the identification of residues and loci that contribute to alteration of a property, such as stability in particular conditions." EX1001, 4:58-62.

In short, the '600 patent data enabled POSAs to make enzymatically active PH20s with single and multiple mutations because the data showed POSAs where to make changes, and what types of changes to make. EX2070, ¶¶45-50, 59-86. As

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[2] Patentee uses the term "activity" throughout as short for hyaluronidase enzymatic activity.

[3] There is no dispute that the '600 patent and the U.S. Patent Application No. 13/694,731 ("the '731 application") share a substantively identical specification. Pet., 6. For convenience, citations are to the disclosure of the '600 patent.

a corollary, it also taught them numerous ways to inactivate PH20.

Based on this expansive body of work—which comprises data for over 5800 variants—the inventors claimed only four variants. Specifically, the inventors claimed those variants in which the D in wild type at position 320 is replaced with an H, K, R, or S ("D320H," "D320K," "D320R," and "D320S"). And, commensurate with the scope of their mutagenesis study, the inventors also claimed subvariants with at least 95% identical primary structure to the four novel variants. EX2068¶¶278, 282-288, EX2070, ¶¶239-43, 421-26, 68-69.

As a result, the claimed genus is extremely narrow. The inventors did not claim, for example, all modified polypeptides that degrade hyaluronan; they did not even claim all modified ***PH20s*** that degrade hyaluronan; nor even the full set of modified PH20 polypeptides that have a substitution at position 320. They instead claimed a highly limited genus.

Additionally, as Patentee's experts, Drs. Simpson and Petsko, explain, within this narrow genus, the claimed proteins 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, including several common structural features (including a common active site).[4] EX2068 33, 207-304, EX2070, ¶¶389-

[4] To the extent inactives fall within the genus under Patentee's construction

420, 78-82. And POSAs would have understood the inventor's work, including their comprehensive characterization of PH20's structure from end-to-end, to provide a detailed specification of the correlations between the structure of PH20 and its hyaluronidase function. This characterization allows POSAs to predictably distinguish between and make and use the full scope of the active (and to the extent Patentee's construction is adopted, inactive) modified PH20s within the scope of the claim. *Id*. That is sufficient for written description and enablement.

Petitioner's written description and enablement challenges are premised on its characterization of claimed genus as "immense" and having "extreme breadth." Pet., 1-2. 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.

In particular, Petitioner relies on cases like *Ariad*, *AbbVie*, and others, which involved both structurally diverse genus and claims that recited "a description of the problem to be solved while claiming all solutions to it [via]…. functional boundaries." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353 (Fed. Cir.

(*see* Section IV), the lack of one or more of these common structural features (e.g. disulfide bridges or catalytic residues critical to activity) distinguishes them from actives. EX2068, ¶¶303-304, EX2070, ¶¶325-42, 427-28.

2010). But unlike those cases, the patent claims do not "claim[] all solutions." Not even close. The claims cover not even a miniscule fraction of all of the proteins that cleave HA (or even all of the PH20s that cleave HA). EX2068, ¶¶284-286. Indeed, all one need to do to avoid the claims is not practice the 320 mutation that the Halozyme inventors indisputably were the first to identify. Or, using the data in the patent itself, mutate the primary structure slightly more than 5%. Given the lack of structural diversity in the genus ((EX2068, 354-359), a patent monopoly could hardly be more limited.

In fact, as explained in depth below as to written description (Ground 1), by limiting the claims to four variants with the D320 mutation and the subvariants to 95% structural identity, the inventors ensured the active PH20s within the genus, including those with single and multiple mutations, share the same common mechanism of action and common PH20 tertiary structure, including the common active site and supporting "scaffolding" of disulfide bridges and other features necessary to activity. EX2068, ¶¶287-293, 299; EX2070, ¶¶389-420. Moreover, the specification teaches a POSA how to reasonably and reliably distinguish those PH20s that will be inactive. *Id*.

As to enablement (Ground 2), Patentee in no way left the invention "unfinished," as Petitioner contends. *Ariad*, 598 F.3d at 1353. Petitioner characterizes the inventors' work—a comprehensive characterization of ***every***

position in the tested PH20 sequence—as effectively useless. According to Petitioner, the inventors left to others only a so-called "research plan" (Pet., 2). But that makes no sense. The inventors did the work to identify the D320 mutation and provided—via a detailed and thorough analysis of over 5800 different PH20 polypeptide mutants—a comprehensive correlation between PH20's structure and its activity—i.e. "some general quality… running through the class that gives it a peculiar fitness for the particular purpose." *Amgen Inc. v. Sanofi,* 598 U.S. 594, 611 (2023).

All POSAs need to do is follow the inventor's guidance to practice the claim. It is trivial to introduce the D320 mutation into PH20—the heart of the claimed invention; beyond what is provided in the specification, it takes no research at all. And POSAs can readily identify other positions to change should they wish, using the comprehensive structure-function data provided in the specification. EX2070, ¶¶276-91. The inventors' work allows POSAs to easily and predictably practice additional mutations or other variants with only ordinary skill. EX2068, ¶¶345-349.

Inventors "rely on the promise of the law to bring the invention forth," describing the invention in the specification in exchange for the limited monopoly granted by the claims. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 730-31. As part of this bargain, as explained in *Ariad*, "the scope of the right to exclude… [must] not overreach the scope of the inventor's contribution

to the field of art as described in the patent specification." *Ariad,* 598 F.3d at 1353–54 (internal quotation marks omitted). Here, the inventors in no way overreached in exchange for their expansive disclosure; they sought and received highly limited claims to a structurally homogeneous set of modified PH20s that require a single amino acid mutation at a single position that is trivially avoided unless one is looking over the inventor's shoulders, copying their work. They described, in full, the results of their work in exchange for a limited, time-bound monopoly, allowing others to practice the invention when the claims expire. The work they disclosed is sufficient for written description and enablement. They deserve the full "promise of the law"—the protection granted by the claims.

Petitioner also challenges the claims as obvious (Ground 3). On the preliminary record, the Board rejected Petitioner's arguments, focusing in particular on the lack of a positive reason to make the claimed 320 substitution that the inventors discovered. ID, 58. The Board found that neither of prior art references "specifically identifies or discusses position 320 of the PH20," and that Petitioner "did not point [] to anything in Dr. Hecht's Declaration that explained why position 320 was of interest in any way, versus position 319 or 321 or any other position within the PH20 polypeptide." *Id*.

The record developed since institution reinforces the Board's conclusion. Petitioner's expert admitted that he did not identify position 320 through

independent scientific reasoning, but instead "conducted [his initial] analysis in a manner that did not focus on any particular position," and was only later "asked by counsel to report [his] conclusions with respect to position 320." EX1004, ¶103. At deposition, Dr. Park further confirmed the hindsight nature of this analysis, explaining that the "backbone" of his analysis was an undisclosed spreadsheet he prepared to perform the analysis Petitioner requested that considered over *800* mutations, not just D320K modification he claimed POSAs would make (Petitioner did not disclose the spreadsheet until Dr. Park revealed its existence and reliance on it under cross-examination EX2177; EX2077, 187:2-195:7. He further testified that after he "***completed all [his] analysis of all of positions, and provided a spreadsheet to counsel, [counsel] then asked [him] to elaborate on certain positions, including 320, 317, and so on***,"[5] at which point he went back and finished the analysis with all the substitutions that were available at those positions. EX2078, 320:10–20; *see also*, EX2076, 87:1-11.

In other words, even taking Petitioner's expert's approach at face value, the only motivation to make a D320 mutation came from Petitioner's lawyers, working backwards from the claims. That is the epitome of hindsight.

As set out further below, Patentee requests that the Board find all the

[5] Emphasis has been added throughout, unless otherwise noted.

challenged claims patentable as to each of Grounds 1-3.

II. BACKGROUND

A. Patentee's Experts

Because Patentee refers to the work of its experts throughout the sections below, Patentee briefly summarizes their background:

Dr. Melanie Simpson is the Head of the Department of Molecular and Structural Biochemistry at North Carolina State University. She is also the Director of Research of the Integrative Sciences Initiative at North Carolina State University, Raleigh, NC. And she serves as the President of the International Society for Hyaluronan Sciences ("ISHAS"). She has extensive practical experience researching hyaluronidases, which have been a focus of her research since 1998, including work that is among the key hyaluronidase mutagenesis studies in the field. EX2068, 9-20.

Dr. Gregory Petsko is a distinguished American biochemist and structural biologist known for his pioneering work in protein crystallography and enzyme mechanisms. He is renowned for his research on protein structure-function relationships, including the use of techniques such as X-ray crystallography and computational modeling. He is a National Medal of Science winner. He is currently Professor of Neurology at the Ann Romney Center for Neurologic Diseases at Harvard Medical School and Brigham and Women's Hospital. EX2070, ¶¶1-23.

Dr. Gary Cherr is a Professor Emeritus at the University of California Davis.

He has over 40 years of experience in the field of reproductive physiology, reproductive and developmental biology, toxicology, sperm cell physiology, fertility, infertility and contraception, and embryo defense mechanisms. He has specifically studied the regulation of sperm motility, sperm surface molecules such as PH20 and beta defensins and their roles in mechanisms of fertilization biology, among other topics. He has authored papers on sperm transport in the female tract and immunoprotection relating to PH20, among many others. EX2072, ¶¶5-11.

Dr. James Moon is the Interim Chair and the J. G. Searle Professor (with tenure) in the Department of Pharmaceutical Sciences in the College of Pharmacy and a Professor in the Department of Chemical Engineering and Biomedical Engineering, all at the University of Michigan, among numerous other appointments. He has spent over 20 years studying immunology, engineering, and pharmaceutical sciences. His research particularly focuses on developing drug delivery systems for vaccines and immunotherapies precisely designed to target specific organs and activate the immune system. EX2074, ¶¶5-13.[6]

B. Technical Background

Patentee briefly summarizes the art as of December 28, 2012[7] regarding the

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[6] Petitioner withdraws the testimony of Dr. Triggs-Raine (EX2001).

[7] Patentee applies the December 28, 2012 filing date of the ’731 application

structure of hyaluronidases, their mechanism of action and the amino acids known to be important for activity.

PH20 is a member of a class of enzymes called hyaluronidases. PH20 occurs on the sperm surface. EX1001, 45:37-46:6. As a hyaluronidase, PH20 cleaves hyaluronan ("HA"), which is a linear, negatively charged glycosaminoglycan made of repeating disaccharide units. EX1006 (Chao), 6911. There are five human hyaluronidases, three of which are known to degrade HA: PH20, Hyal-1, and Hyal-2. *Id*. HA-degrading enzymes also occur in other organisms, including bees (bee venom hyaluronidase helps a bee spread venom from a sting).

By 2012, the crystal structures for bee venom hyaluronidase (EX1033) and human Hyal-1 (EX1006) had been solved. It is not disputed that based on these solved structures, a POSA's knowledge included possession of an accurate homology model of PH20; both Petitioner and Patentee rely on such a model here. As Petitioner's expert testified, "In the year 2011, to consider a mutation, it would have been very common and expected for POSAs to generate a model and consider

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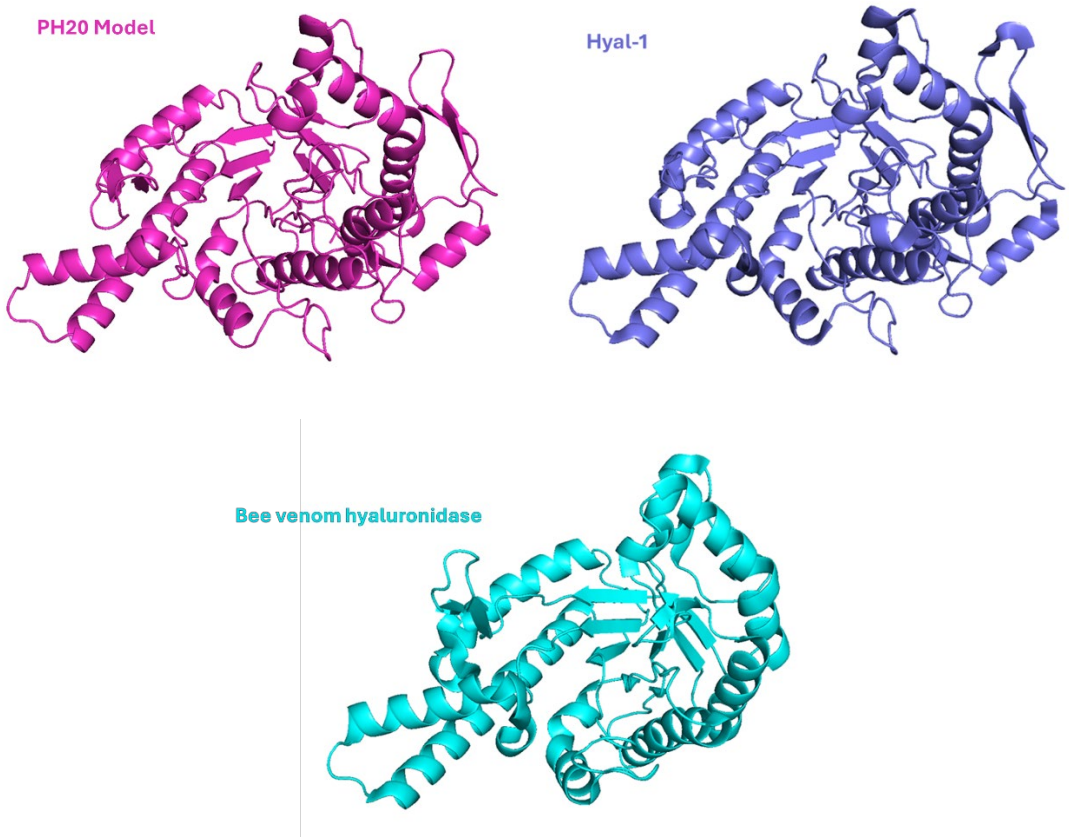
for purposes of responding to Petitioner's written description and enablement challenges (Grounds I–II). *Reiffin v. Microsoft Corp.,* 214 F.3d 1342, 1345 (Fed. Cir. 2000); *Ariad,* 598 F.3d at 1353-54. Patentee applies the December 30, 2011 priority date for purposes of responding to Petitioner's obviousness challenge (Ground III).

the substitution in that structural context." EX2077, 176:2-5; EX2076, 92:22-94:22.

Dr. Petsko provides a detailed summary of a POSA's knowledge of PH20, Hyal-1, and bee venom hyaluronidase, detailing a POSA's knowledge of the critical common features even though these hyaluronidases share only 30-40% sequence identity. EX2070, ¶¶126-213, 112-125, 59-111; EX1006, 6912; EX1008, 826; *see also* EX1004 (Park), ¶¶ 40, 141; EX2077, 93:9-94:8.

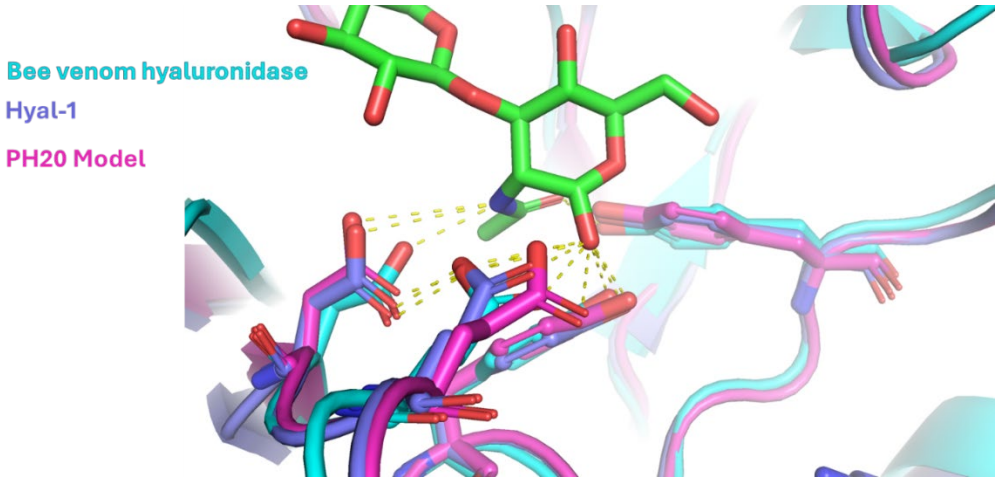
In sum, these hyaluronidases all share a tertiary structure a POSA would recognize as an "alpha-beta barrel fold." Their nearly identical tertiary structures are depicted below:



As Drs. Petsko and Simpson explain, POSAs knew that PH20s (as well as

Hyal-1 and bee venom hyaluronidase) share a common mechanism of action in that they all cleave HA through the same chemical reaction (EX1010, 9433 EX2092; EX2070, ¶¶135-38), via a common structure—the active site in all three proteins, which contains critical residues oriented in about the same position (EX1008, 833; EX1033, 1028; EX2070, ¶¶139-44). *See generally* EX1006 (reporting as to Hyal-1, bee venom hyaluronidase "that the active site clefts are similar in size and shape"); EX1006 (Chao), 6914 ("the active site of hHyal-1 spans an elongated cleft"); EX2070, ¶¶139-44 (showing common elongated cleft/groove on PH20 model); EX2068 ¶¶297-298.

Despite the substantial difference in sequence (60-70%), the critical active site residues in Hyal-1, bee venom hyaluronidase and PH20 are also conserved in terms of their identity, their positioning, and their interactions with HA, as illustrated by Dr. Petsko's analysis in which superimposes and examines the structures. A representative figure below shows the PH20 model superimposed on the Hyal-1 structure and the bee venom structure and illustrates the overlapping primary, secondary and tertiary structural features, including common structural features down to the atomic level, with dotted lines illustrating the overlap between interactions:



EX2070, ¶157.

Those working in the field at the time, including Dr. Simpson, had also conducted some limited mutagenesis experiments to determine the importance of certain Hyal-1 and PH20 residues for enzymatic activity, using the data to draw conclusions on the role of a set of tested residues, including their criticality to the active site and stability. *see also* EX1010, EX2011; EX1033, 1029; EX2070, ¶¶207-30, 297-342; EX2068 ¶¶138-156. It was thus routine in the field to use such data to illuminate common structures.

C. The ’600 Patent

The ’600 patent discloses a comprehensive and systematic analysis of each and every position within the primary structure of PH20 (SEQ ID No: 3), which the inventors performed through large-scale mutagenesis and enzymatic activity testing of over 5800 variants. EX2068 ¶158; EX2070, ¶¶231-38. The patent also discloses significant additional teachings regarding PH20, including other PH20 mutagenesis

studies and studies regarding the effect of serial C-terminal truncations (conducted by some of the inventors), among others, as set out in this section and Sections II.B and II.C.5 below.

Based on the structure/function data provided via the assays described in Examples 2-4, the '600 patent teaches "modified PH20 polypeptides" that "exhibit altered activities or properties compared to a wildtype, native or reference PH20 polypeptide." EX1001, 75:42-47. In particular, the patent teaches that the disclosed modified PH20 polypeptides include those that are active variants, inactive variants, and variants with increased stability. *Id.*, 75:47-58. Among these variants, the inventors identified numerous substitutions that increase enzymatic activity, including the four substitutions at position 320 recited in the claims. EX1001, Table 9.

As Drs. Simpson and Petsko explain, POSAs would have understood this data as useful far beyond identifying individual mutations; considered as a whole, the inventors' work provides a detailed specification of the structure/function correlations in PH20 that identifies for POSAs the extent to which each position in the sequence tolerates substitutions and which do not, which types of residues at each position are likely to be successful in terms of maintaining activity, and which positions in particular could be targeted to maintain or improve (or reduce or abrogate) activity. EX2068 ¶¶159-151, 246-247, 311, 322, 373-375, 379-383;

EX2070, ¶¶248-62, 317-42. As the ’600 patent states, the “[d]etailed structure/function of virtually each amino acid in a PH20 polypeptide is provided herein” along with “the identification of residues and loci that contribute to alteration of a property, such as stability in particular conditions.” EX1001, 4:58-62

As both Drs. Simpson and Petsko confirm, this level of structure/function detail for an individual protein of this size was virtually unheard of as of 2012, and outside of the patent’s disclosure, remains so, at least in the public domain. EX2070, ¶¶233-34; EX2068, ¶¶163-164. Neither are aware of a comparable project, and the data is extraordinarily useful to POSAs in understanding the invention and seeking to practice the claims. *Id*.

Key sequences referred to in the claims and specification are identified below in Section II.C. Key portions of the inventors’ study are also described below in Sections II.C.2-3.

In short, the key examples and tables are as follows:

- Example 2 discloses the generation of the PH20 variant library used in the experiment. EX1001, 200:43-231:40.
    - Table 8 provides a list of the mutations used to prepare the library. EX1001, 202:18-231:17.
- The test methods for the activity assays are described in Example 3. EX1001, 231:41-234:14.

- The results of the activity assays are provided in Example 4.
    - Table 9 identifies the "active" variants for which at least one of the two samples tested exhibited greater than 40% of wildtype (SEQ ID NO: 3) activity, along with corresponding activity data. EX1001, 234:57-257:22. The patent also lists the residues at each position that resulted in active PH20s in Table 3. *Id.*, 82:11-89:44.
    - Table 10 provides confirmed inactive mutants, which achieved less than 20% of wildtype activity. EX1001, 258:38-269:8. The patent also provides the residues at each position that resulted in less than 20% activity in Table 5. *Id.*, 120:52-130:67.

To facilitate consideration of this data in a consolidated format, Dr. Petsko provides a spreadsheet with data imported from Tables 3, 5, 9 and 10 into Excel so that the data could be color coded and sorted. EX2070, ¶¶263-74.

The patent also discloses general teachings regarding the structures common to the active PH20s that are confirmed or further refined by the mutagenesis data, as further discussed below.

1. Key Sequences Referred to in the Patent

The '600 patent provides the following exemplary sequences:

- **SEQ ID NOs: 6 and 7**: SEQ ID NO: 6 is a full length "precursor" PH20 consisting of 509 amino acids, including a 35 amino acid signal sequence.

SEQ ID NO: 7 is the "mature" version, without the 35 amino acid signal sequence (474 amino acids).

- **SEQ ID NO: 3**: A mature, soluble, C-terminally truncated PH20 used as the control in the '600 patent. The PH20 in SEQ ID NO: 3 lacks the signal sequence is also C-terminally truncated by 27 amino acids. It thus consists of 447 amino acids, each of which was varied in the patent's mutagenesis study. The inventors refer to this version as "wild type" in the patent.

- **SEQ ID NOs: 32-66**: These sequences are other C-terminal truncation variants of PH20 disclosed in the specification. Like SEQ ID NO: 3, they lack the signal sequence. They serially increase in length by one amino acid from SEQ ID NO: 32 (430 amino acids) to SEQ ID NO: 66 (465 amino acids). Halozyme's prior work studying C-terminal truncations, discussed below in Section II.C.5, involved testing these truncations and would have taught POSAs their expected effect on activity.

See generally EX2068, ¶¶165-175.

2. Example 2

Example 2 of the patent describes the creation of a mutagenesis library in which a mature, soluble, active PH20 sequence (SEQ ID NO: 3) was systematically mutated at each of its 447 residues by substituting at least one and up to 18 different

amino acids. EX1001, 200:45-231:40. Results are provided for, on average, 13 substitutions at each position. EX2068 (Simpson Decl.), ¶157; EX2070 (Petsko Decl., ¶ 264). Table 8 provides the resulting set of 6753 modified PH20 polypeptides. *Id*. at 201:12-231:17.

The specification describes the inventors' experiment, which involved the design of an expression vector for each variant, along with secreted alkaline phosphatase (SEAP), under a single promoter. This elegant design allowed the inventors to track expression levels (by tracking the amount of SEAP) in order to normalize the results of the activity assay, to account for differences in both transfection and expression levels for each variant. *Id*. at 200:45-231:40, 234:20-47; EX2068, ¶¶201-202.

3. Examples 3 & 4

Examples 3 and 4 describe the development and results of a comprehensive activity assay, cataloging the effect of mutations made at each of the 447 resides of a mature, soluble PH20 sequence (SEQ ID NO: 3).

The inventors assessed the hyaluronidase activity of each variant using an ELISA assay (described in Example 3). In brief, the inventors generated biotinylated hyaluronic acid ("bHA") substrate, which was bound to plates, and then incubated with variant or wild type PH20, allowing the PH20s to degrade the bound bHA substrate (if active). EX1001, 231:42-234:25; EX2068, ¶¶197-200. Ultimately, the

inventors measured the optical density, which correlates to the amount of bHA remaining on the plate, and compared the results to the average activity obtained for of wild-type PH20 (SEQ ID NO: 3) on the same plate. EX2068, ¶¶197-204. The results show the extent to which the substitution impacted HA activity. EX2068, ¶¶204-205.

a. Data on Active Mutants

Using the methods described above, the inventors collected and presented comprehensive activity data for up to 18 substitutions (on average 13 substitutions) at every single one of the 447 positions in the mature PH20 sequence (SEQ ID NO: 3). Each position was changed to a range of amino acids with a wide range of properties (*i.e.,* large, small, hydrophobic, hydrophilic, charged, not charged), and the effect on enzymatic activity was determined. EX2070, ¶¶248-61. This was not a random mutagenesis experiment disclosing the results of a handful of single point mutations in scattered portions of the protein. This was a systematic structure-function mapping exercise that discloses the tolerance of every single position to substitution.

The inventors identified 2527 active variants, which are provided in Table 9. Specifically, Table 9 provides "the average hyaluronidase activity of tested duplicates normalized by SEAP values compared to average of wildtype PH20 activities in each plate, which were also normalized by their own SEAP values." *Id.*,

234:27-38.[8] "For example, a value of 0.40 indicates that the variant exhibits 40% of the hyaluronidase activity of wildtype PH20, a value of 1 indicates that the variant exhibits a similar hyaluronidase activity of wildtype and a value of 3.00 indicates that the variant exhibits 300% of the hyaluronidase activity of wildtype PH20 or 3-fold increased activity compared to wildtype." *Id*., 234:38-45.

"The results in Table 9 show that over 600 tested mutants exhibit activity that is increased compared to wildtype. For example, about 536 mutants exhibit 120% or greater than 120% of the hyaluronidase activity of wildtype PH20 and about 75 of the mutants exhibit 300% or greater than 300% of the hyaluronidase activity of wildtype PH20." *Id*., 234:46-51.

Collectively, at least one amino acid change made in 352 different positions in PH20 generated active polypeptides. EX1001, Table 9; EX2068, ¶¶205; EX2070, ¶¶254-61. As Drs. Petsko and Simpson show, and as is discussed further below, POSAs would have understood the collective data to demonstrate areas and positions within of the PH20 structure that are highly tolerant or intolerant to change and to

[8] As Dr. Simpson explains, there are variants in Table 9 with activity values less than 40% of wild type because one of two samples exhibited an activity greater than 40% of wild type, and the value presented is the average obtained for the two samples.

identify particularly beneficial substitutions. EX2070, ¶¶262, 275-96, 317-42; EX2068, ¶¶352.

b. The D320 Mutation

Some of the disclosed variants exhibited highly significant changes in activity relative to wildtype. For instance, the inventors disclosed sixteen modified amino acids at amino acid residue number D320, including H, K, R, and S. *See* Patent Table 8. Thirteen of the modifications at residue D320 produced enzymatically active PH20s, and four resulted in increased activity—H, K, R, and S. *See* Patent Table 3; Table 9. The substitution to lysine (K) provided the greatest improvement in activity—642% compared to wild-type—and is one of the highest reported increases in the patent. *Id*.

c. Data on Inactive Mutants

The patent also provides extensive data regarding mutations that were *not tolerated* in terms of enzymatic activity—i.e., mutations that reduced hyaluronidase activity to below 20% of wildtype activity. The inventors identified the inactive mutants through initial screening in Example 3.

Then, the inventors rescreened these mutants in a "modified assay" involving a longer incubation time that was "intended to detect PH20 activities below 0.2 U/mL." EX1001, 257:30-32. Specifically, mutants that "exhibited less than 20% hyaluronidase activity of wildtype PH20, in at least one of the duplicates, were

rescreened to confirm that the dead mutants are inactive." *Id*., 257:24-27. Table 10 provides the "reconfirmed inactive mutants," which again are those that achieved less than 20% of wildtype activity. *Id*., 258:35-36.

Table 10 discloses 3320 inactive PH20s. Table 10 shows that at least one amino acid change made in 407 different positions in PH20 generated inactive polypeptides. EX1001, Table 10; EX2068, ¶211; EX2070, ¶¶260, 275. As with the actives data, POSAs would have understood the collective inactives data to provide further guidance on modifying PH20s, demonstrating areas and positions within of the PH20 structure that are intolerant to change or that only tolerate limited substitutions. EX2070, ¶¶293-95; EX2068, ¶¶313, 379 .

d. Tolerability at Each Position Based on Enzymatic Activity Testing

Dr. Petsko illustrates the patent's teaching regarding tolerability to change within PH20's structure by copying the patent data into a spreadsheet and then color coding the 447 positions based on their tolerability to substitution, showing how POSAs would understand the data. That illustration is reproduced below:

Position	WT																
		30	D	61	L	92	A	123	W	154	K	185	L
		31	E	62	G	93	K	124	K	155	Q	186	F
1	L	32	P	63	Y	94	K	125	P	156	E	187	P
2	N	33	L	64	Y	95	D	126	K	157	F	188	D
3	F	34	D	65	P	96	I	127	D	158	E	189	C
4	R	35	M	66	Y	97	T	128	V	159	K	190	Y
5	A	36	S	67	I	98	F	129	Y	160	A	191	N
6	P	37	L	68	D	99	Y	130	K	161	G	192	H
7	P	38	F	69	S	100	M	131	N	162	K	193	H
8	V	39	S	70	I	101	P	132	R	163	D	194	Y
9	I	40	F	71	T	102	V	133	S	164	F	195	K
10	P	41	I	72	G	103	D	134	I	165	L	196	K
11	N	42	G	73	V	104	N	135	E	166	V	197	P
12	V	43	S	74	T	105	L	136	L	167	E	198	G
13	P	44	P	75	V	106	G	137	V	168	T	199	Y
14	F	45	R	76	N	107	M	138	Q	169	I	200	N
15	L	46	I	77	G	108	A	139	Q	170	K	201	G
16	W	47	N	78	G	109	V	140	Q	171	L	202	S
17	A	48	A	79	I	110	I	141	N	172	G	203	C
18	W	49	T	80	P	111	D	142	V	173	K	204	F
19	N	50	G	81	Q	112	W	143	Q	174	L	205	N
20	A	51	Q	82	K	113	E	144	L	175	L	206	V
21	P	52	G	83	I	114	E	145	S	176	R	207	E
22	S	53	V	84	S	115	W	146	L	177	P	208	I
23	E	54	T	85	L	116	R	147	T	178	N	209	K
24	F	55	I	86	Q	117	P	148	E	179	H	210	R
25	C	56	F	87	D	118	T	149	A	180	L	211	N
26	L	57	Y	88	H	119	W	150	T	181	W	212	D
27	G	58	V	89	L	120	A	151	E	182	G	213	D
28	K	59	D	90	D	121	R	152	K	183	Y	214	L
29	F	60	R	91	K	122	N	153	A	184	Y	215	S

216	W	247	V	278	L	309	I	340	M	371	A	402	C	433	F
217	L	248	R	279	K	310	M	341	C	372	I	403	Y	434	L
218	W	249	E	280	F	311	R	342	S	373	Q	404	S	435	K
219	N	250	A	281	L	312	S	343	Q	374	L	405	T	436	P
220	E	251	I	282	S	313	M	344	V	375	E	406	L	437	P
221	S	252	R	283	Q	314	K	345	L	376	K	407	S	438	M
222	T	253	V	284	D	315	S	346	C	377	G	408	C	439	E
223	A	254	S	285	E	316	C	347	Q	378	G	409	K	440	T
224	L	255	K	286	L	317	L	348	E	379	K	410	E	441	E
225	Y	256	I	287	V	318	L	349	Q	380	F	411	K	442	E
226	P	257	P	288	Y	319	L	350	G	381	T	412	A	443	P
227	S	258	D	289	T	320	D	351	V	382	V	413	D	444	Q
228	I	259	A	290	F	321	N	352	C	383	R	414	V	445	I
229	Y	260	K	291	G	322	Y	353	I	384	G	415	K	446	F
230	L	261	S	292	E	323	M	354	R	385	K	416	D	447	Y
231	N	262	P	293	T	324	E	355	K	386	P	417	T		
232	T	263	L	294	V	325	T	356	N	387	T	418	D		
233	Q	264	P	295	A	326	I	357	W	388	L	419	A		
234	Q	265	V	296	L	327	L	358	N	389	E	420	V		
235	S	266	F	297	G	328	N	359	S	390	D	421	D		
236	P	267	A	298	A	329	P	360	S	391	L	422	V		
237	V	268	Y	299	S	330	Y	361	D	392	E	423	C		
238	A	269	T	300	G	331	I	362	Y	393	Q	424	I		
239	A	270	R	301	I	332	I	363	L	394	F	425	A		
240	T	271	I	302	V	333	N	364	H	395	S	426	D		
241	L	272	V	303	I	334	V	365	L	396	E	427	G		
242	Y	273	F	304	W	335	T	366	N	397	K	428	V		
243	V	274	T	305	G	336	L	367	P	398	F	429	C		
244	R	275	D	306	T	337	A	368	D	399	Y	430	I		
245	N	276	Q	307	L	338	A	369	N	400	C	431	D		
246	R	277	V	308	S	339	K	370	F	401	S	432	A		

EX2070, ¶274.

As Dr. Petsko explains, those positions for which all tested substitutions are tolerated are colored green, and those for which no substitutions were tolerated are colored red. Positions for which 60% or more of the substitutions tested were tolerated are colored light green. Positions for which 30% or fewer of the substitutions were tolerated are colored orange. Residues not colored were those that tolerated more than 30% but less than 60% of the tested substitutions. EX2070,

¶¶270-73.

The patent data shows that:

- 158 positions (35%) tolerated 60% or more of the tested substitutions, with 40 positions (9%) tolerating all tested substitutions;
- 214 positions (48%) tolerate 30% or fewer of the tested substitutions, and 95 positions of the 447 (21%) did not tolerate any tested substitutions.

EX2070, ¶¶267-68.

As Dr. Petsko and Dr. Simpson testify, this data is extremely useful to POSAs, because it teaches POSAs what changes can be made in what position(s) to maintain activity (or to abrogate activity). EX2070, ¶¶262, 343-388; EX2068246-247, 372-384.

4. The Patent's Detailed Structure-Function Mapping Significantly Expands The POSA's Knowledge Regarding PH20 Residues Critical for Enzymatic Function

The patent's mutagenesis data also confirms and builds on the summary it provides of residues in PH20 that POSAs knew were important for activity, identifying critical PH20 residues and common structures for active and inactive PH20s alike, including expanding the list of critical residues that, when mutated individually and without potential compensatory mutations, inactivate the protein.

For example, the '600 patent notes the following residues that were identified

in the art as either part of the active site or otherwise important for activity: D111, E113, R176, R246, E249 and R252. EX1001, 70:34-45. Similarly, the patent explains that "PH20 hyaluronidases contain 12 conserved cysteine residues, corresponding to amino acid residue 25, 189, 203, 316, 341, 346, 352, 400, 402, 408, 423 and 429 of the sequence of amino acids of a mature PH20 lacking the signal sequence such as set forth in SEQ ID NO: 3 or 7." EX1001, 70:14-19; EX2068, ¶303. The patent further discloses that these cysteine residues "form disulfide bridges," which are involved in "posttranslational protein maturation and/or in activity modulation." EX1001, 70:21-26; EX2068, ¶303. The patent's mutagenesis data confirms that active PH20 does not tolerate substitutions at positions 25, 111, 113, 176, 189, 203, 246, 249, 252, 316, 341, 346, 352, 400, 402, 408, 423 and 429, with two exceptions. EX1001, 70:46-54; EX2068, ¶303. The patent refines the knowledge regarding those positions in that it teaches that C316D and R176K produced variants with some activity, a result POSAs would not have expected. EX2070, ¶¶275, 314-16, 333.

The patent also recognizes the prior art teaching that "[g]lycosylation also is required for PH20 hyaluronidase activity," and in particular, "at least N-linked glycosylation sites corresponding to amino acid residues N200, N333 and N358 are required for secretion and/or activity of the enzyme." EX1001, 70:57-58, 64-67. "For example…amino acid mutations N200A, N333A, N358A or N333A/N393A"

produce "inactive proteins." *Id.*, 71:1-3. By contrast, "[s]ingle mutations of glycosylation sites N47A, N131A, N219A, N47A/N131A, N47A/N219A, N131A/N219A retain activity." *Id.*, 71:3-5. At the same time, the patent expands on the knowledge regarding these positions, teaching that limited modifications at positions N200 and N358 produced variants with some activity. EX2070, ¶¶214-17, 252.

5. C-Terminal Truncations

The patent also teaches that wildtype PH20 "contain[s] a glycosyl phosphatidylinositol (GPI) anchor attached to the C-terminus of the protein," and that "removal of all or a portion of the GPI anchor attachment signal site" can generate "soluble" forms of the PH20 protein that are secreted from the cell. EX1001, 71:29-44. The patent explains that the secreted "soluble" modified PH20 polypeptides include "soluble PH20 polypeptides set forth in any of SEQ ID NOs: 3 or 32-66, or precursor forms thereof containing a signal sequence." EX1001, 71:45-48.

As Dr. Simpson explains, the soluble polypeptides in SEQ ID NOs: 3 and 32-66 each begin at position 36 of the precursor PH20 sequence (*i.e.* the sequence with the 35 amino acid signal peptide), and differ from each other only at the C-terminus, where they reflect a series of single amino acid truncations. The first 430 residues of these 35 sequences are identical. Starting with position 430 (SEQ ID NO: 32), each

sequence successively adds a single residue up through position 465 (SEQ ID NO: 66). SEQ ID NO: 3, the control for the patent's mutagenesis experiments, is 447 amino acids in length. EX2068, ¶¶172-173, 194; EX2006, 2, 15-26.

The '457 publication, which is incorporated by reference into '600 patent, teaches which of these C-terminal truncation variants are active and which are not. Dr. Petsko provides a table in his declaration showing the activity profile of each of SEQ ID NOs: 3 and 32-66, based on this data. EX2070, ¶385. A simplified version of that table is reproduced below:

SEQ ID NO.	Effect of Truncation on Activity Level
32-33	Inactive
34-35	Reduced
36-55 & 3	Active
56-63	Reduced
64-66	Little to no activity

6. Challenged Claims

The '600 patent includes two independent claims, claims 1 and 21, and dependent claims 2-4 and 8-20, all of which ultimately depend from claim 1.[9] Claim 1[10] is directed to a modified PH20 polypeptide while claim 21 is directed to a method

[9] Dependent claims 5-7 have been statutorily disclaimed. EX2003.

[10] The '600 patent recites two independent claims, claim 1 and claim 21. Petitioner does not raise any arguments unique to claim 21, and so Patentee

of manufacture of a modified PH20. Claim 1, which is reproduced below, is directed to a set of C-terminal truncated PH20 polypeptides with one of four potential substitutions at position 320 (for simplicity, Patentee refers to this set of C-terminally truncated polypeptides collectively as "variants"), and a narrow set of subvariants of those modified C-terminal truncation PH20 polypeptides (*i.e.,* those with 95% sequence identity).

> 1. A modified PH20 polypeptide comprising an amino acid sequence, wherein:
>
> (a) 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 wherein terminal gaps are treated as non-identical; and
>
> (b) 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

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addresses claim 1 throughout.

(c) the modification at position 320 is a replacement selected from among H, K, Rand S.

The issues for all claims are common such that they are addressed together, unless otherwise noted.

III. PERSON OF ORDINARY SKILL IN THE ART

Solely for the purposes of the analysis herein, there is no significant difference between Petitioner's POSA definition (Pet., 16; EX1003, ¶13) and Patentee's, both of which were addressed in the Institution Decision (ID, 7-16). 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." EX2076, 63:8-64:2.

IV. Claim Construction Issues

A. The Challenged Claims Define the Invention by Reference to Structure, Not Function

In its Institution Decision, the Board preliminarily found that the term "modified PH20 polypeptide" in the claims "encompass[ed] polypeptides with some hyaluronidase activity." ID, 15. Patentee does not dispute that the claims encompass PH20s with hyaluronidase activity. As set out below, however, Patentee does contend that the claims are defined by structure only, and encompass ***both*** enzymatically active and enzymatically inactive PH20s.

Specifically, Claim 1 defines the invention by reference to an amino acid

sequence, not a specific function, and thus it encompasses both polypeptides that are enzymatically active ("active") to degrade hyaluronan and those that are not ("inactive"). Claim 1 recites a "modified PH20 polypeptide" with a modification at position 320, wherein at least 95% of the residues of the amino acid sequence are identical to any of SEQ ID NOs: 3 and 32-66. EX1001, claim 1. There is no language in the claim requiring the polypeptide to perform a specific function. EX2076, 172:21-173:9. The parties do not dispute this.

The parties instead dispute whether the term "modified PH20 polypeptide" as defined in the specification requires at least 40% hyaluronidase activity (or, to the extent Petitioner now adopts the Board's preliminary construction, "some" activity).

B. "modified PH20 polypeptide"

The terms of a patent claim "are generally given their ordinary and customary meaning." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc). The Federal Circuit has established, however, that if the patentee "acts as his own lexicographer" then the definition in the specification controls. *Thorner v. Sony Computer Ent Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). "To act as [his] own lexicographer, a patentee must 'clearly set forth a definition of the disputed claim term,'" and must "'clearly express an intent' to redefine the term." *Id*. (citations omitted).

The patent specification contains a lengthy "Definitions" section (Part A of

the Detailed Description) in which it clearly defines "modified PH20 polypeptide." The definition is provided in the italicized sentence in the passage below:

> *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. 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.

EX1001, 48:38-53.

The parties agree that the "modified PH20 polypeptide" term is defined in the specification and that the italicized sentence is definitional. EX2068, ¶¶263-264; EX2076, 178:21-179:10; Pet., 18; Reply, 2 (stating "'modified PH20 polypeptides,' which are defined as 'a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement ... in its sequence of amino acids compared to a reference unmodified PH20 polypeptide.'"). The parties dispute, however, whether that sentence constitutes the entire definition (as Patentee argues)

or whether the following sentence, and other statements teaching that an active polypeptide can have at least 40% activity, are part of the definition, such that the claimed "modified PH20 polypeptide" must have at least 40% hyaluronidase activity.

The Board should find that Patentee's construction is correct, and the definition of "modified PH20 polypeptide" is limited to the first sentence. A statement is definitional if (1) "*the sentence in question* appears under the title 'Definitions'"; (2) "the term to be defined….is *set off in quotation marks*"; (3) the sentence "uses the term '*refers to*'…which generally conveys an intent for that sentence to be definitional"; or (4) "elsewhere in the Definitions section, [the patent used] "non-limiting terms that contrast with the 'refer to' language at issue here." *Alnylam Pharms., Inc. v. Moderna, Inc.*, 138 F.4th 1326, 1333 (Fed. Cir. 2025) (citations omitted); *see also, ParkerVision v. Vidal*, 88 F.4th 969, 977 (Fed. Cir. 2023); *Kyocera Senco Industrial Tools Inc. v. ITC*, 22 F.4th 1369, 1378 (Fed. Cir. 2022). The first sentence in the block quote above plainly satisfies these criteria. That sentence, like claim 1's recitation of the invention, defines the term by reference to "its sequence of amino acids compared to a reference unmodified PH20 polypeptide." EX1001, 48:38-53.[11]

[11] With reference to the criteria considered in *Alnylam*, the term appears in the

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. This is abundantly apparent from the outline provided at the start of the Detailed Description (*Id.*, 43:50-44:53), which lists the topic "Modified PH20 Polypeptides" as Part C, with subsections C.1 and C.2 describing "Active Mutants" and "Inactive Mutants" respectively. POSAs thus could hardly miss that the specification describes both

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"Definitions" section of the patent (EX1001, 44:55-68:42); the term is set off in quotation marks (*id.*, 48:38); the definition statement uses the phrases "as used herein" and "refers to" (*id.*, 48:38-39); and the remainder of the passage uses non-limiting, permissive language ("can have") to differentiate it from the actual definition of "modified PH20 polypeptide" (*id.*, 48:43-44). *See Alnylam* at 1333.

"active" and "inactive" mutants as "modified PH20 polypeptides." *See, e.g.* EX1001, 79:27-29, 119:13-17 ("[p]rovided herein are *modified PH20 polypeptides … that exhibit hyaluronidase activity,*" and also "[p]rovided herein are *modified PH20 polypeptides … that are inactive*, whereby the polypeptides *do not exhibit hyaluronidase activity* or exhibit low or diminished hyaluronidase activity."). Petitioner's construction is irreconcilable with repeated disclosures that a "modified PH20 polypeptide" includes inactive polypeptides, so it cannot be correct.

In the Institution Decision, the Board found on a preliminary basis that the second sentence in the passage above ("[a] modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity") was part of the definition. As a result, for the preliminary purpose of ruling on institution, the Board interpreted "modified PH20 polypeptide" to encompass "some" hyaluronidase activity. ID, 15.

Patentee respectfully submits that adopting the preliminary construction as final would be error.

First, the second sentence is not definitional. Unlike the first sentence, the second sentence does not use the term "refers to" or "as used herein," and instead uses "non-limiting terms that contrast with the 'refer to' language" in the first sentence. *Alnylam*, 138 F.4th at 1333. And the second sentence is expressly permissive in terms of the number of mutations permitted—the modified

polypeptide "can have" up to 150 amino acid replacements.

Second, as explained above, the term "modified PH20 polypeptides" is used throughout the specification as encompassing enzymatically active and inactive polypeptides, so construing the term as limited to active polypeptides contradicts the disclosure. As just one of many examples, the specification explains that "[p]rovided herein are *modified PH20 polypeptides … that exhibit hyaluronidase activity,*" and also "[p]rovided herein are *modified PH20 polypeptides … that are inactive*, whereby the polypeptides *do not exhibit hyaluronidase activity* or exhibit low or diminished hyaluronidase activity." EX1001, 79:27-29, 119:13-17; *see also, id.*, 75:47-49, 75:56-58; 119:30-120:27, 120:36-43, 195:3-6, 257:23-258:37; EX2068, ¶¶266-268

Petitioner's expert, Dr. Hecht, admitted that he did not even "consider this [disclosure]" referring to inactive modified PH20 polypeptides in forming his opinion "because [they] seemed contradictory" to his "interpretation" that the claims require activity.[12] EX2076, 189:1-192:16. But a proper claim construction analysis

[12] In fact, in deposition, Dr. Hecht could not provide any understanding of the legal principles of claim construction at all. Indeed, Hecht's declaration contains no evidence of any application of a legal framework for interpreting claims and he admitted that the extent of his claim construction analysis consisted of "mostly …

involves examining how the term is used throughout the entire specification, without disregarding sections of the specification that may conflict with a preconceived interpretation.

Furthermore, it is black letter law that, absent explicitly narrow claim language or a clear disclaimer in the specification or prosecution history, claims should not be interpreted "in a way that excludes embodiments disclosed in the specification." *See Oatey Co. v. IPS Corp.,* 514 F.3d 1271, 1276 (Fed. Cir. 2008).

As explained above, the specification provides an entire section of disclosure dedicated to "inactive mutants," in which it teaches "*modified PH20 polypeptides* that contain one or more amino acid replacements in a PH20 polypeptide and that are inactive, whereby the polypeptides do not exhibit hyaluronidase activity." EX1001, 119:12-21; EX2068, ¶¶266-268. Thus, the patent makes clear that "modified PH20 polypeptide" encompasses both active and inactive polypeptides. EX2068, ¶¶266-268.

Relying on *TIP Systems, LLC v. Phillips & Brooks/Gladwin, Inc.,* 529 F.3d 1364, 1375 (Fed. Cir. 2008), Petitioner argues that "the language used in the claims may cause them to be limited to only one" embodiment disclosed in the

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common sense with some advice about …. what is a dependent claim…" EX2076, 129:13-130-9.

specification. Pet., 22. But *TIP Systems* merely held that "the claims need not be construed to encompass all disclosed embodiments when the *claim language is clearly limited to one or more embodiments*." *Id.* Here, the claim language is not "clearly limited" to "active mutants" because claim 1 recites no requirement of hyaluronidase activity. EX2068, ¶¶258, 261. Rather, the language of claim 1 is clearly limited to modified PH20 polypeptides *defined solely by their amino acid sequences*, not by a "particular performance property" or "way[] of achieving a desired result." *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.,* 744 F.3d 725, 731 (Fed. Cir. 2014).

Petitioner excuses reading out the inactive mutant embodiments described in the specification and literally covered by the claims by arguing that they are "not scientifically credible." Pet., 24, 80. In fact, Petitioner's expert, Dr. Hecht, admitted that he understood the claims could only cover "useful" PH20s, and thus he interpreted the claims as limited to enzymatically active polypeptides because he considered those to be useful. But Dr. Hecht's analysis is wrong as a matter of law and science. Dr. Hecht's interpretation renders the claim scope subjective—whether a given PH20 is covered depends on whether someone believes it is useful. As Dr. Hecht himself admitted, "since [he does not] use this enzyme as a practitioner, [he is] not sure" what features render a given modified PH20 useful. EX2076, 213:1-21; 137:12-139:13.

In fact, the specification teaches that the inactive polypeptides ***are useful***. As discussed in more detail below in Section VI.B and explained by Patentee's experts who, unlike Dr. Hecht, have experience with PH20 and know what constitutes a useful PH20, inactive PH20s do have a credible utility. EX2068, ¶392; EX2074; EX2072.

Third, Patentee notes that the specification defines a different term—"modified hyaluronan-degrading enzyme"—as requiring hyaluronidase activity. Specifically, the term "modified hyaluronan-degrading enzyme" "refers to ***a hyaluronan-degrading enzyme*** that contains a modification compared to a reference or unmodified hyaluronan degrading enzyme." EX1001, 47:53-56 (emphasis added). The inventors chose to recite a "modified PH20 polypeptide" in the challenged claims—not a "modified hyaluronan-degrading enzyme," further underlining that the claims do not require hyaluronidase activity.

Fourth, Petitioner selectively extracts language from the patent specification disclosing alternative embodiments and presents it out of context, claiming it mandates hyaluronidase activity for the claimed polypeptides. Pet., 26 (citing EX1001, 47:61-65, 76:5-8, 76:67-77:7). But these statements plainly disclose alternative embodiments; they do not override the definition of "modified PH20 polypeptide" or the fact that the term "modified PH20 polypeptide" is used to refer to both enzymatically active and inactive polypeptides. These relied-upon

disclosures only state that modifications *can be* made to create active "modified PH20 polypeptides," not that all claimed "modified PH20 polypeptides" *must* exhibit hyaluronidase activity. EX1001, 76:5-8, 76:67-77:7; EX2068, ¶¶274. Moreoever, one of the statements Petitioner cites (47:61-65) in fact refers to a "modified hyaluronan-degrading enzyme," which, unlike "modified PH20 polypeptide," is defined as requiring enzymatic activity. *Compare* EX1001, 47:53-65 *with* 48:38-43; *Chicago Board Options Exchange v. ITC*, 677 F.3d 1361, 1369 (Fed. Cir. 2012) (discussing the "general presumption that different terms have different meanings."). Also, the relied upon disclosures are in an entirely different section of the specification, disparate from the Definitions section. EX1001, 76:5-8, 76:67-77:7.

Finally, Petitioner has no basis for reading a 40% activity threshold into the claims. Dr. Hecht admitted that none of the claim language specifies 40% hyaluronidase activity, and at deposition he was not willing to defend the construction, stating he was "uncomfortable with fixating on that number." EX2076, 213:1-5, 172:21-173:9. Petitioner improperly imports a specific embodiment from the specification into the claims, which is not permissible under proper claim construction principles. *Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1327-1328 (Fed. Cir. 2002); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1571 (Fed. Cir. 1988).

Accordingly, as a matter of law, the claims and specification unequivocally establish a "modified PH20 polypeptide" is defined by amino acid sequence and does not require any enzymatic activity.

C. Patentee's Application of the Board's Preliminary Construction and Patentee's Proposed Construction in Its Argument

Patentee sets out below the reasons that the specification describes and enables the D320 PH20 variants, and the narrow genus of 95% identical subvariants, under either the Board's preliminary construction (which is limited to active variants) or Patentee's proposed construction (which does not require activity). The specification allows POSAs to visualize or recognize the claimed set of modified PH20 polypeptides with the recited change at position 320, including both those variants that are active and those that are inactive. The specification also provides sufficient guidance for POSAs to make and use the full range of variants, both active and inactive, regardless of whether the claims specify enzymatic activity. Thus, in the sections below, Patentee explains why there is written description and enablement support, assuming POSAs must be able to distinguish between active and inactive modified PH20 variants and predictably make and use them, whether active or inactive.

As explained above, when properly construed, the claims do not require a specific function. Patentee emphasizes that, under established law, there is no requirement to describe or enable subject matter that is not claimed. *In re Entresto*,

125 F.4th 1090, 1097-99 (Fed. Cir. 2025) ("Written description asks whether *that which is claimed* is adequately described."), *see also id* ("As we have long recognized, '[t]he invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*.'" (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1564 (Fed. Cir. 1991)); *United Therapeutics Corporation v. Liquidia Technologies, Inc.*, 74 F.4th 1360, 1370-71 (Fed. Cir. 2023) ("[i]t would be incorrect to fractionate a disease or condition that a method of treatment claim is directed to, and to require a separate disclosure in the specification for each individual variant of the condition… in order to satisfy the enablement and written description provisions of 35 U.S.C. § 112, *unless these variants are specified in the claims*").

Therefore, the law does not obligate the Patentee to describe or enable an unclaimed function, whether it pertains to hyaluronidase activity or contraceptive use; nor does the law require Patentee to establish a structure-function correlation to unclaimed function. Thus, like the patent challenger in *Boehringer Ingelheim Animal Health USA Inc. v. Kansas State Univ. Res. Foundation* ("*Boehringer II*") PGR2022-00021, Paper 13, 25-26 (P.T.A.B. Mar. 22, 2023), Petitioner's Section 112 argument improperly "focuses on certain functional characteristics disclosed in the Specification that are not recited in the challenged claims, and therefore, lacks sufficient merit in the context of the challenged claims." *Id*. Petitioner's arguments can be rejected for the same reason as in *Boehringer II*.

For the sake of simplicity, however, and given the robustness of the patent's teachings, the Patentee assumes—without conceding—that the specification must enable POSAs to reliably distinguish, create, and utilize the full range of active and, if Patentee's construction is accepted, inactive modified PH20 polypeptides encompassed by the claims. For the reasons stated below, it does.

V. THE SPECIFICATION PROVIDES WRITTEN DESCRIPTION OF THE INVENTION (GROUND 1)

"'[A] sufficient description of a genus… requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ajinomoto Co., Inc. v. International Trade Commission*, 932 F.3d 1342, 1358-61 (Fed. Cir. 2019) citing (*Ariad*, 598 F.3d at 1350).

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.[13] ID, 16; EX2068, ¶¶277-342, 419.

A. The Specification Describes Common Structural Features of the Four D320 Modified PH20 Variants and Their Subvariants

The 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.

As Patentee's experts explain, based on the patent's description and extensive mutagenesis data, POSAs would have understood modified PH20 polypeptides within the scope of the claims to include a common mutation at position 320 to one of four specified amino acids and 95% identity in primary structure (*i.e.,* amino acid sequence). EX2068, ¶¶287-288; EX2070, ¶¶239-247. They also 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

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[13] As set out in fn. 7, *supra*, sufficiency under §112 is properly judged as of December 28, 2012, the filing date of the '731 application Merck assessed. Petitioner and its experts erroneously rely upon a December 30, 2011 date (Pet. 26-84; *see also,* Pet 40, 41, 56, 74, EX 1003, ¶ 11), rather than the proper December 28, 2012 date. Petitioner nowhere explains this substantial error—the use of a date a full year earlier—despite the fact that, as Patentee noted in its preliminary papers (Paper 12, 10-11), analysis under the proper date was required to establish PGR-eligibility.

active site and the same key catalytic residues, absent changes of the type the patent identifies as inactivating. *Id*.

This is not just conjecture. For example, 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, ¶¶410-412. 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 teaches is active). [14] In other words, they are multiply mutated.

As Dr. Petsko's figures show, these multiply-mutated D320K subvariants all share a common tertiary alpha-beta barrel structure:

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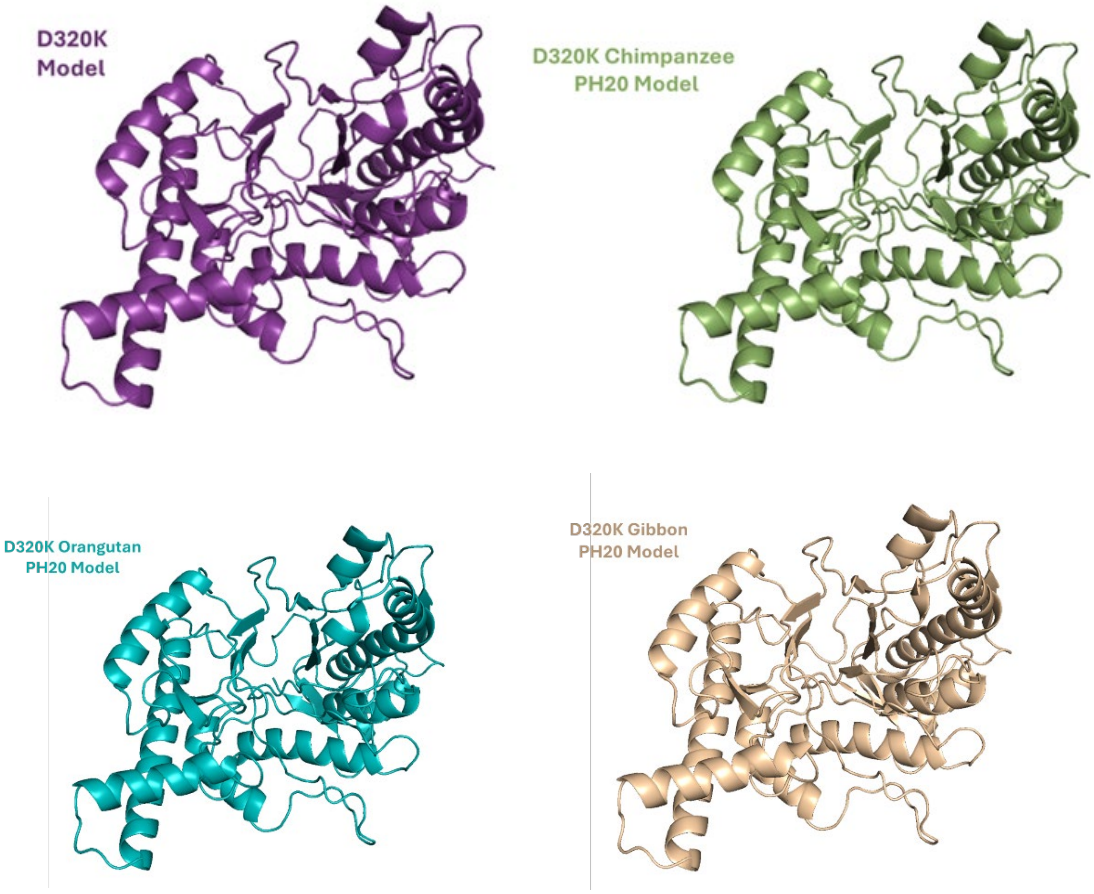
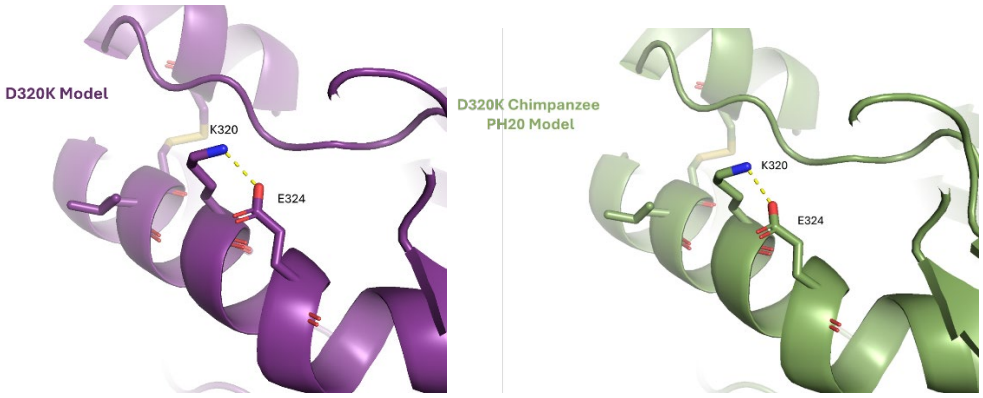
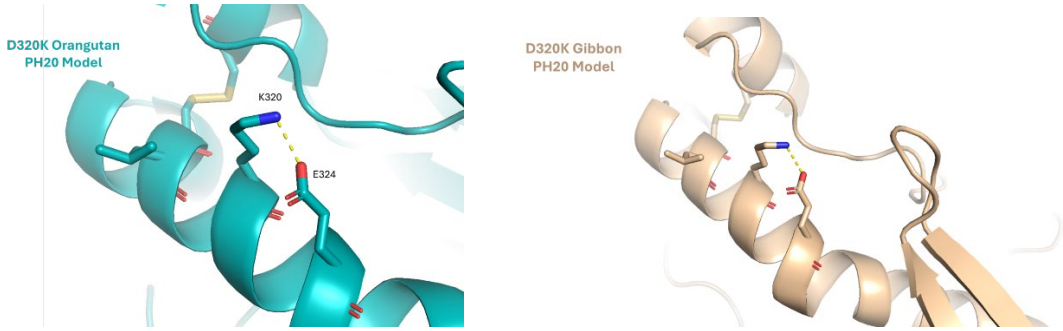
[14] Dr. Simpson explains that based on the patent alignments and disclosure regarding C-terminal truncations in PH20s, POSAs would have expected that truncating these primate PH20s at the same position as SEQ ID NO: 3 would have produced a soluble, active PH20, and introducing the D320K mutation would similarly have produced an active subvariant. EX2068, 227-242, 300.



Similarly, these subvariants also share common interactions (illustrated with dotted lines in the figures below) at position D320:





Thus, POSAs would have understood from the teachings of the patent that the claimed subvariants would share this same tertiary structure unless that structure was broken by inactivating changes of the kind identified by the patent. EX2068, ¶303. Those inactivating changes include changes to the following:

- **Specific amino acid positions in PH20 that are necessary to enzymatic activity** such that they should not be disturbed, such as "positions 25, 111, 113, 176, 189, 203, 246, 249, 252, 316, 341, 346, 352, 400, 402, 408, 423 and 429 of … SEQ ID NO: 3 or 7 … since mutagenesis of these residues results in an enzyme that is not active…." EX1001, 70:46-54; EX2068, ¶303. The patent further characterizes the roles of these specific amino acid positions in detail, **including**:

  - **Disulfide bridges -** 12 cysteine residues "corresponding to amino acid residue 25, 189, 203, 316, 341, 346, 352, 400, 402, 408, 423 and 429 of … SEQ ID NO: 3 or 7" that "form disulfide bridges. EX1001, 70:14-26; EX2068, ¶303.

  - **Sites contributing to substrate binding / activity -** The patent also identifies amino acids at positions 111, 113, 249, 176, 246, and 252 of SEQ ID NO: 3 or 7 as "contribut[ing] to substrate binding and/or hyaluronidase activity." EX1001, 70:34-41; EX2068, ¶303.

The patent also identifies other positions that do not tolerate modification or only tolerate limited modifications. EX2070, ¶¶292-296,. As Dr. Petsko explains, the POSA would have understood that such positions should be maintained, with some exceptions (like "rescue" mutations that restore activity) that the POSA could determine from the patent data. *Id*.

In other words, because the specification discloses the structural features necessary for activity, POSAs would have understood them as common to active D320 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).

Petitioner thus cannot seriously dispute that the four D320 variants and their active subvariants share common structural features. Nor is it surprising that these nearly identical sub-variants share common structural features. As Dr. Petsko explains, proteins with far less than 95% sequence identity—in fact proteins with 40% sequence identity—share common structural features down to the atomic level. EX2070, ¶¶95-104, 126-213. Dr. Petsko shows in detail how Hyal-1 and PH20 share common residues critical for activity and stability that are positioned in about the same place and form similar chemical interactions. EX2070, ¶¶126-213. If two hyaluronidases that share less than half of their amino acids have such similarities, then surely the recited D320 variants and their 95% identical active subvariants will

share common structural features.

B. The Specification Provides Structure-Function Correlations Allowing for Single and Multiple Mutations

In addition to these common structural features, the specification's working examples provide POSAs with an extensive catalog of modifications at every position of a mature, soluble PH20 (SEQ ID NO: 3), showing which positions tolerate modifications (retain activity) or do not tolerate them (lose activity). EX1001, Example 4, Tables 9-10; EX2068, ¶¶246, 311, 322; EX2070, ¶¶233, 262. These examples provide structure/function correlations POSAs can use to identify the active 95% identical D320 subvariants and distinguish them from inactive subvariants.

Specifically, as Drs. Petsko and Simpson explain, POSAs would have understood that the '600 patent teaches how to correlate the structure of modified active PH20s—their primary structure and characteristic tertiary structure (an alpha-beta barrel fold)—to the hyaluronidase function of modified PH20. EX2070, ¶¶44, 54; .EX2068, ¶¶305-306. Through the comprehensive mutagenesis data (Tables 9-10), the patent shows, for each of the 447 positions in SEQ ID NO: 3, the tolerance of each position to substitution as it relates to enzymatic activity. This allows POSAs to distinguish between positions that are (1) critical to activity, (2) generally intolerant in that they permit only very limited substitution, (3) generally tolerant in that they permit a broad range of substitutions. *Id*. 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.*

To illustrate the structure/function correlation provided by the patent, Dr. Petsko mapped the patent's functional data onto Dr. Park's PH20 homology model, which the parties do not dispute was part of a POSA's knowledge. That mapping is reproduced below in figures showing 90-degree rotations of PH20's tertiary structure, color coded as follows: tolerant (green), intolerant or generally intolerant (red or orange), and those falling between (aqua). It shows an example of how a POSA would have understood the patent's mutagenesis data in to the context of PH20's structure, identifying areas for potential modification and areas to avoid unless the POSA wishes to reduce or eliminate activity:

EX2070, ¶¶297-299.

The ’600 patent thus provides the information a POSA requires to identify both single and multiple mutations within various areas of the PH20 structure that can be reasonably predicted to retain hyaluronidase activity, or eliminate it. EX2070, ¶¶54-56, 262. This functional map of PH20 identifies for POSAs the extent to which each position in the sequence tolerates substitutions and which do not, which types of residues at each position are likely to be successful in terms of maintaining activity, and which positions in particular could be targeted to maintain or improve activity.

This detailed structure-function correlation of a narrowly defined, structurally homogeneous genus, demonstrates the inventors were in possession of the full scope of the invention. These 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. EX2068, ¶311; *In re Ruschig*, 379 F.2d 990, 994-995 (CCPA 1967); *Ajinomoto*, 932 F.3d at 1358-61 (adequate description where “skilled artisan could make relatively predictable changes to the native promoter to arrive at a more potent promoter”).

Notably, this is not a case like *Ariad*, as the Board suggested on the limited record pre-institution, where the patent “recite[s] a description of the problem to be solved while claiming all solutions to it and . . . cover[s] 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; ID at 35.

Indeed, unlike *Ariad* (and *Abbvie*) the patent claims here are exceedingly narrow, and in no way "claim[] all solutions" or even a tiny fraction of the possible solutions to degrading HA with modified PH20s. EX2068, ¶¶284-286. The patent claims only what was invented; that is what written description asks.

Moreover, for the same reasons, the claims in no way "cover any compound later actually invented and determined to fall within the claim's functional boundaries." *Ariad*, 598 F.3d at 1353; ID at 35. Indeed, the claims do not have functional boundaries that would permit this—they have structural ones—even if they do require function. 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.

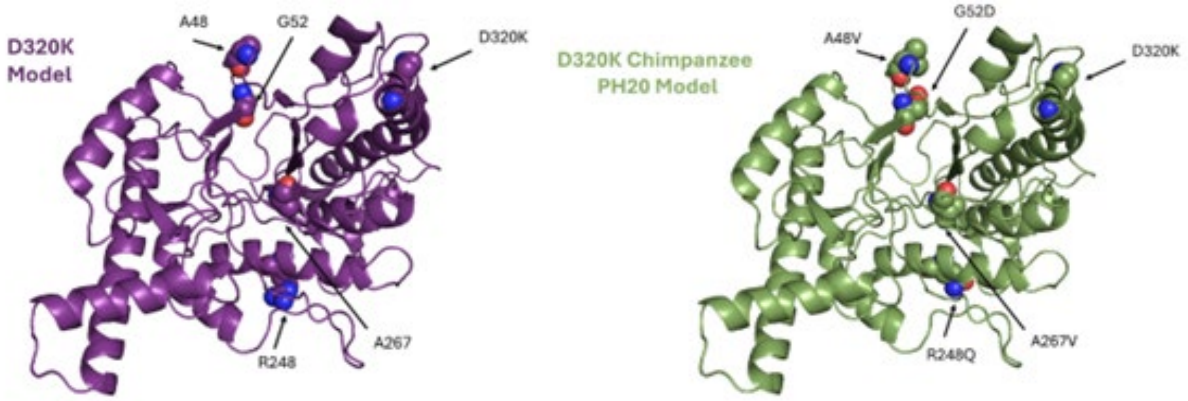
In other words, Patentee received a narrow monopoly in return for contributing its novel 320 mutation ***and*** a complete characterization of PH20. That is more than sufficient written description.

C. The Example D320 Variants Are Representative of the Claimed 95% Identical Subvariants

POSAs would have understood that the four D320 variants recited in the claims are representative of their 95% identical subvariants. After all, the subvariants share ***at least 95% of their primary structure*** with the recited D320 variants. As a result, as Dr. Simpson and Dr. Petsko explain, there is almost no structural diversity within the claimed set of subvariants.

For example, as Dr. Simpson explains, the set of active PH20s with the recited substitution at position 320 share a common structural "scaffold" with minor variations across the surface of the protein's tertiary structure. EX2068, ¶¶316, 318. As a result, the claimed modified PH20s that are active are structurally homogeneous, and the four examples of D320 modified PH20s are representative of this narrow set of proteins. *Id.*, ¶317.

Dr. Petsko illustrates this concept in his declaration using examples of multiply mutated PH20 polypeptides that POSAs would have expected to be active based on the disclosure of the patent. EX2070, ¶421-26. As is evident from the figure below, the multiply modified PH20 shares the same tertiary structure (the characteristic PH20 alpha-beta barrel fold), with minor modifications dispersed across the surface of the protein, as shown with labeled annotations (A48, G52, A267, R248):



But despite that minor variability, POSAs would understand that these multiply modified subvariant PH20s all share significant structures in common with the D320K variant, as explained above. Dr. Petsko's and Dr. Simpson's analyses show that the claimed D320 variants are representative of the 95% identical subvariants.

Moreover, while the exemplified variants with mutations at the other 446 positions in the protein (other than 320) are not representative species (because they do not meet the claims), they provide valuable information to POSAs in terms of where additional variation in the structure will be tolerated and where it will not. POSAs would understand this information is applicable when making multiply mutated D320 variants EX2068, ¶ 323. *See Ajinomoto*, 932 F.3d at 1358-61.

Petitioner criticizes these working examples as "limited" because they do not include examples of multiply modified polypeptides. Pet., 55-56. But Petitioner misunderstands the purpose of the patent's core experiment. By changing every single amino acid in the 447 amino acid sequence of PH20 (SEQ ID NO: 3) to, on average, 13 other amino acids, the inventors were able to map the tolerance of each

position to change and to identify those positions that generally tolerate change (and what types of changes) and those that generally do not. As Dr. Petsko explains, POSAs can use those data to determine which positions to modify for both singly and multiply modified PH20s. EX2070, ¶¶54-56, 262.

In the Preliminary Decision, the Board reasoned, based on the limited record in front of it, that the modified PH20 polypeptides were not homogeneous based on the data in the ’600 patent disclosing that under 10% of the mutations exhibited increased activity, and that the ’600 patent data showed that approximately “57.1% were inactive, and 29.4% had activity <100%.” *Id.* ¶ 105.

But as explained above, Dr. Petsko’s and Dr. Simpsons’ analyses show that in fact the claimed subvariants are structurally homogeneous. And the large number of inactivating mutations are not evidence of unpredictability. EX2068, ¶¶379-380. To the contrary, the patent data make modifying PH20 predictable by teaching POSAs where to make changes, and perhaps more importantly, where not to make changes, providing predictability.

The Board reasoned that working with PH20 may be unpredictable given of the large number of mutations that inactivate the protein. ID, 32. But 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. EX2070, ¶¶353-65; EX2068, ¶¶316-323; *see*

Ajinomoto, 932 F.3d at 1358-61 (holding "amount of disclosure necessary to satisfy the written-description requirement 'will necessarily vary depending on the context'" including "predictability of the aspect at issue"; finding four examples sufficient where POSAs could make "relatively predictable changes") (citing *Ariad*, 598 F.3d at 1351).

To the extent inactive variants fall within the claimed genus, they are distinguishable in the same manner and under the same framework. They must include the recited change at position 320 and a primary structure that is at least 95% identical to one of the four D320 variants. A POSA could identify them, however, as including the types of changes the patent teaches will inactivate the protein—*e.g.,* . modifications the POSA would predict abolish activity by disrupting the common structures, such as changes at essential positions in the active site. EX2068, 379-380. POSAs could thus reliably distinguish actives from inactives.

D. The Patent Teaches the Effect of C-terminal Truncations

Petitioner's arguments for lack of representativeness and unpredictability consistently ignore the teachings of the patent. For instance, relying on the prior art '429 patent, Petitioner argues that there is no data in the patent relating to "PH20 polypeptides ***having fewer than 447 residues (or even unmodified PH20s with such lengths***)." Pet., 37-38 (emphasis added). Petitioner argues this creates "significant uncertainty" because, allegedly, the "common disclosure and the prior art report that

PH20 polypeptides with fewer than 442 residues significantly reduce or eliminate hyaluronidase activity," citing the '429 patent which was filed in 2004. *Id*. Similarly, Petitioner argues that modifications to SEQ ID NO: 3, which terminates at position 447, cannot be representative of the SEQ ID NOs: 32-66, which terminate between positions 430 and 465, because it alleges the patent does not teach the effect of C-terminal truncations throughout this range.

This is flatly incorrect. Throughout the '600 patent, the inventors discuss U.S. Publication No. US20100143457 (the "'457 publication") in relation to C-terminal truncations in PH20. The '457 publication was filed five years after the '429 patent, and discloses follow-on work to the '429 patent that Halozyme inventors conducted (including one of the '600 patent inventors). This work refined the findings of the '429 patent, providing data showing the effect that serial single amino acid C-terminal truncations had on activity—truncations that run ***from position 465 in the mature sequence all the way down to 430***. In other words, the '457 publication 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 '457 publication's results what the activity would be for each recited sequence in the '600 claims. EX2068, ¶¶324-335; EX2070, ¶¶226-30. Additionally, POSAs would have understood that for the sequences shown to be active in the '457 publication, if they were to further modify the sequence within the scope of the

claims (i.e. by adding the D320 mutation and up to 5% additional variation), the effect on activity would be the same whether the sequence was SEQ ID NO: 3 or the other recited active sequences. EX2068, ¶¶332-335; EX2070, ¶¶384-88, 428.

Similarly, if a POSA used sequences where the truncation rendered them inactive, they would have remained inactive even after further modification, because they lack the minimum sequence length required for hyaluronidase activity. Finally, if a POSA were to start from a sequence where the truncation reduced activity as shown in the '457 publication, and then introduced additional mutations (i.e. D320, etc.), the POSA would have expected the modified PH20 would exhibit a level of activity that would be reduced compared to, for instance, SEQ ID No: 3, but still be active. EX2068, ¶¶330-332; EX2070, ¶¶387-88.

Petitioner and its experts did not consider or discuss the '457 publication at all, and thus confess great confusion as to the effect of C-terminal truncations. POSAs would not have been so confused. The '600 patent in fact guides POSAs to the systematic study of the effect of C-terminal truncations in the '457 publication, and POSAs would have thus understood the effect of combining mutations like those disclosed with respect to SEQ ID NO: 3 with the various C-terminal truncations taught in the '457 publication. EX2068, ¶¶324-335; EX2070, ¶¶384-88, 428.[15]

[15] To the extent Petitioner suggests Patentee need redescribe the results, that

E. The Claims Expressly Do Not Cover the Modified PH20s the Specification Excludes From the Claims

Finally, Petitioner alleges that the claims capture polypeptides "the common disclosure explicitly says to not make," and "affirmatively excluded" subject matter. Pet., 60-61. Petitioner refers to the following six combinations of replacements:

- P13A/L464W, N47A/N131A, N47A/N219A, N131A/N219A, and N333A/N358A, which the specification states should not be made if the polypeptide contains only two amino acid replacements and
- N47A/N131A/N219A, if the polypeptide contains only three amino acid replacements. Pet., 60; EX1001, 77:51-57.

Again, Petitioner is wrong regarding claim scope, because none of the six combinations is encompassed by the claims. EX2068, ¶337. The disclosed combinations all limit replacements at positions that do not include the claimed modification at position 320. EX1001, 77:45-57, claim 1; EX2068, ¶337. Accordingly, the claims never captured these six combinations of replacements. ID,

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is incorrect. *See Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1063 (Fed. Cir. 2020) ("It is well-established that a patent specification need not re-describe known prior art concepts.") (citing *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005) ("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge.")

32.

But the claims do cover multiply modified polypeptides with the following changes: N47A/N131A, N47A/N219A, N131A/N219A and N47A/N131A/N219A in addition to the recited substitution at position 320 (for example, D320K). And, as Dr. Petsko and Dr. Simpson explain, 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. EX2068, ¶¶338-339; EX2070, ¶¶214-15. POSAs would have expected that introducing the modification at position 320 as taught in the '600 patent into one of these multiply modified PH20s would have produced an active subvariant. EX2068, ¶340; EX2070, ¶¶214-15, 410-20.

F. *AbbVie* Is Distinguishable

In the Institution Decision, the Board reasoned on the limited record in front of it that "[t]hese facts are analogous to those in *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1300 (Fed. Cir. 2014), where the claims contained structurally diverse antibodies, but the patent at issue only described structurally similar antibodies." ID, 34. As set out above and shown definitively by Dr. Petsko, however, 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.[16] In *AbbVie*, there were no working examples to illuminate the common structures of the diverse genus claimed. Thus, *AbbVie* is not on point.

G. The Petition Fails To Demonstrate That The Challenged Dependent Claims Lack Written Description

Petitioner contests the written description of the dependent claims only on the same grounds addressed above, and thus its challenge fails for the same reasons. Pet., 61-65; EX2068, ¶¶342; Sections IX, X.

VI. THE CHALLENGED CLAIMS ARE ENABLED (GROUND 2)

Enablement requires that the specification teach POSAs how to make and use the full scope of the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Record evidence demonstrates that the patent's specification provides precisely that: a detailed structure-function correlation that enables POSAs to predictably practice the full scope of the claims.

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. Pet., 38-39. The "key enablement question," as explained in *Idenix* as cited by the Board, is whether "a person of ordinary skill

[16] As to inactives, see fn 4, *supra*.

in the art would know, without undue experimentation, which species would be effective." ID, 48 (citing *Idenix*).

They would. As an initial matter, the challenged claims do not encompass an "immense genus" of unrelated polypeptides, as Petitioner contends (Pet., 42–45), but instead four variants with the D320 mutation and a narrowly defined and structurally homogeneous set of PH20 subvariants with 95% sequence identity. *See* Sections V.A, C. Each claimed polypeptide must (i) include a defined substitution at position 320, and (ii) share at least 95% sequence identity with SEQ ID NOs: 3 or 32-66. EX2068, ¶¶254. 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). EX2068, 287-293, 303, 316; EX2070, ¶¶49-51, 53. This dual limitation to a single mutation and only a small range of subvariants leaves POSAs with a narrow, well-defined set of PH20 variants with common structural characteristics, not the vast, unpredictable, "immense genus" Petitioner describes.

Within this narrow and homogeneous set of PH20 variants, 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. By systematically testing (on average 13 and up to 18) substitutions at every amino acid position in SEQ ID NO: 3, the patent shows the substitutions that consistently destroy activity by eliminating, for instance, catalytic residues or disulfide-forming cysteines. Similarly, buried residues important for protein structure or involved in orienting secondary structures to achieve the characteristic alpha-beta barrel fold are generally intolerant to change. EX2068, ¶313; EX2070, ¶¶325-333. By contrast, changes in certain peripheral loops or solvent-exposed regions are more likely to be tolerated with little effect on function. EX2070, ¶¶317-24. Some positions tolerate some types of substitutions but not others. *Id*.

Taken as a whole, these data provide significant guidance to POSAs in terms of what changes to make at which positions. This guidance gives POSAs a how-to for designing and using the claimed PH20 variants and subvariants without undue experimentation. This is sufficient for enablement, as the Supreme Court explained in *Amgen*:

> That is not to say a specification always must describe with particularity how to make and use every single embodiment within a claimed class. For instance, it may suffice to give an example (or a few examples) if

> the specification also discloses 'some general quality ... running through' the class that gives it "a peculiar fitness for the particular purpose. In some cases, disclosing that general quality may reliably enable a person skilled in the art to make and use all of what is claimed, not merely a subset.

Amgen, 598 U.S. at 610-611. Here, based on the patent's working examples and extensive mutagenesis data identifying common structures, POSAs can reasonably distinguish between active and inactive modified PH20 variants, and can predictably make and use either type of variant, whether singly or multiply mutated.

Patentee addresses the *Wands* factors individually below. Patentee separately addresses, after that analysis, unique questions relating to the use of the recited PH20 polypeptides as a contraceptive.

A. The *Wands* Factors Weigh in Favor of Enablement

1. Scope of Claims and Nature of the Invention

As discussed in Section V.A-C, the challenged claims recite a narrow and structurally homogeneous genus of four PH20 variants with one of four substitutions at position D320, as well as subvariants of each that must maintain at least 95% sequence identity. The scope of the claims is extremely narrow. While Petitioner focuses on the raw number of the subvariants, this is not how a POSA would consider the scope of the genus (EX2068, ¶¶352-355)) because it misses the forest for the trees. The claims require the "modified PH20 polypeptides" to have a

previously-undiscovered mutation at a single position in the sequence. They would consider the scope of the claims by considering the variation across the claimed set of proteins. *Id*. As set out above, there is only minor variation—5% variation within primary sequence—such that the enzymatically active claimed variants and sub-variants share common structures, including the same alpha-beta barrel tertiary structure and common "scaffolding" (*e.g.* disulfide bonds). *Id*.

As to the nature of the invention, As Dr. Simpson explains, POSAs would have understood that making active or inactive modified PH20 polypeptides required only routine molecular biology and protein biochemistry techniques in view of the patent's teachings. EX2068, ¶360; EX1001, 143:1-142:57.

Petitioner, for its part, did not make a serious attempt to understand the nature of the invention. Petitioner primarily relies on its expert's opinion that proteins, in general, are unpredictable when mutated. But Petitioner's experts have zero experience with the actual subject matter of the invention—PH20s, or even hyaluronidases in general. EX2077, 13:10-17; EX2076, 64:9-13, 67:1-8. And they dismissed the mutagenesis data disclosed in the patent as "no guidance." EX2062, 88.

The nature of the invention, however, is not proteins in general. The invention is modified PH20 variants with a defined set of structures, which the inventors characterized via expansive disclosure in the specification regarding the tolerance of

every position in a mature, soluble, active PH20 sequence to modification, making modification (and the nature of the invention) reasonably predictable. Thus, as Patentee's experts show, given the nature of the particular invention claimed—a structurally homogeneous set of PH20s—with the knowledge in the art and the mutagenesis data, POSAs could reasonably identify and predictably make and use the subvariants. *Id*.

Accordingly, the nature of the invention and the scope of the claims weigh strongly in favor of enablement under the *Wands* factors.

2. Level of Skill in the Art And State of the Art

As set forth in Section III, Patentee applies Petitioner's definition of a POSA, who would have had an undergraduate degree, a Ph.D., and post-doctoral experience in scientific fields relevant to study of protein structure and function and 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 as with techniques used to analyze protein structure (i.e., sequence searching and alignments, protein modeling software, etc.). ID, 7.

Patentee also notes that it is undisputed that POSAs would have been able to speak with someone with hyaluronidase experience as part of a multi-disciplinary team. EX2076, 63:8-64:2.

As set forth in Section II.B, the structural biology of hyaluronidases was well developed as of December 28, 2012. For instance, by then, the crystal structures of bee venom hyaluronidase and human Hyal-1 had been solved (EX1033; EX1006), and it was undisputed that these structures allowed POSAs to generate accurate homology models of PH20's tertiary structure. Petitioner's own expert confirmed that by 2011 it was routine for POSAs to model PH20 and assess amino acid substitutions in that structural context. EX2077, 94:4-22, 176:2-5.

The art also recognized that hyaluronidases, despite only 30-40% sequence identity, share a conserved alpha-beta barrel fold, a common active site, and a conserved set of catalytic residues positioned similarly across Hyal-1, bee venom hyaluronidase, and PH20. EX1006, 6912, 6914; EX1008, 826, 833; EX1033, 1028; EX2070 ¶¶126-27. Mutagenesis studies in Hyal-1 and PH20 had further confirmed the criticality of these residues for enzymatic activity and stability. EX1010; EX1011; EX1033, 1029; EX2070 ¶¶167-206; EX2068 ¶¶130-133, 369.

Accordingly, as of December 28, 2012, POSAs, already 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. EX2068 ¶¶362, 371; EX2070 ¶¶52, 234, 262.

3. Guidance in the Specification and the Presence of Working Examples

As set forth in Sections II.C and V.B, the specification supplies detailed instructions on how to make and used the claimed variants and sub-variants. EX1001, 69:13-71:48, 73:2-10, Tables 5, 9–10; EX2068, ¶¶372-377; EX2070, ¶¶248-61.

Together, these disclosures provide a structure-function correlation for PH20 that informs POSAs which regions are essential, which resist change, and which can accommodate or even benefit from substitution. With this map, along with the routine use of homology modeling, POSAs could readily distinguish between actives and inactives, whether singly or multiply mutated, to practice the invention. EX2070, ¶¶54-56, 262; EX2068, ¶¶159-151, 246-247, 311, 322, 373-383. As Dr. Simpson testifies, "[a]s someone with decades of experience studying hyaluronidases, including common structural features and structure-function correlations for hyaluronidases, I cannot emphasize enough the value of these data to a POSA in the field." *Id.*, ¶376.

Moreover, the inventors provided working examples of the four variants of the D320 mutation recited in the claims. Given the extensive experimental data fleshing out the functional map of PH20, further working examples of the

subvariants are not necessary. *See* Section V.B-C; EX1001, 200:45-269:8, Tables 8–10, 289:45-291:66; EX2068, ¶377.

The specification also provides guidance on how to use the claimed modified PH20 polypeptides. It teaches, for instance, that modified PH20s are useful as spreading factors to increase delivery and bioavailability of subcutaneously administered therapeutic agents—a fact not in dispute. It also teaches they are useful as contraceptive vaccine agents, which Petitioner addresses at length below. EX1001, 181:27-33, 194:55-56; EX2068, ¶392.

The specification's guidance, reinforced by its extensive working examples, therefore weighs strongly in favor of enablement.

4. Predictability of the Field and Quantity of Experimentation

As set forth in Section V.A-C, the specification's identification of common structural features and the associated correlation it provides between PH20s structure and hyaluronidase activity makes the effects of modifications to PH20 reasonably predictable. *See also*, EX2070, ¶¶263-342; EX2068, ¶¶378-384.

Moreover, POSAs could and would have used routine homology modeling to reinforce this predictability, making any experimentation routine. EX1004, ¶¶36-38; EX2076, 93:4-22; EX2077, 53:22-54:5; EX2070, ¶¶117-20. Both Hecht and Park admitted that homology modeling was widely available and would be used to assess whether substitutions were likely to be tolerated.

And Dr. Petsko describes in detail how POSAs could use the functional data in connection with homology models known in the art to make active subvariants. For example, Dr. Petsko mapped the functional data on the homology model and 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 with the data without trial-and-error experimentation. EX2070, ¶¶297-342. As Dr. Simpson explains, "[t]he immense disclosure in the specification makes generating and using the modified PH20 variants and sub-variants in the claims predictable. That is because the detailed structure-function map provided by the patent allows POSAs to reasonably predict, using their structural biology knowledge, whether substitutions are likely to retain or abolish enzymatic activity." EX2068, ¶384.

In view of this guidance, the quantity of experimentation required would not have been undue. Petitioner's assertion that POSAs would need to screen an "immense number" of variants is misplaced because the specification itself already discloses extensive data showing which substitutions preserve activity and which eliminate it. EX1001, Tables 9–10; EX2068, ¶¶378-380, 388-390; EX2070, ¶¶52, 234, 262. No doubt Petitioner argues that POSAs would have to screen because the term "screening" suggests POSAs must engage in trial-and-error experimentation to practice the claims. But that simply is wrong. The patent teaches POSAs how to

make the claimed variants with no "screening" required.

And Petitioner's argument that POSAs would need to generate impossibly large libraries and screen them for activity to practice the claims is not credible. Where, as here, the patent teaches POSAs a structure-function map of PH20, including which changes to make and which positions are generally tolerant to change, there is no reason to randomly screen to identify active PH20s with the D320 mutation. POSAs seeking to make PH20s through random screening would be, in effect, ignoring the teachings of the specification.

Finally, relying on Dr. Hecht, Petitioner argues that there was supposedly uncertainty "about the activity of truncation mutants in the C-terminal region of PH20." Patentee addressed this point above in Sections II.C.5 and V.D. Petitioner's expert appears to not even have considered the relevant teaching in the '457 publication, which is discussed throughout the '600 patent. EX2029, 82-83. Dr. Simpson explains what a POSA would have reasonably and reliably expected when making mutations in PH20s of varying lengths, including those that terminate before or after position 447. EX2068, 188, 329-330, 385.

In sum, POSAs would have relied on the patent's disclosure, which could be supplemented by routine modeling, to make and use the claimed modified PH20 variants and sub-variants using only routine methods well within the skill of the art. EX2068, ¶¶344-349. Accordingly, the specification provides the framework for

POSAs to predictably make and use the full scope of both active and inactive PH20 polypeptides, weighing strongly in favor of enablement.

B. Specification Enables Credible Use of the Claimed PH20 Variants as Contraceptives

Having shown that POSAs could make and distinguish the claimed variants, the record also establishes that the specification teaches how to use them.

As an initial matter, the specification expressly teaches that the claimed PH20 variants with enzymatic activity can be used as spreading factors to enhance the delivery and bioavailability of subcutaneously administered therapeutic agents. EX1001, 181:27-33. This was a well-recognized application in the field, and Petitioner does not dispute that active modified PH20 variants within the claims provide that established utility—only that they can be identified, which is addressed above.

Petitioner instead challenges the utility of inactive variants as contraceptives, contending (at 28 and 80) it is "implausible" and "not scientifically credible." That contention is unfounded. The record confirms that the claimed modified PH20 polypeptides have a credible and enabled utility as contraceptives across the full scope of the genus.

First, the specification expressly teaches that PH20 variants can be used in contraceptive applications (EX1001, 194:55-56, 195:2-4) and incorporates prior studies showing that administration of PH20 induces infertility (EX2010; EX1023;

EX1029; EX2074, ¶45). Petitioner's own references likewise acknowledge these findings, reporting strong contraceptive effects of PH20 in animal models. EX1019, Abstract, 332; EX1020, Abstract, 175; EX2072, ¶47. POSAs, reading the specification in light of this knowledge, would have understood that the claimed modified PH20 polypeptides could reliably function as a means of contraception.

Second, as Dr. Cherr explains, by December 28, 2012, POSAs would have expected that PH20 polypeptides would be useful as contraceptive vaccines in humans and other mammals, particularly because it was widely known that PH20 plays a vital role in fertility and affects several stages of conception, including the critical final step of allowing the sperm to physically reach the egg. EX2072, ¶¶19-28. POSAs would have expected that regulating the presence and quantity of PH20 at the relevant biological site would directly impact fertilization. EX2072. ¶¶29-34.

In particular, PH20, a sperm-associated protein, can be seen as a foreign entity by the female body – an antigen to be bound by antibodies. EX2074, ¶20; EX2072, ¶21. The female body does this by generating a collection of different antibodies ("polyclonal antibodies") to attack PH20. EX2074, ¶¶21; EX2072, ¶31. These polyclonal antibodies attach themselves to a large number of different binding sites on PH20 called "epitopes." EX2074, ¶¶21, 22, 33, 42, 50; EX2072, ¶31. Notably, one would have expected that at least some of these epitopes were *not* in the hyaluronidase enzymatic activity region. EX2074, ¶¶44. This is why PH20

polypeptides, whether they are active or inactive, would be expected by POSAs to be functional as contraceptives. EX2074, ¶¶44, 45.

To assist in contraception, a modified PH20 is introduced into a female to induce an immune response, resulting in the production of polyclonal antibodies that bind to wildtype PH20 present in the reproductive tract following sperm deposition. EX2072, ¶¶29-36, 43; EX2074, ¶¶42-45. As Dr. Moon explains, polyclonal antibodies raised against modified PH20 polypeptides with ≥95% identity to SEQ ID NOs: 3 or 32–66 would have been expected to bind wildtype PH20 *in vivo* in both humans and non-human mammals. EX2074, ¶¶33-57; *see also* EX2072, ¶¶12, 31.

Further, because polyclonal antibodies recognize multiple epitopes, POSAs would have expected that even if the claimed modified PH20 had some epitopes that were not present in wildtype PH20, other epitopes would likely be conserved between modified PH20 and wild-type PH20, ensuring that the polyclonal antibodies would bind to wild-type PH20 and block fertilization. EX2074, ¶¶21-23, 41-57; EX2072, ¶¶31-34. Further, because epitopes can be linear in form, a POSA would have expected that conformational changes in the modified PH20 (even if the polypeptide were to be denatured) would not abrogate the ability of polyclonal antibodies to recognize epitopes on wild-type PH20. EX2074, ¶¶23, 45, 57.

Further, a POSA would have understood there were additional routine

methods of enhancing the contraceptive effect, including, for example, mucosal adjuvants and booster doses administered after the initial vaccine dose that were known to be effective to further improve an antibody response against an antigen. EX2074, ¶¶29-31, 46, 58; EX2072, ¶¶38, 55. A POSA would have also considered delivering, in addition to the PH20 vaccine, an agent, such as sialidase, that exposes the surface PH20 polypeptide on sperm to the anti-PH20 antibodies generated in response to the PH20 vaccine. EX2072, ¶¶27, 28, 39, 41.

Third, both Dr. Cherr and Dr. Moon also explain that by 2012, POSAs would have expected that anti-PH20 monoclonal antibodies could be successfully delivered directly to the vaginal cavity of human females to target PH20 in the reproductive tract. EX2074, ¶¶60-63; EX2072, ¶¶57-61. POSAs would have known that local delivery formulations—such as gels, films, or intravaginal rings—were established methods for administering antibodies, and that binding of such antibodies to PH20 on sperm would be expected to prevent fertilization irrespective of where on PH20 the antibodies bound. EX2074, ¶61; EX2072 ¶¶40, 57.

Petitioner contends that PH20 had already been shown to be ineffective as a contraceptive. That is false. First, the relevant time period for considering a POSA's knowledge is as of December 12, 2012. Petitioner's references Rosengren 2015 (EX1061) and Rosengren 2018 (EX1024) are therefore not prior art, being published in 2015 and 2018, respectively. EX2072, ¶45. Moreover, these studies were not

focused on contraception, but the dispersion and spreading capability of PH20 to deliver fluids and drugs. EX2072, ¶45.

The purported prior art cited by Petitioner that are dated prior to December 2012 do not improve Petitioner's argument. Hardy 2004 (EX1019), Pomering 2002 (EX1020), and Baba 2002 (EX1021) are focused on mice and rabbit models and used routes of administration that were not ideal for delivering contraception because they generated low quantities of anti-PH20 antibody where they were needed, the female reproductive tract. EX2072, ¶¶47-52, 54-56. By contrast, POSAs would have expected mucosal administration to be more effective than subcutaneous or intraperitoneal routes, because it was known to elicit a stronger antibody response in the female reproductive tract. EX2072, ¶¶37, 49, 55; EX2074, ¶¶24-28, 46, 58.

Petitioner's own references still acknowledge that strong contraceptive effects were nevertheless observed in the guinea pig. EX2072, ¶47. As Dr. Cherr explains, POSAs would have understood that there are differences in the reproductive anatomy and biology between the guinea pig and other animals such as mice. EX2072, ¶¶51-53. For example, unlike in guinea pigs, female mice have a high tolerance to PH20 self-antigen and non-mucosal administration routes do not generate a sufficiently strong antibody response to PH20 polypeptide vaccines. EX2072¶51. As another example, the region where the PH20 in rabbit is found on a sperm makes low levels of antibody generated by subcutaneous vaccination

particularly ineffectual. EX2072, ¶52.

These observations further supports why POSAs would have chosen the mucosal route to administer PH20 polypeptides as contraception because the mucosal route would maximize the quantity of the anti-PH20 antibody in the reproductive tract. Therefore, Petitioner's references would not have led POSAs to doubt the utility of PH20 as a contraceptive vaccine antigen. EX2072, ¶¶44-56. The specification's explicit teachings, success of prior animal studies, and the general state of the art in reproductive immunology confirm that both claimed PH20 variants across the full scope of the genus had credible contraceptive vaccine utility.

Even if utility were not conclusively demonstrated (it was), Petitioner's enablement challenge based on its assertion that contraceptive vaccine use is "not scientifically credible" (Pet., 80) misapplies the law. Enablement does not require a guarantee of success or working examples; prophetic disclosures suffice if they allow POSAs to make and use the invention without undue experimentation. *Alcon Research Ltd. v. Barr Labs.*, Inc., 745 F.3d 1180, 1189 (Fed. Cir. 2014). Here, the specification provides explicit teachings, incorporates peer-reviewed studies never retracted or disavowed, and aligns with well-established immunological principles and know-how. POSAs would have understood that the claimed modified PH20 polypeptides could function as contraceptive vaccines.

Petitioner's case law does not alter this conclusion. *Atlas Powder* affirmed

enablement where the art taught basic principles POSAs could apply—here, the same is true with the specification's functional and immunological teachings. 750 F.2d 1569, 1576–77 (Fed. Cir. 1984). *Pharmaceutical Resources* involved inventor admissions that the field was highly unpredictable, which is not the case here. 253 F. App'x 26, 29–30 (Fed. Cir. 2007). *Rasmusson* found no disclosure or art suggesting that finasteride would treat prostate cancer, unlike here, where the specification cites and incorporates Primakoff 1988 and Tung 1997 directly demonstrating PH20's contraceptive vaccine utility. 413 F.3d 1318, 1324 (Fed. Cir. 2005). And *In re Kirk* involved purely structural claims without a disclosed use, whereas the present specification expressly describes the immunological rationale for PH20 vaccines and incorporates studies showing their effectiveness. 376 F.2d 936, 941–42 (CCPA 1967). These authorities underscore, rather than undermine, that the challenged claims are fully enabled.

C. Inactive Mutants, Even If Lacking Utility, Are Merely Inoperative Embodiments a POSA Could Readily Identify

Petitioner argues that "the vast majority of 'inactive mutants' PH20 polypeptides would have no utility at all." Pet., 92. If true (it is not), those embodiments would simply be inoperative, and "[e]ven if some of the claimed combinations [are] inoperative, the claims are not necessarily invalid." *Atlas Powder*, 750 F.2d at 1576. The relevant question is whether undue experimentation would have been required to distinguish operative from inoperative variants. *Id.; see*

also Pharm. Resources, 253 F. App'x at 30.

As noted above, the specification, together with well-established tools in the art, provided the means to draw that distinction. As discussed in Section V-VI, the functional map disclosed in the patent, reinforced by extensive working examples, identifies PH20's critical residues, tolerant regions, and the consequences of specific substitutions. EX1001, 178:1-181:22, 231:42-234:13; EX2068, ¶¶287-335; EX2070, ¶¶248-262. With this disclosure, POSAs could apply routine sequence alignment and homology modeling software, both widely available by December 28, 2012, to predict whether a variant would be active or inactive, and then readily confirm that prediction using standard testing methods. EX2096, 268; EX2097, ¶¶[0666]-[0679]; EX2098, 39–40; EX2099, 262; EX2068, ¶¶311, 348, 350, 360; EX2070, ¶¶87-111, 343-52; As the Federal Circuit has held, "[e]nablement is not precluded by the necessity for some experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Because the map delineates intolerant regions, POSAs would have immediately recognized these inoperative embodiments as falling outside tolerated substitutions.

Accordingly, POSAs reading the specification in light of the general knowledge in the art would have been able to identify inactive versus active polypeptides without undue experimentation.

D. The Challenged Dependent Claims Are Enabled

Petitioner contests the enablement of the dependent claims only on the same grounds addressed above, and thus its challenge fails for the same reasons. 1. Pet., 77-79; EX2068, ¶¶393; EX2070, ¶¶343-88.

VII. THE CHALLENGED CLAIMS ARE NOT OBVIOUS (GROUND 3)

Petitioner contends (at Pet., 84-112) that the ’429 patent in view of Chao and the knowledge of a skilled artisan would have rendered the challenged claims obvious. In particular, Petitioner argues that POSAs would have been motivated “to design and produce the single-amino acid substituted PH20 covered by the claims” because the ’429 patent “teaches making a particular type of modification (a single amino acid substitution) at a particular location (non-essential region of PH20) in a particular PH20 sequence…to yield equivalents of PH20.” Pet., 88. In view of the ’429 patent, Chao and “familiarity with conventional rational protein design principles,” Petitioner asserts (at Pet., 85-86), POSAs would have been able to “identify D320K as one such amino acid substitution in [the non-essential region of] PH20 that would be expected to retain hyaluronidase activity.”

Petitioner reduces obviousness to nothing more than possibility: that among

thousands of conceivable substitutions across PH20, POSAs could have modified position 320 in light of Chao, the ’429 patent, and conventional rational protein design principles, and that alone, according to Petitioner, suffices to show the obviousness of the challenged claims.

On a preliminary record, the Board rejected Petitioner’s arguments. The Board found that neither the ’429 patent nor Chao “specifically identifies or discusses position 320 of the PH20,” and that Petitioner “did not point [] to anything in Dr. Hecht’s Declaration that explained why position 320 was of interest in any way, versus position 319 or 321 or any other position within the PH20 polypeptide.” ID., 58. The Board also rejected Petitioner’s reliance on multiple sequence alignments to show tolerance to substitution, explaining that “tolerance is not a positive reason to make a substitution” at D320. *Id*. The Board concluded that Petitioner “has not satisfied [its] burden of showing specific reasons to modify position 320 of the PH20 polypeptide,” and therefore the challenged claims were not shown to be obvious. *Id.*, 60.

The record developed since institution only reinforces that conclusion. It shows not only that the prior art provided no reason to modify position 320, but also that Petitioner’s experts focused on that residue only at the direction of Petitioner’s counsel, underscoring the hindsight nature of Petitioner’s obviousness theory. In his declaration, Petitioner’s expert Dr. Park, for example, noted that he did not identify

position 320 through independent scientific reasoning, but instead "conducted [his] analysis in a matter that did not focus on any particular position," and was "asked by counsel to report [his] conclusions with respect to position 320." EX1004, ¶103. At deposition, Dr. Park further confirmed this understanding:

> **Q.** So why did you evaluate those substitutions?
>
> **A.** ***By that time, I had already completed all my analysis of all of positions, and provided a spreadsheet to counsel, who then asked me to elaborate on certain positions, including 320, 317, and so on***. And since I'm being asked to provide detailed description of the substitutions and evaluation at those positions, I went back and finished the analysis with all the substitutions that were available at those positions.

EX2078, 320:10–20.

Hecht confirmed as much at his own deposition:

> **Q.** So [Park] just, to the best of your knowledge, randomly picked examples and showed them to you and you discussed them on PyMOL -- with PyMOL?
>
> **A.** I think, in the overall initial project, [Park] went through all -- everything, right? Looked at it position by position by position and considered, you know, is this position evolutionarily conserved? Is this position, you know, whatever. And then ***after having done that, he was asked to focus upon and show me certain examples.***

EX2078, 87:1-11.

As set out further below, the prior art provides no disclosure or motivation to make the claimed D320K substitution, and the only alleged basis to fill that gap is counsel's instruction to Petitioner's experts. Such attorney direction cannot substitute for a teaching or motivation in the prior art, and the Board should affirm its decision that POSAs would not have found the challenged claims obvious.

A. Prior Art

1. The '429 Patent (EX 1005)

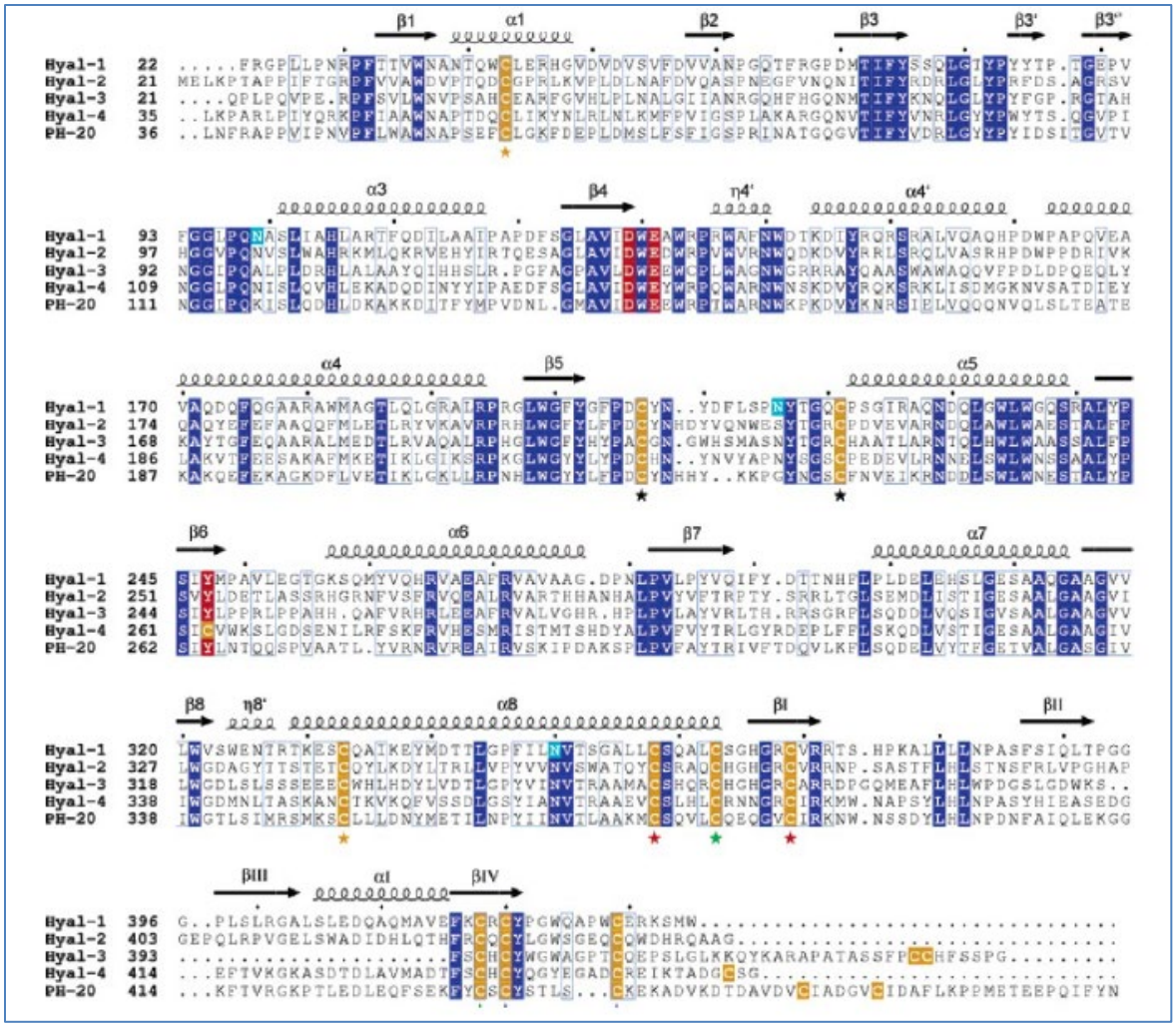
The '429 patent discloses "members of the soluble, neutral active Hyaluronidase Glycoprotein family, particularly the human soluble PH-20 Hyaluronidase Glycoproteins (also referred to herein as sHASEGPs)." *Id.* at 3:51–54. The '429 patent teaches that "PH20 is the prototypical neutral-active enzyme" that is " locked to the plasma membrane via a glycosylphosphatidyl inositol ["GPI"] anchor," unlike Hyal-1, which is "soluble" and the "prototypical acid-active enzyme." EX1005, 2:33-60. The '429 patent also teaches that "[a]ttempts to make human PH20" without the GPI anchor "resulted in either a catalytically inactive enzyme, or an insoluble enzyme." *Id.*

The '429 patent teaches how to make soluble, neutral active PH20 without the GPI anchor. *Id.*, 3:51-62. Specifically, the '429 patent "invention is based upon the discovery that a soluble, neutral-active hyaluronidase activity can be produced with high yield in a mammalian expression system by introducing nucleic acids that lack

a narrow region encoding amino acids in the carboxy terminus of the human PH20 cDNA." *Id*. The '429 patent states: "single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity." *Id.* at 9:46-52. The '429 patent claims a specific truncated version of PH20 composed of positions 36–482 of SEQ ID NO: 1. *See id*. at 153:39.

2. Chao (EX 1006)

Chao reports the crystal structure of human hyaluronidase-1 ("hHyal-1"), a lysosomal enzyme "responsible for the hydrolysis of intracellular HA." EX 1006, 6911-14. Chao explains that "[t]here are five homologous hyaluronidases encoded in the human genome: hHyal-1 through -4 and the sperm adhesion molecule 1 (termed PH-20)" and that "[w]ith the exception of hHyal-1, the expressed hyaluronidases contain glycosylphosphatidylinositol-signal sequences and are membrane-bound upon maturation." *Id.* Chao also observes that "[h]uman hyaluronidases exhibit 33–42% sequence identities and even higher conservation of active site residues. Yet, the enzymes differ in their catalytic efficiencies and pH profiles." *Id.* Figure 3 of Chao, reproduced below, illustrates conserved versus nonconserved residues across the human hyaluronidases.



B. POSAs Would Have Had No Motivation to Introduce Substitutions at Position 320

Based on the teachings of Chao and the ’429 patent, POSAs would not have had a reason to introduce substitutions at position 320. EX2068, 405-416.

As an initial matter, neither Chao nor the ’429 patent discloses “an amino acid modification at a position corresponding to position 320” as required by the challenged claims. EX1001, Claim 1; EX1005–EX1006; EX2068, ¶404. Nor do they disclose replacing D320 with an amino acid “selected from among H, K, R and S.”

EX1001, Claim 1; EX1005; EX1006; EX2068 ¶404.

For example, Petitioner contends (at Pet., 89) that Chao provides "new insights" in PH20 that informs the selection of position 320. Chao, however, reports the crystal structure of human hyaluronidase-1 ("hHyal-1") and (i) identifies conserved residues, including key catalytic residues shared among various hyaluronidases and (ii) predicts secondary structures across the human hyaluronidases. Pet., 89–91; EX1006, 6912, 6916–17; EX2068 ¶400-404. None of these alleged "insights" provides a reason to modify position 320 in PH20. EX2068 ¶405-416.

The '429 patent teaches how to make soluble, active C-terminal truncated PH20s. EX2068, ¶399. It describes the minimum PH20 sequence needed for activity. EX2068, ¶408. But it nowhere identifies position 320 or suggests substituting D320 with H, K, R, or S. EX2068, ¶¶395, 404.

Additionally, Petitioner relies on the '429 patent's statement that POSAs would "recognize that, in general, single amino acid substitutions in non-essential regions of polypeptide do not substantially alter biological activity" to argue that POSAs would have been motivated to modify PH20, use sequence alignments and Chao's structural information on HYAL1 to identify "non-essential" regions, and select D320 for substitution with lysine (K).

That is incorrect. First, the '429 patent does not identify any region or residue

of PH20 as "non-essential," nor provide any guidance on which sites to modify. EX1005. Chao likewise does not use the term "non-essential" or designate residues in this way. EX1006, 6916, FIG. 3; EX2068, ¶¶406-07. Nothing in Chao or the '429 patent supports treating D320 as "non-essential" or as a target for substitution. EX2068, ¶¶406-10.

And Petitioner's expert Dr. Park's analysis confirms that nothing in the art would have motivated POSAs to modify position 320. Dr. Park was tasked with "identifying non-essential positions in PH20" and "evaluat[ing] various substitutions at those positions to see if there are substitutions…that would be tolerated." EX2078, 67:22-68:7. To perform that task Dr. Park generated an alignment of 88 hyaluronidase sequences, identified residues conserved more than 95% of the time, and termed those 68 residues "essential." EX1004 ¶¶26–29, 31–32, 44; EX2078, 267:13-20. Dr. Park concluded the other ***379*** residues were "non-essential" and identified potential substitutions at those positions using his alignment. In total, Dr. Park identified over ***2800 potential substitutions*** in so-called "non-essential" positions, and he evaluated ***approximately 830*** of them to determine whether they would have been tolerated. EX2078, 268:15-269:4, 280:3-7, 282:19-283:18, 299:3-14. Of those 830 substitutions, Dr. Park concluded that over 90% would have been tolerated.

Thus, even in the narrow slice of data he examined, Dr. Park's analysis

produced hundreds of what he expected would be tolerated substitutions, with thousands more left unevaluated. EX2078, 280:3-283:3; Spreadsheet. POSAs would have seen not a single promising target, but an overwhelming number of possible options scattered across the protein. EX2068, ¶¶404-16. 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. EX2068, ¶¶404-16. ***Dr. Park only focused on changes at position 320 because counsel asked to him to do so.***

Furthermore, the teaching in the '429 patent on which Petitioner so heavily relies—that "single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity"—would not have motivated POSAs to make any substitutions in PH20. The '429 patent simply informs POSAs that modifications can be made to the disclosed truncated PH20 without substantially altering activity. Petitioner has not provided any reason why POSAs, who has in hand a working enzyme, would tinker with that enzyme with the sole purpose of maintaining the same activity profile. The '429 patent disclosure certainly would not have motivated POSAs to undertake Dr. Park's exercise of evaluating over 800 potential substitutions. EX2068, ¶415. None of the prior art offered any reason to pursue a substitution at D320, and Petitioner identifies none, except with the benefit of hindsight. *Kingston Tech. Co., Inc. v. North Star*

Innovations, Inc., IPR2018-01784, Paper 32, 55 (P.T.A.B. Feb. 26, 2020) (rejecting petitioner's obviousness arguments for "*rest[ing] on hindsight*" and "us[ing] the challenged patent as a *roadmap to reconstruct the claimed invention*."); *Intel Corp. v. VLSI Tech. LLC*, IPR2018-01033, Paper 32, 88-89 (P.T.A.B. Feb. 6, 2020) (similar); EX2068, ¶¶396-418.

C. POSAs Would Have Had No Motivation to Replace Aspartic Acid (D) with Lysine (K) at Position 320

Even if position 320 were somehow selected (it would not be), there is no reason POSAs would have substituted aspartic acid (D) with lysine (K). EX2068, ¶¶417-18. Neither Chao nor the '429 patent suggests replacing D320 with lysine. *Id.* Such a change is nonconservative, and POSAs examining the residue's environment would recognize that D320 lies within an alpha-helix, a defined secondary structure that would not attract the attention of a POSA as a candidate for modification. *Id.* POSAs would have had no reason to target this position at all, much less to replace a negatively charged amino acid in an alpha-helix with a positively charged one. *Id.*

In sum, Petitioner recasts obviousness as the question of to whether POSAs could have modified position 320 in view of Chao, the '429 patent, and rational protein design principles. But Petitioner bears the "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)). And "obviousness concerns whether a skilled artisan not only ***could have made*** but ***would have been motivated to make*** the combinations or modifications of prior art to arrive at the claimed invention." *Belden Inc. v. Berk–Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015); *Personal Web Technologies, LLC v. Apple, Inc.*, 848 F.3d 987, 993 (Fed. Cir. 2017); *AT&T Services v. Innovative Sonic*, IPR2024-01143, Paper 15 at 37-38 (P.T.A.B. Feb. 11, 2025).

As the Board noted in its Decision, "[n]othing in the prior art or Dr. Park's analysis *directs the ordinary artisan to position 320 itself*…." ID, 59. POSAs would not have been motivated to mutate D320 to lysine and would not have found the challenged claims obvious.

VIII. CONCLUSION

Petitioner fails to meet its burden of persuasion in this proceeding. The Board should reject the Petition and find all of the challenged claims not unpatentable.

Respectfully submitted,

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CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

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