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Paper 25
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

HALOZYME, INC.,
Patent Owner.

PGR2025-00003
Patent 11,952,600 B2

Before JEFFREY N. FREDMAN, SUSAN L. C. MITCHELL, and CYNTHIA M. HARDMAN, *Administrative Patent Judges.*

FREDMAN, *Administrative Patent Judge*.

DECISION
Granting Institution of Post-Grant Review
35 U.S.C. § 324

Halozyme EX2032
Merck v. Halozyme
IPR2026-00314

I. INTRODUCTION

Merck Sharp & Dohme LLC ("Petitioner") filed a Petition (Paper 1, "Pet.") requesting post-grant review of claims 1–21 (the "challenged claims") of U.S. Patent No. 11,952,600 B2 (Ex. 1001, "the '600 patent"). Halozyme, Inc. ("Patent Owner") filed a Preliminary Response. Paper 12 ("Prelim. Resp."). Patent Owner filed a statutory disclaimer of claims 5–7 of the '600 patent, leaving claims 1–4 and 8–21 of the '600 patent in effect. Ex. 2003. In response, Petitioner requested authorization to file a brief in reply, and Patent Owner a brief in sur-reply, which we granted. Paper 16 ("Reply"); Paper 17 ("Sur-Reply").

We have authority to determine whether to institute a post-grant review under 35 U.S.C. § 324. Institution of a post-grant review is authorized by statute when "the information presented in the petition . . . would demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable." 35 U.S.C. § 324(a). Applying that standard on behalf of the Director (37 C.F.R. § 42.4(a)) and in consideration of the Petition, Preliminary Response, Reply, Sur-Reply, and the evidence of record, we determine that the information presented shows that it is more likely than not that Petitioner would prevail in establishing unpatentability of claims 1–4 and 8–21 of the '600 patent.

This decision to institute trial is not a final decision as to patentability of claims for which post-grant review is instituted. Our final decision will be based on the full record developed during trial.

II. REAL PARTIES-IN-INTEREST

Petitioner identifies Merck Sharp & Dohme LLC as the real party-in-interest. Pet. 6. Patent Owner identifies Halozyme, Inc. and Halozyme Therapeutics, Inc. as the real parties-in-interest. Paper 4, 1.

III. RELATED PROCEEDINGS

Petitioner states, regarding related matters, "[t]here are no related proceedings to this Petition." Pet. 6. Patent Owner states that the '600 patent is related to a number of pending U.S. Patent Applications and patents subject to post-grant review proceedings including U.S. Patent 12,018,298 B2 (PGR2025-00004) (Paper 4, 1); U.S. Patent 12,152,262 (PGR2025-00006) (Paper 6, 1); U.S. Patent 12,123,035 (PGR2025-00009) (Paper 7, 1); U.S. Patent 12,110,520 (PGR2025-00017) (Paper 8, 1); U.S. Patent 12,060,590 (PGR2025-00024) (Paper 11, 1);U.S. Patent 12,054,758 (PGR2025-00030) (Paper 10, 1); U.S. Patent 12,049,652 (PGR2025-00033) (Paper 14, 1); U.S. Patent 12,104,185 (PGR2025-00039) (Paper 18, 1); U.S. Patent 12,037,618 (PGR2025-00042) (Paper 20, 1) and U.S. Patent 12,091,692 (PGR2025-00046) (Paper 22, 1).

IV. THE '600 PATENT

A. Background

The '600 patent issued April 9, 2024, from U.S. Application 18/338,189, filed June 20, 2023. Ex. 1001, codes (45), (21), (22). The '600 patent is a divisional application of U.S. Application 17,327,568, filed May 21, 2021 which is a continuation in a lengthy set of applications claiming continuity to U.S. Application 13/694,731, filed Dec. 28, 2012, which claims the priority benefit of provisional applications U.S. 61/796,208, filed

November 1, 2012 and U.S. 61/631,313, filed Dec. 30, 2011. *Id.* at codes (63), (60).

The '600 patent is drawn to "[m]odified PH20 hyaluronidase polypeptides, including modified polypeptides that exhibit increased stability and/or increased activity." Ex. 1001, 4:16–18. The '600 patent teaches "[h]yaluronan (hyaluronic acid; HA) is a polypeptide that is found in the extracellular matrix of many cells, especially in soft connective tissues." *Id.* at 4:23–25. The '600 patent teaches "[c]ertain diseases are associated with expression and/or production of hyaluronan. Hyaluronan-degrading enzymes, such as hyaluronidases, are enzymes that degrade hyaluronan. By catalyzing HA degradation, hyaluronan-degrading enzymes (e.g., hyaluronidases) can be used to treat diseases or disorders associated with accumulation of HA or other glycosaminoglycans." *Id.* at 4:30–36. The '600 patent teaches that "[v]arious hyaluronidases have been used therapeutically . . . . Many of these are ovine or bovine forms, which can be immunogenic for treatment of humans." *Id.* at 4:41–47.

With regard to modified PH20 hyaluronidase polypeptides, the '600 patent teaches:

> Single amino acid abbreviations for amino acid residues are well known to a skilled artisan . . . and are used herein throughout the description and examples. For example, replacement with P at a position corresponding to position 204 in a PH20 polypeptide with reference to amino acid residue positions set forth in SEQ ID NO:3 means that the replacement encompasses F204P in a PH20 polypeptide set forth in SEQ ID NO:3.

Id. at 5:6–13. The '600 patent teaches "modified PH20 polypeptides provided herein exhibit altered activities or properties compared to a wildtype, native or reference PH20 polypeptide." *Id.* at 75:45–47.

B. Post-Grant Review Eligibility

As a threshold issue, we must determine whether the '600 patent is eligible for post-grant review. There are two requirements that must be met for post-grant review to be available. First, post-grant review is only available if the petition is filed within nine months of the issuance of the challenged patent. 35 U.S.C. § 321(c). Petitioner certifies that the petition was filed on November 12, 2024, which is within nine months of the '600 patent's April 9, 2024, issue date. Pet. 4; Ex. 1001, code (45).

Second, post-grant review is available only for patents that issue from applications that at one point contained at least one claim with an effective filing date of March 16, 2013, or later. *See* Pub. L. No. 112-29, §§ 3(n)(1), 6(f)(2)(A). Here, the priority dates recited for the '600 patent include three filings prior to March 16, 2013. These prior filings include U.S. Application 13/694,731 (the "'731 application"), filed December 28, 2012, U.S. provisional application 61/796,208, filed Nov. 1, 2012, and U.S. provisional application 61/631,313, filed December 30, 2011.

Petitioner asserts the "disclosure of the '731 Application (including subject matter incorporated by reference) does not provide written description support for and does not enable any claim of the '600 Patent." Pet. 6.

Patent Owner asserts that Petitioner "failed to establish that the '600 patent is PGR-eligible." Prelim. Resp. 1. Patent Owner asserts "rather than assess the '731 application as of its *2012* filing date, Merck's analysis consistently *and only* applied a *2011* date, while fatally ignoring the '731 Application's *December 28, 2012* filing date." *Id.* at 11.

Because the analysis of priority and PGR-eligibility in this Institution Decision will rely on substantially the same facts and law as analysis of the Written Description Ground, we will address these issues together below where we determine that the '600 patent is eligible for post-grant review.

V. ILLUSTRATIVE CLAIMS

Claim 1 is illustrative of the challenged claims in the '600 patent, and is reproduced below.

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

Ex. 1001, 309:2–17.

VI. ASSERTED GROUNDS

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

Ground	Reference(s)/Basis	35 U.S.C. §	Claim(s) Challenged
1	Written Description	§ 112	1–4, 8–21
2	Enablement	§ 112	1–4, 8–21
3	The '429 patent,[1] Chao[2]	§ 103	1–4, 8–21

Petitioner also relies on the Declarations of Michael Hecht, Ph.D. and Sheldon Park, Ph.D. Exs. 1003, 1004. Patent Owner relies on the Declaration of Barbara Triggs-Raine, Ph.D. Ex. 2001.

VII. LEVEL OF ORDINARY SKILL IN THE ART

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

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

Pet. 16.

[1] US 7,767,429 B2, issued Aug. 3, 2010 (the "'429 patent").

[2] Chao et al., *Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis*, 46 Biochemistry 6911–20 (2007) (Ex. 1006).

Patent Owner contends that this definition is incomplete "[b]ecause the patent relates to modified PH20 polypeptides and the prior art Merck cites (e.g., the '429 Patent and Chao) relates to hyaluronidases, a POSA or a member of a multi-disciplinary team that includes the POSA would have *at least two years of practical experience with hyaluronidases*." Prelim. Resp. 11. Patent Owner contends the "practical experience with hyaluronidases must come from either the POSA's own experience or through collaborations with a member of a multidisciplinary team having experience studying and characterizing hyaluronidases." *Id.* at 12.

Patent Owner's contentions are, at this stage, unavailing because Patent Owner's proffered definition of a POSA is too restrictive. Petitioner's proposal is sufficiently comprehensive to encompass the prior art relevant to the '600 patent. It is reasonably clear that, in indicating that a POSA would have an advanced degree (like a Ph.D.) and years of experience in analysis of protein structure, Petitioner is asserting that knowledge of proteins generally is sufficient to understand the types of problems encountered in the art and the prior art solutions to those problems, and the ordinary artisan need not be an expert in hyaluronidases. *See* Pet. 16. Petitioner requires that the POSA would be able to apply key scientific concepts (e.g., biochemistry, recombinant biology, sequence analysis and protein modeling) to enzymes such as hyaluronidases.

Moreover, although Patent Owner faults Petitioner's POSA definition as lacking expertise in hyaluronidases, Patent Owner's POSA definition is unpersuasive as it requires hyaluronidase expertise, but fails to persuasively explain why Petitioner's definition that includes a person with expertise in other enzymes is insufficient. Patent Owner's assertion that Petitioner's

alignment of hyaluronidase amino acid sequences is inadequate because of different enzymatic activities is belied by Patent Owner's repeated argument that Claim 1 "does not require the 'modified PH20 polypeptide' to exhibit hyaluronidase activity and is purely structural." Prelim. Resp. 18 (internal footnote omitted). If hyaluronidase enzymatic activity is not relevant to the claimed invention, then it need not be a core competency of the POSA. Even if we were to apply Patent Owner's POSA definition, it is not clear on the record before us that Petitioner's experts lack relevant expertise or qualifications of at least a POSA.

Patent Owner will have the chance to cross-examine Dr. Hecht and Dr. Park in this proceeding to develop a full record for us to determine the weight that each expert's testimony should be given. Patent Owner will have further opportunity on a full record to assert that we should discount either experts' testimony due to lack of qualifications.

At this stage of the proceeding and on the record before us now, we apply Petitioner's proposed POSA level, which appears consistent with the level of skill shown in the prior art references of record. *See Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007).

VIII. CLAIM CONSTRUCTION

In a post-grant review, we interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.200(b). Under this standard, we construe the claim "in accordance with the ordinary and customary

meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*

A. Petitioner's Position

Petitioner asserts the "terms used in the claims are either expressly defined in the specification of the common disclosure[3] or are used with their common and ordinary meaning. Consequently, no term requires an express construction to assess the grounds in this Petition," in addition to those expressly defined in the specification. Pet. 17. Petitioner asserts "the specification describes two mutually exclusive categories of 'modified PH20 polypeptides' (*i.e.*, 'active mutants' vs. 'inactive mutants') but the claims are limited to one of them: 'active mutants.'" *Id.* at 22. Petitioner asserts the claims are limited to "active mutants" for three reasons:

> First, every claim requires each modified PH20 polypeptide in its scope to have one of four replacements at position 320 that yielded an "active mutant" as a single-replacement $PH20_{1-447}$ polypeptide (*i.e.*, D320H, D320K, D320R, or D320S). These mutants are listed in Table 3 and reported as having >40% activity in Table 9.
>
> Second, claims 5 and 6 restrict the genus of active mutants in claim 1 (*i.e.* those with at least 40% activity) to active mutant modified PH20 polypeptides that have at least 100% or 120% of the activity of unmodified PH20, respectively.
>
> Third, the specification defines a "modified PH20 polypeptide" as "a PH20 polypeptide that contains at least one modification," but can also "have up to 150 changes, so long as the resulting modified PH20 polypeptide ***exhibits hyaluronidase activity***."

[3] Petitioner uses the term "common disclosure" to refer to the Specifications of both the '600 patent and all of its parent applications including the earliest non-provisional filing of U.S. application 13/694,731, filed on December 28, 2012. *See* Pet. 1.

Id. at 25–26 (footnotes omitted). Petitioner asserts that even if the claims include inactive mutants, "every claim still necessarily includes (and thus must describe and enable) the full subgenus of 'active mutants' defined by claims 5 and 6." *Id.* at 26; *cf. id.* at 80 ("[T]he common disclosure provides no guidance about which epitopes on the PH20 protein must be preserved in an 'inactive mutant.'").

B. Patent Owner's Position

Patent Owner asserts that the term "modified PH20 polypeptide" is implicitly defined by Petitioner who "relies on a requirement for hyaluronidase activity, but [Petitioner] failed to provide any reasoned basis for such an assertion." Prelim. Resp. 15–16. Patent Owner asserts that "modified PH20 polypeptide" is defined in the Specification "as 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." *Id.* at 16; *cf. id.* at 17 (citing Ex. 1001, 48:38–43; Ex. 2001 ¶ 67). Patent Owner asserts that based on the definition "a POSA would have understood that 'modified PH20 polypeptide' is solely defined by its structure, i.e., its sequence of amino acids, and not by function." *Id.* at 17 (citing Ex. 2001 ¶ 68).

Patent Owner also points out that the '600 patent discloses "*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* or exhibit low or diminished hyaluronidase activity." *Id.* at 20 (citing Ex. 1001, 119:13–20, 257:24–27, 75:47–49,

75:56–58, 119:30–120:27, 120:36–43, 195:3–6, 257:23–258:37, Tables 5 and 10; Ex. 2001 ¶¶ 75–76).

Patent Owner asserts that Petitioner's alleged "attempt to discredit the utility of 'inactive mutants' to justify importing a hyaluronidase activity limitation into the claims is improper: claims must be read 'in light of the specification,' not in spite of the specification." *Id.* at 26. Patent Owner asserts that

> the specification merely states that modifications *can be made to* create active "modified PH20 polypeptides;" it does not state that all claimed "modified PH20 polypeptides" must exhibit hyaluronidase activity. The identified statements—divorced from the express definition of "modified PH20 polypeptide" and uses of the term elsewhere—do not indicate that Patent Owner "clearly express[ed] an intent to redefine" "modified PH20 polypeptide" to require enzymatic activity.

Id. (citing Ex. 1001, 119:13–20, 257:24–27; Ex. 2001 ¶ 87).

Patent Owner contends Petitioner "wrongly argues that the claims are limited to 'active mutants' because they require each 'modified PH20 polypeptide' to have one of four replacements at position 320 that yielded an 'active mutant.'" *Id.* at 27 (citing Pet. 25; Ex. 1003 ¶¶ 126–128; Ex. 2001 ¶¶ 86, 89). Patent Owner argues that the doctrine of claim differentiation applies because claims 9 and 10 require glycosylation "which the patent states is critical for hyaluronidase activity," and therefore imply that the mutants in claim 1 need not be glycosylated or active. *Id.* (citing Pet. 13; Ex. 2001 ¶¶ 72, 86; Ex. 1001, 70:57–71:1; Ex. 1003 ¶ 197).

C. Analysis

We find that on the present record, the evidence supports a broad definition of "modified PH20 polypeptide" that includes active molecules.

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

Southwall Tech., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1578 (Fed. Cir. 1995). "[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005).

Here, the '600 patent defines "PH20" as a type of hyaluronidase enzyme and "includes those of any origin including, but not limited to, human, chimpanzee, Cynomolgus monkey, Rhesus monkey, murine, bovine, ovine, guinea pig, rabbit and rat origin." Ex. 1001, 45:60–62. The '600 patent further explains that "[r]eference to PH20 includes precursor PH20 polypeptides and mature PH20 polypeptides (such as those in which a signal sequence has been removed), truncated forms thereof that have activity, and includes allelic variants and species variants, variants encoded by splice variants, and other variants." *Id.* at 46:6–11. The '600 patent states that "PH20 polypeptides also include those that contain chemical or posttranslational modifications and those that do not contain chemical or posttranslational modifications." *Id.* at 46:15–18. The '600 patent provides a specific definition of the term "modified PH20 polypeptide" which

> refers to a PH20 polypeptide that contains at least one amino acid modification, such as at least one amino acid replacement as described herein, in its sequence of amino acids compared to a reference unmodified PH20 polypeptide. A modified PH20 polypeptide can have up to 150 amino acid replacements, so long as the resulting modified PH20 polypeptide ***exhibits***

> ***hyaluronidase activity***. Typically, a modified PH20 polypeptide contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 amino acid replacements. It is understood that a modified PH20 polypeptide also can include any one or more other modifications, in addition to at least one amino acid replacement as described herein.

Id. at 48:38–53 (emphasis added).

Based on this express definition, the current record does not support the interpretation of Dr. Triggs-Raine that the "term 'modified PH20 polypeptide,' therefore, has a purely structural meaning in the context of the specification." Ex. 2001 ¶ 68.[4] Indeed, when reproducing the definition from this column of the '600 patent, Dr. Triggs-Raine does not include any text after the first period, but the '600 patent text continues to detail specific elements required including a requirement that replacements in the PH20 polypeptide are permitted "so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity." Ex. 1001, 48:44–46. On this

[4] Indeed, *Kirk* taught regarding a purely structural claim without a disclosed use that:

> We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound *in terms of possible use so general as to be meaningless* and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.

In re Kirk, 376 F.2d 936, 942 (CCPA 1967).

record, Dr. Triggs-Raine does not address this statement. And Dr. Triggs-Raines states "the modified PH20 polypeptides have multiple credible uses, including 'therapeutic uses of modified PH20 polypeptides that have the ability to degrade hyaluronan.'" Ex. 2001 ¶ 115.[5] That is, Dr. Triggs-Raines recognizes hyaluronidase as the primary utility for the modified PH20 polypeptides recited in claim 1.

Thus, the evidence of record shows the '600 patent recognizes a broad understanding of a "modified PH20 polypeptide" as encompassing PH20 sequences from a variety of different mammalian species, with or without precursor or signal sequences, with or without post-translational modifications, and with up to 50 amino acid replacements.

The definition of "modified PH20 polypeptide" in the '600 patent even permits up to 150 amino acid replacements but ***only*** "so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity." Ex. 1001, 48:44–46. That is, the definition of "modified PH20 polypeptide" in the '600 patent expressly requires some hyaluronidase activity. And Patent Owner's disclaimer of claims 5 and 6 does not impact the claim differentiation argument. The record reflects that the original issuance of these claims indicates that the Examiner allowed claim 1 with the understanding that it encompassed modified PH20 polypeptides with hyaluronidase activity, and there is no limitation in claim 1 limiting the PH20 polypeptides to inactive polypeptides with no hyaluronidase activity.

[5] We recognize Dr. Triggs-Raines also cites "a credible use as contraceptives," but on this record, provides no evidence that a single modified PH20, as opposed to the naturally occurring PH20, functions as a contraceptive in any species. *See* Ex. 2001 ¶ 115.

See Ex. 1001, 309:2–17. On the current record, we therefore adopt the definition for "modified PH20 polypeptide" as recited in the '600 patent to encompass polypeptides with some hyaluronidase activity.[6]

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

Any final written decision entered in this case may include final claim constructions that differ from the preliminary understanding of the claims set forth above. Any final claim constructions will be based on the full trial record.

IX. 325(d) – DISCRETION TO DECLINE TO INSTITUTE

Petitioner asserts

> Chao and other references discussed herein were not cited to the Office, and the Examiner did not have the benefit of Dr. Park or Dr. Hecht's detailed expert testimony. Finally, the Examiner did not consider Petitioner's § 112 arguments regarding the lack of support for the immense genus of claimed modified PH20 polypeptides (or any substantially similar arguments) during

[6] As to Patent Owner's assertion that the term "modified PH20 polypeptide" encompasses enzymatically inactive polypeptides, we note the '600 patent imposes functional requirements on inactive polypeptides as well, stating that in addition to "[a]lso provided are modified PH20 polypeptides that are inactive, and that can be used, for example, as antigens in contraception vaccines." Ex. 1001, 75:56–58. We address this concept in the written description analysis.

> prosecution. Rather, the only § 112 rejection concerned whether two dependent claims to treatment of cancers were supported, which was mooted when the Applicant cancelled those claims.

Pet. 113.

Patent Owner urges us to decline to institute the asserted grounds under 35 U.S.C. § 325(d) because in

> rejecting claims 21 and 22, it is clear that the Examiner also considered written description for *all* of the then-pending claims. EX2001, ¶¶233–236. And those claims are the same as issued claims 1–21. EX1002, 678–680 (last response before allowance); EX2001, ¶236. The Board should not reconsider written description here.

Prelim. Resp. 83.

Patent Owner also asserts the "'429 Patent was cited to and considered by the Examiner, and it was discussed in the specification." *Id.* at 84 (citing Ex. 2001 ¶¶ 237–263; Ex. 1002, 641; Ex. 1001, 70:6–8, 71:44–45, 73:46, 74:14, 136:11, 181:64, 191:49, 195:26; Ex. 2001 ¶¶ 237–240). Patent Owner asserts that the "Examiner considered Stern (EX1008), Zhang (EX1010), and Arming (EX1011). Stern alone includes teachings substantially similar and cumulative to the relevant teachings in Chao. EX2001, ¶¶242–254. Zhang and Arming provide teachings that, considered in combination with Stern, further confirm the cumulative nature of Chao." *Id.* (citing Ex. 2001 ¶¶ 241–263). Patent Owner explains that Chao is cumulative to Stern because Stern "discloses a lysine (K) at residue 320 in Hyal-1, 2, and 4" and Stern "includes an alignment of five human hyaluronidases with bee venom hyaluronidase ('bvHyal'), which had 'an established 3D structure,' and secondary structures are identified in Stern's Figure 3." *Id.* at 86–87 (citing Ex. 2001 ¶¶ 249–254; Ex. 1008, 824, 826).

Patent Owner asserts Petitioner "does not allege any material error during prosecution. Pet., 113. Accordingly, the Board should deny institution of Grounds (a) [written description] and (c) [obviousness]." *Id.* at 90–91.

1. Principles of Law

Institution of post-grant review, like *inter partes* review, is discretionary. *Harmonic Inc. v. Avid Tech, Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (explaining that "the PTO is permitted, but never compelled, to institute an IPR proceeding"). The Patent Office may, for example, deny institution under 35 U.S.C. § 325(d), which provides, in pertinent part, that "[i]n determining whether to institute or order a proceeding under this chapter . . . the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office."

In evaluating whether the same or substantially the same prior art or arguments were previously presented to the Office, the Board has identified several non-exclusive factors for consideration. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) ("the *Becton, Dickinson* factors"). Those factors are as follows:

(a) the similarities and material differences between the asserted art and the prior art involved during examination;

(b) the cumulative nature of the asserted art and the prior art evaluated during examination;

(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;

> (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
>
> (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Id. (footnote omitted); *see also* Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019)[7] 62–63.

As explained in *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) ("*Advanced Bionics*") (precedential), we further apply the following two-step framework in determining whether discretionary denial under § 325(d) is appropriate:

> (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
>
> (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Becton, Dickinson Factors (a), (b), and (d) relate to the first step, and *Becton, Dickinson* Factors (c), (e), and (f) relate to the second step. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether the petitioner has demonstrated error. *Advanced Bionics*, at 8–10. "If the petitioner fails to show that the

[7] *Available at* https://www.uspto.gov/TrialPracticeGuideConsolidated.

Office erred, the Director may exercise [her] discretion not to institute *inter partes* review." *Id.* at 8–9 ("If a condition in the first part of the framework [i.e., substantially same art or arguments] is satisfied and the petitioner fails to make a showing of material error, the Director generally will exercise discretion not to institute *inter partes* review."). "At bottom, this [§ 325(d)] framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." *Id.* at 9. An "example of a material error" could be "misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Id.* at 8 n.9.

2. Analysis

Under the first step of the *Advanced Bionics* framework, we must determine whether the same or substantially the same prior art was previously presented to the Office. *Advanced Bionics*, at 8. Patent Owner asserts that the '429 Patent was cited to and considered by the Examiner and was also discussed in the '600 patent specification itself. Prelim. Resp. 84. Petitioner does not dispute that the '429 patent was made of record. Pet. 113.

Thus, the '429 patent was "previously presented to the Office." *See Advanced Bionics*, at 7–8 ("Previously presented art includes . . . art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS), in the prosecution history of the challenged patent"). Here, Patent Owner points to the '429 patent as included in an IDS received June 20, 2023, which included the '429 patent along with about 156 other US patents, about 24 foreign patent documents, and about 387 nonpatent literature documents.

We note that Petitioner's Grounds 1 and 2 do not rely on prior art or the '429 patent but, rather. address written description and enablement issues. Only Petitioner's Ground 3 relies on the '429 patent in combination with other prior art not presented to the Office.

In the Examiner's Non-Final Office action and Reasons for Allowance, the Examiner does not appear to rely on the '429 patent in any way, and Patent Owner does not identify any such reliance by the Examiner. *See* Ex. 1002, 422–441, 687–690. Nor does the Examiner rely on Stern, Zhang, or Arming identified by Patent Owner. *See id.*; *cf.* Prelim. Resp. 84. And while the Examiner does reject two methods of treatment of cancer claims as failing to comply with the written description requirement, the Examiner does not address the breadth of the claimed modified PH20 polypeptide itself, but rather focuses on the failure to describe the treatment of a sufficient number of different kinds of cancer. *See* Ex. 1002, 423–426.

In this situation, where the petition includes grounds with additional prior art that are not the same as or cumulative of previously presented prior art, we may determine that these combinations support a finding that the same or substantially the same prior art was not previously presented. *See, e.g.*, *Halliburton Energy Servs., Inc. v. U.S. Well Servs., LLC*, IPR2021-01036, Paper 12 at 19–20 (PTAB Jan. 19, 2022). Nevertheless, because the '429 patent that is part of the combination asserted for Ground 3 was previously presented to the Office, even if the sole evidence of record of consideration is a listing in an IDS, we proceed to the second step of the *Advanced Bionics* framework.

Under the second step of the *Advanced Bionics* framework, we must determine whether Petitioner has demonstrated Examiner error in a manner

material to the patentability of the challenged claims. *Advanced Bionics*, at 10. *Becton, Dickinson* Factors (c), (e), and (f) inform our analysis at this step. *Id.* at 8.

As to *Becton, Dickinson* Factor (c), "the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection," is significant to this analysis. *Compare Boragen, Inc. v. Syngenta Participations AG*, IPR2020-00124, Paper 16 at 7–8 (PTAB May 5, 2020) (denying institution under § 325(d) where the primary reference and a secondary reference in the petition were the basis for five obviousness rejections during the prosecution of the patent at issue), *with DraftKings Inc. v. Interactive Games LLC*, IPR2020-01107, Paper 10 at 16 (PTAB Jan. 6, 2021) (declining to deny institution under § 325(d) where the primary reference in the petition was not the basis of a rejection and disclosed the limitations upon which the Examiner relied to allow the patent).

Here, we note that Patent Owner does not identify any rejection based on the '429 patent, and there is no evidence of record that the Examiner meaningfully considered the relevant disclosures of the '429 patent. We find unpersuasive Patent Owner's reliance on the Examiner's issuance of an office action with a written description rejection over a different issue that also included some double patenting rejections.

As to *Becton, Dickinson* Factor (e), "whether Petitioner has pointed out sufficiently how the [E]xaminer erred in its evaluation of the asserted prior art," Petitioner provides persuasive evidence of Examiner error. *See* Pet. 36–39 (citing Ex. 1009, 21–27). We agree with Petitioner that the Examiner overlooked the written description requirement with regard to

claim 1. As discussed below, we find that, on the current record, the evidence sufficiently shows that it is more likely than not that the claims fail to comply with the written description requirement. *See* Section X. We, thus, find that the Examiner erred by either overlooking, or failing to appreciate, the factual underpinning necessary to support a written description for the breadth of an enormous genus claim such as claim 1 of the '600 patent.

Finally, as to *Becton, Dickinson Factor* (f), "the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments," Petitioner relies upon the Hecht and Park Declarations to support the analysis. *See* Ex. 1003; Ex. 1004. The addition of two expert Declarations in this case that support the grounds at issue significantly adds evidence that was unavailable to the Examiner, even assuming the Examiner meaningfully reviewed the '429 patent.

Considering *Becton, Dickinson* Factors (c), (e), and (f) together, we conclude that Petitioner sufficiently demonstrates Examiner error based on the grounds in its Petition, with support from expert testimony, which shows, in particular, that the Examiner overlooked, or did not appreciate, the written description and enablement requirements relating to the claims at issue.

3. Conclusion

For the reasons discussed above, we conclude that the Petition presents facts and evidence that, in this case, sufficiently demonstrate the Examiner erred in a manner material to the patentability of the challenged claims, and we therefore decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

X. GROUND I - WRITTEN DESCRIPTION

A. Principles of Law

In a post-grant review, as in an *inter partes* review, "the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

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

We analyze the asserted grounds of unpatentability in accordance with these principles to determine whether Petitioner has met its burden to establish that it would more likely than not prevail at trial.

B. Petitioner's Position

Petitioner asserts "the claim language defines enormous genera: between 10^{49} and 10^{65} distinct polypeptides. . . . Testing every polypeptide within the claims' scope in search of 'active mutants' is impossible—literally." Pet. 27 (citing Ex. 1003 ¶¶ 123, 189). Petitioner asserts:

> Most significantly, the use of a *maximum* sequence identity boundary with no condition or restrictions other than one required substitution means the claims capture mutants with 2

> substitutions, 3 substitutions and so on up to a number set by the boundary (*i.e.*, 17 for claim 3, 21 for claim 4, and 23 for claim 1). . . . Each claim -also encompasses substitutions being made in PH20 sequences that vary in length. Claim 1 does this explicitly, specifying 35 alternative sequences ranging from 430 to 465 residues.

Id. at 32–33 (citing Ex. 1003 ¶¶ 119–120).

Petitioner asserts the '600 patent "directs the skilled artisan to blindly make-and-test all such candidate mutants using trial-and-error experimentation." *Id.* at 34 (citing Ex. 1003 ¶ 193). Petitioner acknowledges that the '600 patent identifies six double mutations to avoid and indicates "the substitutions listed in Tables 5 and 10 should not be included in enzymatically active multiply-modified PH20 polypeptides," but Petitioner notes that "nothing in the claim language operates to exclude" these avoided or inactive combinations. *Id.* at 37 (citing Ex. 1003 ¶¶ 151, 161–162, 169).

Petitioner asserts that based on "the prior art and the common disclosure, a skilled artisan in 2011 would believe that C-terminal deletions yielding PH20 polypeptides that terminate before position 430 would be inactive" but asserts that the '600 patent "provides no examples of (and provides zero guidance concerning producing) enzymatically active PH20 mutants that terminate below position 447, thus ignoring the uncertainty existing in 2011 about PH20 truncation mutants that terminate between positions 419 to 433." *Id.* at 41 (citing Ex. 1003 ¶¶ 143, 159–165, 167–169).

Petitioner asserts that of 5,917 tested single amino acid changes, "~87% of the single-replacement $PH20_{1-447}$ polypeptides had ***less*** activity than unmodified $PH20_{1-447}$." *Id.* at 43 (citing Ex. 1003 ¶¶ 103–104). Petitioner asserts the data shows the unpredictability of mutation where "introducing different amino acids into a single position in $PH20_{1-447}$ resulted

in (i) increased activity, (ii) decreased activity or (iii) inactive mutants." *Id.* at 44 (citing '600 patent, Tables 3, 5, 9, 10). Petitioner asserts that

> multiple concurrent mutations can cause complex and unpredictable effects on a protein's structure and resulting function. The patent's empirical set of test results provides no insights of value to a skilled artisan attempting to identify which of the many possible mutants with different sets of 2-22 substitutions will be enzymatically active modified PH20 polypeptides.

Id. at 44–45 (internal footnote omitted) (citing Ex. 1003 ¶¶ 133, 140, 142, 143). Petitioner asserts the '600 patent does "not identify to the skilled artisan which multiple substitutions may improve stability. They provide no probative insight regarding multiply-modified PH20 polypeptides." *Id.* at 46 (internal footnote omitted) (citing Ex. 1003 ¶¶ 75–76).

Petitioner asserts that the '600 patent fails to "identify ***any*** actual multiply-modified PH20 polypeptides—it does not identify ***any*** sets of specific amino acid substitutions. They simply draw boundaries around a theoretical and immense genus of modified PH20 polypeptides." *Id.* at 49–50. Petitioner asserts that the '600 patent "outlines an 'iterative' make-and-test research plan for discovering modified PH20 polypeptides with multiple substitutions that might exhibit hyaluronidase activity" but that:

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

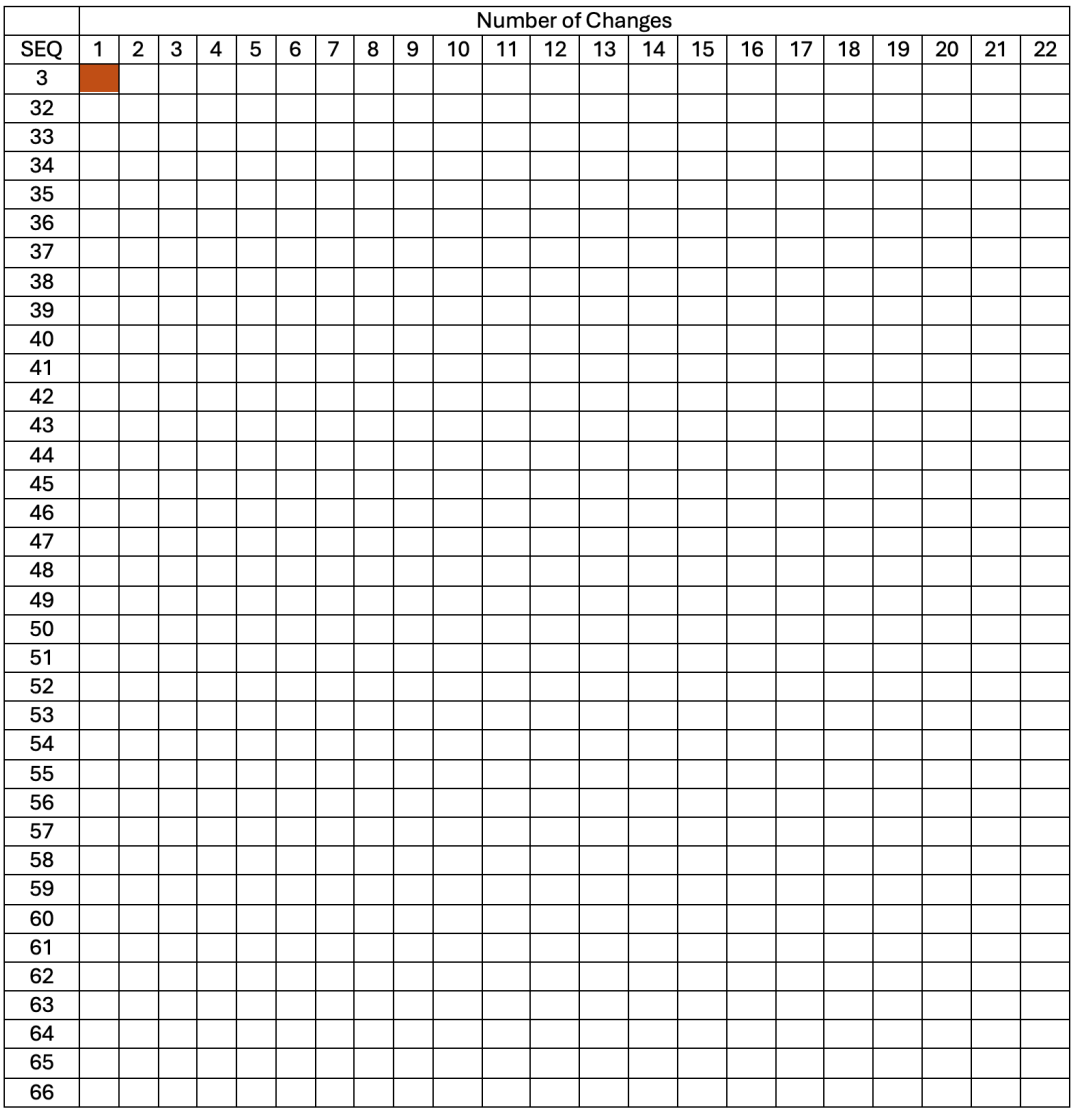
Id. at 50 (citing Ex. 1003 ¶¶ 187–190).

> Petitioner asserts the '600 patent does not identify
>
> the structural significance of any of the ~2,500 mutations that yielded single residue "active mutant" $PH20_{1-447}$ polypeptides (or the ~3,400 inactive mutants). For example, it does not identify the effect of any replacement on any domain structure, any structural motif(s) or even the local secondary structure at the site of the substitution in the PH20 polypeptide, nor does it identify how any such (possible) structural change(s) is/are responsible for the measured change in hyaluronidase activity.

Id. at 52–53 (citing Ex. 1003 ¶¶ 139–140, 151).

Petitioner asserts the "single-replacement $PH20_{1-447}$ examples are not representative of the trillions and trillions of $PH20_{1-447}$ polypeptides with between ***2 and 22 substitutions*** at any of hundreds of positions within the protein." *Id.* at 55 (citing Ex. 1003 ¶¶ 61, 143, 159). Petitioner asserts the "effects of those numerous substitutions on a protein's various secondary structures and structural motifs within the protein is not described in the common disclosure." *Id.* at 55–56 (citing Ex. 1003 ¶ 224).

Petitioner asserts that the figure below illustrates "how ***nonrepresentative*** the examples are: all of the Patents' examples of single-replacement $PH20_{1-447}$ mutants fit into a shaded red box of the array below:



The figure depicts a 22 x 36 array with a single shaded red box representing all of the tested single nucleotide mutations in SEQ ID NO: 3. Pet. 58–59.

Petitioner asserts that the other claims in the '600 patent lack written descriptive support for the same or similar reasons. *See id*. at 61–65.

C. Patent Owner's Position

Patent Owner asserts "[b]ecause Merck failed to identify any authority supporting its written-description challenge of *structural*, not functional,

claims, Merck's arguments fall short." Prelim. Resp. 30. Patent Owner asserts that

> the PTAB has found that a disclosure of structural features common to the genus is sufficient to establish written-description support for structural claims. For example, claims reciting an "isolated polynucleotide… at least 95% identical to the polynucleotide sequence of SEQ ID NO:2" were adequately supported by the specification because "*the complete structure of the polynucleotide of SEQ ID NO: 2 has been described*, and the genus [is] limited to [] polynucleotide[s] comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2." *Ex parte Bandman*, No. 2004-2319, Decision on Appeal at 4-5 (B.P.A.I. Jan. 6, 2005).

Id. at 33.

Patent Owner asserts "the recited structural features allow POSAs to visualize or recognize the identity of all members of the genus, because the members share "at least 95%" of the structure of disclosed amino acid sequences (SEQ ID Nos: 3 and 32-66) while limiting any amino acid sequence variation to 5%." *Id.* at 35 (citing Ex. 1001, claim 1; Ex. 2001 ¶¶ 90–92). Patent Owner asserts that a POSA "would have been able to visualize or recognize the identity of all members of the claimed genus of modified PH20 polypeptides manually or by using a computer and sequence-comparison software like CLUSTAL-Omega and BLAST, given the disclosed sequences." *Id.* at 36 (citing Ex. 1001, 59:25–61:5; Ex. 1039, 125; Ex. 2001 ¶¶ 96–98). Patent Owner asserts:

> The Petition makes no effort to explain why disclosures of single-modified PH20 polypeptides are not representative of multiply modified PH20 polypeptides when the claims do not require hyaluronidase activity. Merck focuses myopically on the alleged absence of "any multiply-modified PH20 polypeptides

> that are 'active mutants,'" but the claims do not require "active mutants."

Id. at 40 (citing Pet. 48–61; Ex. 2001 ¶¶ 113–114).

Patent Owner asserts Petitioner "is wrong regarding claim scope, because none of the six combinations[8] is encompassed by the claims. EX2001, ¶¶105–109. The disclosed combinations all require replacements at positions that do not include the claimed modification at position 320." *Id.* at 41 (citing Ex. 1001, 77:45–57, claim 1; Ex. 2001 ¶ 107).

Patent Owner asserts the "term 'modified PH20 polypeptide' in Claims 2–4 and 8–21 does not require hyaluronidase activity. These claims, too, are adequately supported by the specification for at least the same reasons identified for claim 1." *Id.* at 41 (citing Ex. 2001 ¶¶ 113–114).

D. Analysis

On the current record, we find the evidence taken as a whole better supports Petitioner's position.

"Every patent must describe an invention. It is part of the *quid pro quo* of a patent." *Ariad*, 598 F.3d at 1345. *Ariad* explains that for generic claims

> the question may still remain whether the specification, including original claim language, demonstrates that the

[8] The six combinations referred to here are as follows:

- 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.

Prelim. Resp. 40 (citing Pet. 60; Ex. 1001, 77:51–57).

> applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.

Id. at 1349. *Ariad* "explained that an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." *Id.* at 1350. *Ariad*

> also held that functional claim language can meet the written description requirement when the art has established a correlation between structure and function. . . . But merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species.

Id.

As we noted, on the current record claim 1 is reasonably interpreted to encompass PH20 polypeptides with some hyaluronidase activity. But even if we were to agree with Patent Owner that immunization using PH20 polypeptide as a contraceptive antigen serves to satisfy the utility requirement for the instant claims, there is a similar concern as to whether modified PH20 polypeptides with significant differences from the native protein as encompassed by claim 1 would maintain the antigenic determinants necessary to function as contraceptives. *See* Ex. 1003 ¶ 113.

While we agree with Patent Owner on the current record that the claims do not encompass the six species specifically excluded by the '600 patent, *see* Ex. 1001, 77:45–57, we are not persuaded by Dr. Triggs-Raine's statement that "the diversity of the claims is significantly limited to at least 95% sequence identity; therefore, a POSA would have understood that the claims encompass a very homogeneous group of modified PH20 polypeptides." Ex. 2001 ¶ 104.

That the modified PH20 polypeptides would be very homogenous in function is contradicted both by evidence in the '600 patent itself and by Dr. Hecht and Dr. Parker. The '600 patent discloses synthesis of 6753 single amino acid mutations in residues 1–447 of SEQ ID NO: 3. *See* Ex. 1001, 201:13–202:1. The '600 patent teaches that just under 10% of these mutations, i.e. over 600, "exhibit activity that is increased compared to wildtype." *Id.* at 234:46–47. Dr. Hecht, reviewing the '600 patent, states that "Table 10 contains a compilation of tested 'inactive mutants' with 3,380 entries in it." Ex. 1003 ¶ 103. While Dr. Hecht notes some inconsistencies in the data in the '600 patent, he stated that the '600 patent data showed that approximately "57.1% were inactive, and 29.4% had activity <100%." *Id.* ¶ 105.

Thus, the '600 patent evidences that even when only a single mutation is made in the PH20 polypeptide, that single mutation is more likely than not to alter the structure in such a way as to inactivate the hyaluronidase activity found in the native PH20 polypeptide.

On this record, Dr. Hecht persuasively demonstrates that when the full scope of claim 1 is addressed, which includes not just single mutations in the PH20 polypeptide but also multiple mutations, there is no expectation of

structural homogeneity, stating that "[i]ntroducing multiple amino acid changes simultaneously . . . could prevent the folding of sequences into secondary structures and structural motifs and can destabilize those structures if they do form." Ex. 1003 ¶ 59. Dr. Hecht notes that claim 1 allows "17-23 changes, with each change being to 1 of 19 other amino acids. But the 17-23 changes also can be at any of between 430 and 465 different positions depending on which unmodified PH20 sequence is used." *Id.* ¶ 120. Dr. Park calculates that "95% sequence identity to $PH20_{1-465}$ means that the protein can have 23 total changes," and that where one of those changes is one of four choices at position 320 as required by claim 1, the number of possible PH20 polypeptides with twenty-two additional changes is 1.35×10^{66}. *See* Ex. 1004 ¶¶ 170–171. Dr. Hecht characterizes the number of possible mutations as "astronomical in size." Ex. 1003 ¶ 125.

Dr. Park cites Zhang (Ex. 1010), which states "analysis of Hyal1 point mutants highlights the importance of specific conserved residues in catalytic function, but also identifies active site conformation as a critical factor. Disrupted activity resulted from the R265L mutation but not from N216A or global disulfide reduction." Ex. 1010, 9441. Dr. Park notes that Zhang found "a mutation at Asn350 in the 'c-terminal EGF-like domain' abolished hyaluronidase activity but one at Asn216 did not." Ex. 1004 ¶ 96; Ex. 1010. 9438–9439. Dr. Park also cites Ex. 1011 (Arming), which states:

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

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

Dr. Hecht also addressed the use of PH20 polypeptides as antigens for contraceptives, a use contemplated by the '600 patent. *See* Ex. 1001, 194:55–195:6; Ex. 1003 ¶ 109. Dr. Hecht stated "subsequent publications reported negative results in experiments attempting to induce contraceptive by immunizing mammals (rats, mice) with PH20." Ex. 1003 ¶ 110. Dr. Hecht cites to Rosengren (Ex. 1061), which states "several attempts were made to immunize males with PH20 as an immunocontraceptive approach in animal models. These studies involved rabbits, mice, and guinea pigs, and only the latter experienced infertility following PH20 immunization." Ex. 1003 ¶ 111; Ex. 1061, 1154 (internal citations omitted). This shows that even the native PH20 polypeptide does not necessarily function as a contraceptive, and a "skilled artisan could not predict from the ['600 patent] disclosures' limited discussion of contraceptive vaccines which, if any, mutated PH20 polypeptides would confer contraceptive effect in humans." Ex. 1003 ¶ 113. These 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.

Here, Patent Owner is asserting the '600 patent claims any sequence 95% identical to a PH20 polypeptide as an antigen that causes contraceptive activity, but the only evidence of contraceptive activity is for the native protein without any mutations. The evidence demonstrates that not all native

PH20 molecules necessarily function as contraceptives, much less mutated forms that might differ in structure and binding affinities as antigens. Rather, even for the single mutations tested, the '600 patent employed a trial and error approach for hyaluronidase activity and did no testing to determine if any of the mutations had contraceptive function. *See* Ex. 1001, 201:12–202:17; *see also In re Alonso*, 545 F.3d 1015, 1020 (Fed. Cir. 2008) ("We have previously held in a similar context that 'a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated.'" (quoting *Noelle v. Lederman*, 355 F.3d 1343, 1350 (Fed. Cir. 2004))).

On the current record, the evidence shows it is more likely than not that the claims of the '600 patent fail to satisfy the written description requirement because they "recite a description of the problem to be solved while claiming all solutions to it and . . . cover any compound later actually invented and determined to fall within the claim's functional boundaries—leaving it to the pharmaceutical industry to complete an unfinished invention." *Ariad*, 598 F.3d at 1353.

Accordingly, on the current record, we find that Petitioner has demonstrated that it is more likely than not that the '600 patent does not comply with the written description requirement. Similarly, the current record does not appear to provide evidence of possession of the full scope of the claims of the '600 patent in any of the applications in the extensive priority chain, which all have the same specification, including the provisional application 61/631,313, filed Dec. 30, 2011; provisional

application 61/796,208, filed Nov. 1, 2012, or non-provisional application 13/694,731 filed Dec. 28, 2012 for the reasons given above. Therefore, the '600 patent might not receive the benefit of priority to the earlier filed applications and based on this preliminary determination is eligible for post-grant review because the effective filing date is no earlier than the '600 patent's filing date of June 20, 2023. *See* Ex. 1001, code (22).

XI. GROUND II - ENABLEMENT

A. Principles of Law

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

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

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

B. Petitioner's Position

Petitioner asserts

> the common disclosure utterly fails to enable the immense genus of modified PH20 polypeptides claimed. Using that disclosure and knowledge in the prior art, the skilled artisan would have to

> perform undue experimentation to identify which of the 10^{49}+ PH20 polypeptides having multiple amino acid replacements and/or truncations are "active mutant" PH20 polypeptides within the scope of the claims.

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

Petitioner asserts the '600 patent "provides an extremely narrow set of working examples: ~5,916 randomly generated single-replacement $PH20_{1-447}$ polypeptides, of which ~2500 were 'active mutants.' Those examples are a tiny fraction of the 10^{49} to 10^{66} modified PH20 polypeptides covered by the claims." *Id.* at 70 (citing Ex. 1003 ¶ 103).

Petitioner asserts the "prospective research plan in the common disclosure demands that a skilled artisan engage in undue experimentation to practice the full scope of the claims. First, it requires manually performing iterative rounds of ***randomized*** mutations" and "provides no meaningful guidance in producing 'active mutant' modified PH20 polypeptides." *Id.* at 71–72 (citing Ex. 1003 ¶¶ 144, 158, 172, 184–185, 188–190). Petitioner asserts the "disclosure is indistinguishable from the '***iterative, trial-and-error process[es]***' that have consistently been found to not enable broad genus claims to modified proteins." *Id.* at 73 (citing *Idenix Pharm. LLC v. Gilead Sci. Inc.*, 941 F.3d 1149, 1161–63 (Fed. Cir. 2019)).

Petitioner asserts "the skilled artisan could ***not*** have predicted the effects of making more than a few concurrent amino acid replacements within a PH20 polypeptide in 2011-2012." *Id.* at 74 (citing Ex. 1003 ¶ 224). Petitioner asserts the "cumulative effects of multiple changes would also

have rapidly exceeded the capacity of computer-based, rational design protein engineering techniques to reliably predict the effects of each change on the protein's structure." *Id.* at 75 (citing Ex. 1003 ¶¶ 158, 224).

Petitioner asserts

> while a skilled artisan was highly skilled, the field of protein engineering was unpredictable and tools did not exist that permitted accurate modeling of multiply-changed PH20 polypeptides. Likewise, while there was significant knowledge in the public art about hyaluronidases, there was no solved structure of the PH20 protein, experimental reports generally reported on ***loss of activity*** from mutations, and did not predictably teach how to introduce changes that ***enhanced*** stability or activity.

Id. at 76–77 (citing Ex. 1003 ¶¶ 158, 224) (footnote omitted).

C. Patent Owner's Position

Patent Owner asserts Petitioner "again improperly imports a functional requirement (hyaluronidase activity) in an effort to align its arguments with the cited cases (*Amgen*, *Idenix*, *Wyeth*, and *Baxalta*). But all cited cases involved claims having functional, not structural, limitations." Prelim. Resp. 41–42 (citing Pet. 65–67).

Patent Owner asserts the "nature of the invention—modified PH20 polypeptides—weighs in favor of enablement, because making such polypeptides was well within the skill of a POSA in December 2012 given the guidance in the specification and the general knowledge in the art." *Id.* at 43 (citing Ex. 2001 ¶¶ 116–119). Patent Owner asserts "the guidance in the specification, the prior art, and the relative skill of a POSA each weigh in favor of enablement." *Id.* (citing Ex. 2001 ¶¶ 118–120).

Patent Owner asserts the "quantity of experimentation required also weighs in favor of enablement" and that Dr. "Triggs-Raine confirms that

making the claimed polypeptides in light of the specification's guidance would have involved only routine, not undue, experimentation and known, commonly used molecular biology and protein biochemistry techniques." *Id.* at 44 (citing Ex. 2001 ¶ 128). Patent Owner asserts "Hecht agrees that the methodology was conventional." *Id.* at 45 (citing Ex. 1003 ¶¶ 198–200; Ex. 2001 ¶¶ 124–126).

Patent Owner asserts the "specification discloses thousands of examples of modified PH20 polypeptides, weighing in favor of enablement" and "[b]ecause the claims are not limited to 'active mutants,' Merck failed to show that these examples do not provide practical guidance for making the claimed polypeptides." *Id.* at 46.

Patent Owner asserts "the breadth of the claims weighs in favor of enablement. The purely structural claims are not unreasonably broad because they recite at least 95% identity to sequences disclosed in the specification." *Id.* at 47 (citing Ex. 2006; Pet. 68–70; Ex. 2001 ¶ 127).

Patent Owner asserts "the specification discloses that the claimed polypeptides are useful as 'antigens in contraception vaccines,' irrespective of whether they exhibit hyaluronidase activity." *Id.* at 49 (citing Ex. 1001, 75:56–58, 194:54–195:6, 72:45–73:47; Ex. 1011, 814; Ex. 2001 ¶¶ 140–141). Patent Owner cites teachings in the '600 patent to "Primakoff 1988 (EX2010) and Tung 1997 (EX1023) as teaching that '[i]mmunization with PH20 has been shown to be an effective contraceptive in male guinea pigs.'" *Id.* at 50 (citing Ex. 1001, 194:65–197:2; Ex. 2001 ¶¶ 137–138, 142).

Patent Owner asserts "the specification draws no distinction between inactive or active mutants, reflecting that all modified PH20 polypeptides 'provided herein' can be used as contraceptives." *Id.* at 52 (citing Ex. 2001

¶¶ 88, 140). Patent Owner further asserts that Petitioner's "cited art does not undermine the specification" because "[n]one of these cited references refute or contradict the reported success in using PH20 as a contraceptive in both male and female guinea pigs in Primakoff 1988, Primakoff 1997, or Tung 1997." *Id.* at 53 (citing Ex. 2001 ¶¶ 144–151).

D. Analysis

Because Petitioner has the initial burden to specifically identify how the specification fails to enable the claims, we address the *Wands* factors and the parties' respective arguments and evidence.

1. Breadth of Claims and Nature of the Invention

Patent Owner's declarant Dr. Triggs-Raines states, "the diversity of the claims is significantly limited to at least 95% sequence identity; therefore, a POSA would have understood that the claims encompass a very homogenous group of modified PH20 polypeptides." Ex. 2001 ¶ 104. Dr. Triggs-Raines cites Dr. Park as stating that "bee venom hyaluronidase and human PH20 are 'highly homologous' despite only 'sharing about 30% sequence identity. EX1004, ¶¶ 40, 151. The claimed modified PH20 polypeptides require more than three times that sequence identity." *Id.* Dr. Triggs-Raines states "I further disagree with Dr. Hecht's opinion regarding the sufficiency of the number of representative species because his analysis is undergirded by his general misunderstanding that the claims require hyaluronidase activity. As I explained above, claims 2-4 and 8-21 do not require any hyaluronidase activity." *Id.* ¶ 113.

Petitioner's declarant Dr. Park states, regarding the breadth of claim 1, that he "calculated the number of distinct polypeptides that exist that meet the specified criteria." Ex. 1004 ¶ 171. Dr. Park's table is reproduced below:

PH20 length	# Changes	Pos. 320 Choices	Add'l Changes	# Distinct Polypeptides
465	23	4	22	1.35×10^{66}
447	22	4	21	1.50×10^{63}
447	22	1	21	3.76×10^{62}
430	21	4	20	1.76×10^{60}
433	17	4	16	6.14×10^{49}

Dr. Park's table shows that the "number of distinct peptides is extremely large by all accounts, ranging from 10^{49} to 10^{66}." *Id.* ¶ 171. Petitioner's declarant Dr. Hecht agrees, stating the "sequence identity language causes the claims to encompass an immense number of distinct PH20 polypeptides." Ex. 1003 ¶ 120. To illustrate how large a number like 10^{66} is, Dr. Hecht states that an "aggregate weight of the smallest set containing one molecule of each of the PH20 mutants would be . . . = 5.49×10^{27} kg. The weight of the Earth is 'only' ~ 5.97×10^{24} kg." *Id.* ¶ 123.

That is, a complete set of one single molecule of protein that comprises all possible mutations in PH20 as recited in claim 1 would weigh about one thousand times more than the entire mass of planet Earth. *See id.* ¶ 123.

On the current record, we find the evidence demonstrates that the breadth of claim 1 and the dependent claims is immense.

2. Skill in the Art

The parties both separately addressed the skill in the art that is discussed *supra* Section VII. On the current record, we find both parties indicate that the skill in the art is high.

3. State of the Prior Art

Dr. Triggs-Raines states "the state of the prior art regarding making modified polypeptides generally was well established as of December 2012." Ex. 2001 ¶ 117. Dr. Triggs-Raines states "making the claimed modified PH20 polypeptides would have required nothing more than routine molecular biology and protein biochemistry techniques." *Id.* ¶ 118 (citing Ex. 1001, 149:59–67). Dr. Triggs-Raines acknowledges that "non-conserved residues 'may be responsible for the *different catalytic properties* of the human hyaluronidases' and that sequence variations 'may contribute to the apparent different substrate specificity' between different hyaluronidases." *Id.* ¶ 182 (citing Ex. 1006, 6915–6916). Dr. Triggs-Raines states "nonconserved residues may impact the activity and function of proteins." *Id.* ¶ 190 (citing Ex. 1014, 21, 55). Dr. Triggs-Raines states "in homologous proteins (such as Hyal-1 and PH20), non-conserved loop regions are often responsible for catalytic differences between the homologous proteins." *Id.* ¶ 191 (citing Ex. 1014, 21, 55). Thus, Dr. Triggs-Raines acknowledges that mutational differences in hyaluronidase proteins generally may result in differences in activities. *See id.* ¶¶ 182, 190.

Dr. Hecht also acknowledges protein expression is routine, stating the "conventional procedures relating to production of the wild-type $PH20_{1-447}$ protein could be applied to produce forms of $PH20_{1-447}$ that incorporate a single amino acid substitution . . . with little effort." Ex. 1003 ¶ 200.

Dr. Hecht further states that "[t]he first experimentally determined structure of a hyaluronidase was bvH, both alone and in complex with HA (published in 2007)" and that "Markovic-Housley identified the catalytic site and residues involved in catalytic activity using this structure." Ex. 1003 ¶ 80 (citing Ex. 1033, 1028–1031).

However, Dr. Hecht also states "[d]ata in the '429 Patent and a 2007 paper by Frost (EX1013) also showed that truncations of varying length at the C-terminus of PH20 caused significant variations in hyaluronidase activity." *Id.* ¶ 90. Dr. Hecht states the "Zhang paper reported that a truncation just upstream of the start of the Hyal-EGF domain in HYAL1 reduced its activity to ~6%." *Id.* ¶ 92. Dr. Hecht states that "[n]either the scientific literature existing by 2011 nor the common disclosure provides an explanation why these PH20 truncation mutations that differ by one residue (i.e., $PH20_{1-446}$ vs. $PH20_{1-447}$ vs. $PH20_{1-448}$) exhibit variability in their activity." *Id.* ¶ 94.

Dr. Hecht states "[t]here were limits to using rational design techniques in the 2011-timeframe." *Id.* ¶ 50 (citing Ex. 1059, 1225–1226). "The complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational design." *Id.* at n.16. Dr. Hecht states regarding another approach to protein modification, termed directed evolution, that the "challenge with directed evolution is scale. One has to identify the successful mutant out of an immense number of possibilities, which presents different kinds of challenges." *Id.* ¶ 52 (internal footnote omitted). Dr. Hecht states "changing many amino acids simultaneously risks disrupting the pattern necessary to induce formation of the original secondary structure . . . and [can] be highly

destabilizing to the overall protein structure." Ex. 1003 ¶ 55. Dr. Hecht states that in a smaller, ten amino acid substitution situation, "[t]here are approximately 6 x 10^{12} different scenarios of 10 substitutions." *Id.* ¶ 58.

On the current record, we find the evidence shows that simply making and expressing modified PH20 polypeptides was well within the state of the prior art. However, the evidence of record also demonstrates that the prior art was aware that mutations, whether conservative or non-conservative, may impact protein function and physical shape. *See, e.g.*, Ex. 1003 ¶¶ 92, 97, 113, 140–142. The evidence of record demonstrates that identifying which of the 10^{49} to 10^{66} members of the PH20 polypeptide genus would either retain functional hyaluronidase activity or contraceptive activity was not established as known in the prior art.

4. Presence of Working Examples

Dr. Triggs-Raines states the '600 patent "provides a library of '6,753' PH20 mutants—which a POSA would have recognized as a significant number of exemplified species." Ex. 2001 ¶ 103 (citing Ex. 1003 ¶¶ 103, 159). Dr. Triggs-Raines states the '600 patent "explains that each modified PH20 polypeptide within this ~6,800 mutant library contains 'a single amino acid mutation compared to … residues 1–447 of SEQ ID NO:3.'" *Id.* (citing Ex. 1001, 201:12–202:4).

Dr. Hecht agrees that the '600 patent "provides a compilation of all the mutants that apparently were produced by the inventors in Table 8. There are 6,753 entries in this table. These are all mutants generated by substituting one amino acid from $PH20_{1-447}$." Ex. 1003 ¶ 103. Dr. Hecht states "[t]able 10 contains a compilation of tested 'inactive mutants' with 3,380 entries." *Id.* Dr. Hecht calculates that based on the data in the '600

patent "57.1% were inactive, and 29.4% others had activity <100%." *Id.* ¶ 105.

Dr. Hecht states the '600 patent "does not identify any mutated PH20 proteins that were shown to be effective in [contraceptive] vaccines." *Id.* ¶ 113.

On the current record, we find the evidence demonstrates the presence of a limited set of working examples relative to the genus recited in the claims, though the evidence also shows that more than half of these working examples would not be encompassed by the claims because they were enzymatically inactive and no mutated PH20 protein was shown to be an effective contraceptive.

5. Amount of Direction or Guidance Presented

The '600 patent states "[p]roteins, such as modified PH20 polypeptides, can be purified using standard protein purification techniques known in the art." Ex. 1001, 152:42–44. Dr. Triggs-Raines states

> the specification of the '600 patent details how to test modified PH20 polypeptides for their ability to degrade hyaluronan (*i.e.*, for their hyaluronidase activity) and cites multiple known assays for doing so. EX1001, 140:13-26; 178:1-180:11; 231:41-290:31, Examples 3-5; 293:15-301:7, Examples 8-11; 303:44-306:44, Examples 14-15. And the specification further explains that such hyaluronidase assays were known in the art as of 2012. EX1001, 52:13-15 ("Assays to assess hyaluronidase activity are known to one of skill in the art and described herein.").

Ex. 2001 ¶ 134 n.28.

Dr. Hecht states the '600 patent "uses the 40% activity threshold to classify a mutant as an 'active mutant'" and that "'inactive mutants' are mutants with 20% or less of the activity of unmodified PH20." Ex. 1003 ¶¶ 100–101. Dr. Hecht states that the data in the '600 patent shows "most of

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

Dr. Hecht states the '600 patent

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

Id. ¶ 113. Dr. Hecht states "the data for testing the 409 mutants reported in Tables 11 and 12 [of the '600 patent] does not provide any meaningful guidance to a skilled artisan about the types of mutations that would improve the stability of PH20 polypeptides generally, or for the $PH20_{1-447}$ form specifically." *Id.* ¶ 76. Dr. Hecht states the '600 patent

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

Id. ¶ 172. Dr. Hecht characterizes the disclosure of the '600 patent as "best described as a research plan, as it generally outlines the types of steps one might take to carry out a mutagenesis and screening research program." *Id.* ¶ 173.

On the current record, we find the evidence demonstrates significant guidance on synthesis and expression of modified PH20 polypeptides. However, the evidence shows that the '600 patent provides minimal guidance regarding effective methods to identify which members of the

immense modified PH20 polypeptide genus function to retain either hyaluronidase activity or contraceptive activity.

6. Quantity of Experimentation

Dr. Triggs-Raines states:

> Regarding the quantity of experimentation, a POSA would not have needed to perform undue experimentation as of December 2012 because, as explained above, a POSA would have been able to make the claimed modified PH20 polypeptides in light of the guidance provided in the common disclosure and doing so would have required nothing more than repetition of routine molecular biology and protein biochemistry techniques, which could be further facilitated by the large-scale methods exemplified in the common disclosure.

Ex. 2001 ¶ 128. Dr. Triggs-Raines states "Dr. Hecht fails to address the fact that the *nature* of any experimentation is merely routine; it is, therefore, not undue." *Id.* ¶ 130.

Dr. Hecht states

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

Ex. 1003 ¶ 158 (emphasis added). Dr. Hecht states that "the single-replacement $PH20_{1-447}$ polypeptides reported in the common disclosure are not representative of all the types of mutated $PH20_{1-447}$ polypeptides that have sets of between 2 and 22 substitutions at any of hundreds of positions within the PH20 protein." *Id.* ¶ 159.

Dr. Hecht states "[m]aking and identifying all of the multiple-modified PH20 polypeptides that are within the immense set of polypeptides (between 10^{49} and 10^{65} distinct mutants) defined by the claims' sequence identity parameters is not only undue experimentation, it likely is impossible." *Id.* ¶ 170. Dr. Hecht states the directed evolution methods of the '600 patent are "the quintessential 'make and test' trial and error technique. By definition, the scientist carrying out a directed evolution protocol does not know which of the potentially trillions of possible mutants might incorporate a substitution that causes the protein to exhibit an improved characteristic." *Id.* ¶ 186.

We find the facts here similar to those in *Idenix Pharm. LLC v. Gilead Sci. Inc.*, 941 F.3d 1149, 1156 (Fed. Cir. 2019) where, in a genus of billions, the "key enablement question is whether a person of ordinary skill in the art would know, without undue experimentation, which [species] would be effective." *Idenix* states because of the "many thousands of [species] which need to be screened for . . . efficacy, the quantity of experimentation needed is large and weighs in favor of non-enablement." *Id.* at 1159.

On the current record, we find the evidence demonstrates that a very large amount of experimentation would be necessary to enable the scope of the claims of the '600 patent.

7. Predictability of the Art

Dr. Triggs-Raines states

> a POSA as of December 28, 2012 would have been able to align these at least 95% identity sequences with SEQ ID No. 3 and then visualize replacing the amino acid corresponding to position 320 of SEQ ID No. 3 with H, K, R and S in an entirely predictable manner.

Ex. 2001 ¶ 97 (citing Ex. 1001, 59:25–61:5). Dr. Triggs-Raines also states "a POSA would have been able to readily and predictably apply to make the claimed modified PH20 polypeptides, as of December 2012 in light of the guidance in the common disclosure." *Id.* ¶ 121 (citing Ex. 1011, 195:14–200:41).

Dr. Hecht states that the

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

Ex. 1003 ¶ 61. Dr. Hecht states, citing the '429 patent, that the "varying effects of changing residues in the Hyal-EGF region of PH20 show that [] a skilled artisan's belief that changes in this region would be unpredictable were warranted, and would be more so if multiple changes were made concurrently." *Id.* ¶ 96. Dr. Hecht states the "effects of these myriad sets of combinations of multiple substitutions within PH20 could not have been predicted by a skilled artisan in the 2011 timeframe using the tools that were available then." *Id.* ¶ 158. Dr. Hecht notes that "[a]nother problem caused by the use in the claims of sequence identity language to define the sets of proteins is that it captures many multiply-modified PH20 polypeptides with

changes that common disclosures says are deleterious or eliminate hyaluronidase activity in PH20 enzymes." *Id.* ¶ 160.

Dr. Hecht states the "skilled artisan also could not predict whether any combinations of up to 9 or up to 2 additional substitutions could be made anywhere in the $PH20_{1-419}$ sequence or comparably truncated PH20 polypeptide that would restore hyaluronidase activity to an inactive D320K containing $PH20_{1-419}$ mutant." *Id.* ¶ 168. Dr. Hecht continues:

> In other words, the common disclosure also does not help the skilled artisan identify which of the trillions of possible PH20 polypeptides of varying length[s] with 2 to 22 combinations have hyaluronidase activity, to practice the full scope of the claims it requires the skilled artisan to ignore what little guidance is in the specification about single-substitutions and truncations that render PH20 polypeptides inactive.

Id. ¶ 169. Dr. Hecht states that the artisan following the '600 patent's "iterative mutagenesis and screening research plan cannot know in advance of conducting multiple rounds of experiments, whether modified PH20 polypeptides will be produced that have sets of 5, 10, 15, or more substitutions and retain sufficient activity that will be selected for the next round of the process." *Id.* ¶ 184. We credit Dr. Hecht's testimony as showing it is highly unpredictable which polypeptides would have hyaluronidase or contraceptive activity. *Id.* ¶¶ 144, 151, 168–184.

On the current record, we find the evidence shows it is highly unpredictable which modified PH20 polypeptides within the scope of the claims of the '600 patent would have any functional utility such as hyaluronidase activity or contraceptive activity.

8. Conclusion

As we balance the *Wands* factors, we find that the totality of the evidence shown in the current record as discussed above better supports Petitioner's position that undue experimentation would have been required to enable the broad scope of the claims, and that the claims therefore fail to comply with the enablement requirement of 35 U.S.C. § 112(a).

XII. GROUND III - OBVIOUSNESS

A. Principles of Law

The Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). In *KSR*, the Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art;[9] and (4) considering objective evidence indicating obviousness or non-obviousness. *KSR*, 550 U.S. at 406.

B. Overview of the Asserted Prior Art

1. The '429 patent (Ex. 1005)

The '429 patent was filed on March 5, 2004 and issued on August 3, 2010. Ex. 1005, codes (22), (45). The '429 patent is drawn to "members of the soluble, neutral active Hyaluronidase Glycoprotein family, particularly

[9] *See supra* Section VII.

the human soluble PH-20 Hyaluronidase Glycoproteins (also referred to herein as sHASEGPs)." *Id.* at 3:51–54.

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

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

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

2. Chao (Ex. 1006)

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

Chao states "[t]here are five homologous hyaluronidases encoded in the human genome: hHyal-1 through -4 and the sperm adhesion molecule 1 (termed PH-20)." *Id.* Chao states "[i]n humans, eight alternative splice transcripts of *HYAL1* encode the full-length enzyme and five splice variants. Variants 1-5 (designated v1 through v5) are each truncated to a different extent. They lack enzymatic activity." *Id.* at 6912 (citation omitted). Chao reports "the crystal structure of the enzyme showing that it contains an EGF-like domain not seen previously, and examine the impact of alternative splicing on the enzyme structure and function." *Id.*

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

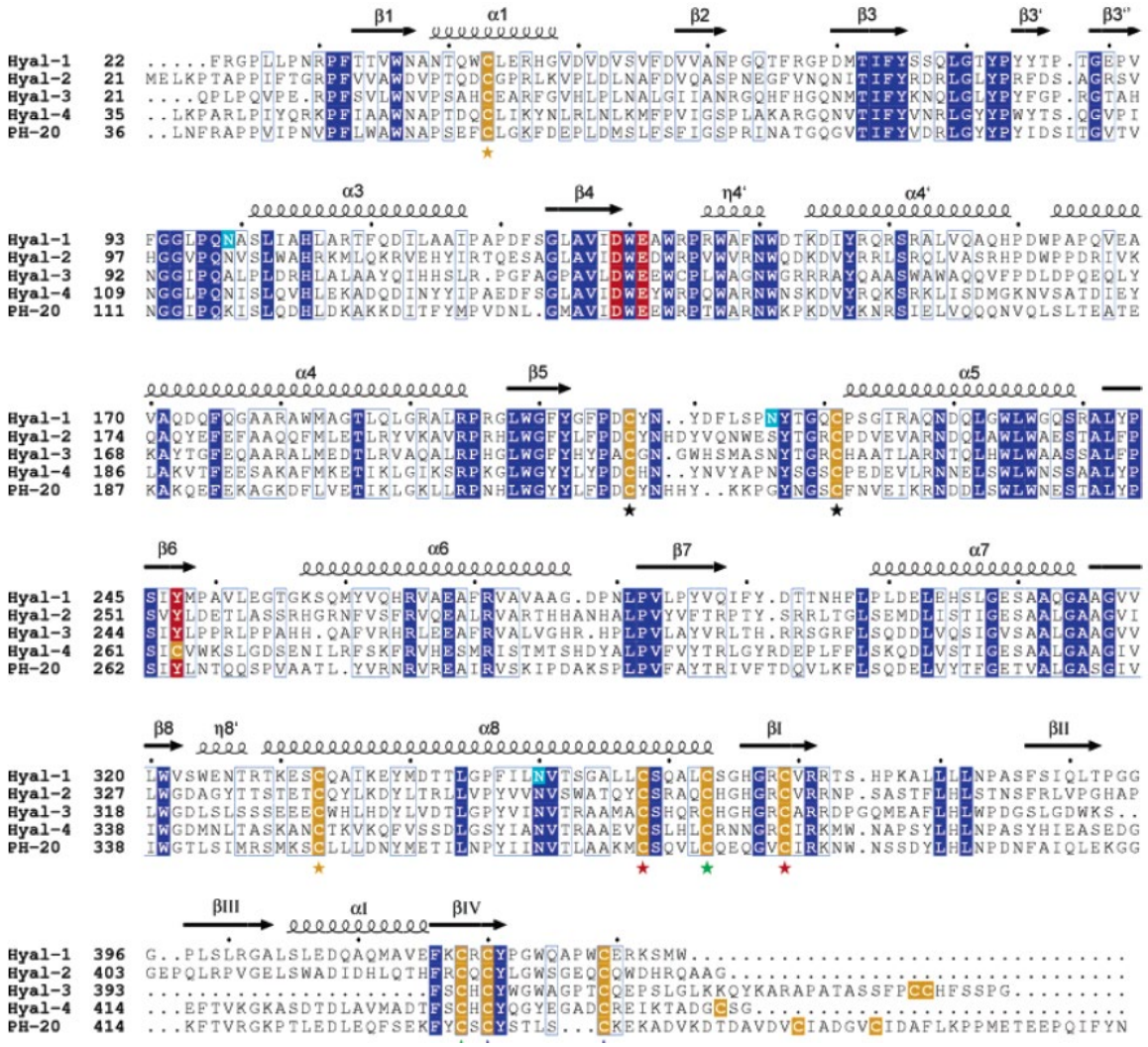


Figure 3 shows:

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

> replacements are blocked in blue. Pairs of cysteine residues that form disulfide bonds are indicated by stars with matching colors. Secondary structure units are labeled.

Id. at 6916.

C. Asserted Obviousness over the '429 Patent and Chao

1. Petitioner's Position

Petitioner asserts that the '429 patent "teaches making a *particular* type of modification (a single amino acid substitution) at a *particular* location (non-essential regions of PH20) in a *particular* PH20 sequence ($PH20_{1–447)}$ to yield equivalents of $PH20_{1–447}$ (*i.e.*, those that do not substantially alter the activity or function of $PH20_{1-447}$)." Pet. 88 (citing Ex. 1003 ¶¶ 202–204). Petitioner asserts "Chao identifies a characteristic pattern for the Hyal-EGF domain in PH20 (at 337–409)." *Id.* at 91 (citing Ex. 1006, 6912; Ex. 1004 ¶¶ 97–98).

Petitioner asserts that a "skilled artisan would use a multiple sequence alignment to identify the essential residues in PH20 using proteins homologous to PH20 that were known as of December 2011. The alignment also identifies the non-essential regions in PH20." *Id.* at 92 (citing Ex. 1003 ¶¶ 209–210; Ex. 1004 ¶¶ 22–30). Petitioner asserts that Dr. Park performed such an analysis and that "Position 320 is within a non-essential region of $PH20_{1–447}$. This is shown not only by Dr. Park's analysis, but also by Chao's Figure 3, which both report the same bounding essential residues (*i.e.*, C316 and L327)." *Id.* at 94 (footnote omitted) (citing Ex. 1004 ¶¶ 32, 31; Appendix D-2; Ex. 1003 ¶ 213).

Petitioner asserts that in Dr. Park's alignment, the "wild-type residue at position 320 in PH20 is aspartic acid (D), which occurs in ~10% of the

proteins (including PH20). The most prevalent amino acid found at position 320 in this set of homologous sequences is lysine (K) (57.95%), which is present in 51 different hyaluronidase proteins." *Id.* at 96 (citing Ex. 1003 ¶ 214.

Petitioner asserts that a "skilled artisan would also have had several specific reasons to make the single substitution of lysine for aspartic acid at position 320." *Id.* at 97. Petitioner asserts "[f]irst, lysine is the most prevalent amino acid at this position in the set of homologous hyaluronidase enzymes . . . . The high frequency with which lysine occurs in this position makes it an obvious candidate for being incorporated into position 320 of PH20." *Id.* at 97–98 (Citing Ex. 1004 ¶ 116; Ex. 1003 ¶¶ 216–217). Petitioner asserts "[s]econd, lysine has a high helix propensity, meaning it is more likely to be favored in sequences that form α-helix secondary structures. Position 320 of PH20 is within the middle of a long α-helix sequence." *Id.* at 98 (footnote omitted) (citing Ex. 1050, 422 (abstract), 423–424, Table 2; Ex. 1004 ¶¶ 69–70, 108; Appendix C; Ex. 1003 ¶ 215; Ex.1006, Figure 3).

Petitioner asserts that Patent Owner "relied on an affirmative statement that a skilled artisan would have expected ***any*** single amino acid substitution in ***any*** non-essential position of $PH20_{1–447}$ to not substantially affect the biological activity of the enzyme." *Id.* at 99–100. Petitioner also asserts "a skilled artisan would have reasonably expected that the D320K substitution in $PH20_{1-447}$ would not substantially alter the biological activity (hyaluronidase activity) of $PH20_{1-447}$." *Id.* at 100 (citing Ex. 1001, 75:47–52, 79:29–33).

2. Patent Owner's Position

Patent Owner asserts Petitioner "cannot deny that a modified PH20 polypeptide with an amino acid modification at position 320 is not mentioned in the '429 Patent or Chao, much less the specific H, K, R, and S replacements claimed for position 320. The elements of the claims are absent from the asserted prior art." Prelim. Resp. 56. Patent Owner asserts that neither Petitioner nor "its declarants provide[] a claim chart identifying where each claim limitation is found in the art, because they cannot do so." *Id.* at 57.

Patent Owner asserts Petitioner "has not asserted nor shown that common sense might supply this limitation. . . . Nor has Merck provided a reasoned explanation supported by evidence that POSAs would have had a reason to make the claimed modification at position 320 in the first place." *Id.* at 57–58 (citing Ex. 2001 ¶ 165). Patent Owner asserts Petitioner "also fails to demonstrate that common knowledge supplied this missing limitation" and Petitioner "fails to provide a reasoned explanation supported by evidence that POSAs would have had a reason to combine the '429 Patent and Chao to arrive at the claimed invention with a reasonable expectation of success." *Id.* at 59.

Patent Owner asserts the "Petition provides no *reason* why a POSA would have been motivated to make an amino acid substitution(s) in non-essential regions of PH20, let alone identify position 320 as one such position, particularly given that the '429 Patent does *not* identify any non-essential residues." *Id.* at 60. Patent Owner asserts that Petitioner and its declarants "do not explain why a POSA would have been motivated to expend resources to make an amino acid substitution in non-essential

regions of PH20 when [Petitioner's] cited art suggests that doing so would be pointless ("without altering biological activity")." *Id.* at 61 (citing Ex. 2001 ¶ 171). Patent Owner asserts that in "falsely equating non-conserved residues as 'non-essential,' Merck fails to establish that POSAs would have considered position 320 as a region to modify in view of the '429 Patent and Chao." *Id.* at 64 (citing Ex. 2001 ¶¶ 188–193).

Patent Owner asserts that Petitioner's argument based on rational protein design principles "is simply a restatement that such mutations *can be* made, and Merck never provides a *reason why* a POSA would have been motivated to combine the two references (or any of the dozen or so references Merck also cites) to make the claimed amino acid substitution in PH20." *Id.* at 65. Patent Owner notes that the '429 patent "disclosed that conservative amino acid substitutions are made, in accordance with those set forth in Table 1, and Table 1 does not disclose lysine as a substitute for aspartic acid." *Id.* at 69 (citing Ex. 1001, 16:24–36; Ex. 2001 ¶ 207).

Patent Owner asserts:

> Under 37 CFR §42.65(b)(2), Merck must explain how the test was performed and the data was generated. Here, Park does not explain how he prepared "Perl scripts" and how the data was generated using his bespoke scripts. Park merely states that he "wrote" and "ran" several "perl scripts," but failed to disclose what Perl code he used in his scripts, how he determined that these scripts would work as intended, or how he ran the scripts.

Id. at 71–72 (citing Ex. 1004 ¶¶ 145–146; Ex. 2001 ¶¶ 215–216). Patent Owner asserts simply because "lysine was the 'most prevalent' amino acid found at position 320 in Park's 88-sequence alignment is of no moment because [Petitioner] has not shown why a POSA would have selected the most frequent amino acid at a position from among a set of hyaluronidases

having different substrates and activities." *Id.* at 73 (citing Ex. 2001 ¶¶ 176–181, 204–206).

Patent Owner asserts that Petitioner "fails to establish that [the '429 patent] combined with Chao provides the requisite reasonable expectation of success that a D320K substitution in PH20 would not only be tolerated, but would result in a protein that exhibits at least comparable hyaluronidase activity to unmodified $PH20_{1-447}$." *Id.* at 78. Patent Owner asserts "[o]nly hindsight—provided by counsel—led Park and Hecht to position 320." *Id.* at 80.

3. Analysis

On the current record, we agree with Patent Owner that Petitioner has not provided any persuasive reason to particularly target the aspartic acid at position 320 of a PH20 polypeptide for modification with one of histidine, lysine, arginine, or serine as required by claim 1 of the '600 patent. It is undisputed that neither of the cited prior art references, the '429 patent or Chao, specifically identifies or discusses position 320 of the PH20 polypeptide. *See, e.g.*, Pet. 92; Prelim. Resp. 56–57.

We are not persuaded by Petitioner's argument that multiple sequence alignments identify amino acids that are tolerated at particular positions (*see* Pet. 97–98), because tolerance is not a positive reason to make a substitution. "It is not enough, even after *KSR*, to support a determination of obviousness that a reference includes a broad generic disclosure and a common utility to that in the claims and other prior art references—there must be some reason to select a species from the genus." *Knauf Insulation, Inc. v. Rockwool Int'l A/S*, 788 Fed. Appx. 728, 733 (Fed. Cir. 2019).

Dr. Park identified 379 positions in PH20 with evolutionary variation, that is, where "homologous proteins have tolerated different amino acids at those positions." Ex. 1004 ¶ 31. Dr. Park distributes the twenty standard amino acids into four categories depending on their roles in forming secondary structure such as alpha helices or beta sheets, with each category having a minimum of six members. *See id.* ¶ 70. Nothing in the prior art or Dr. Park's analysis directs the ordinary artisan to position 320 itself, and Dr. Park notes that Chao did not identify position 320 of PH20 as part of the catalytic active site, unlike positions 146, 148, and 219, nor was position 320 one of the residues identified as being in the cleft where ligand binds. *See id.* ¶ 91. Dr. Park indicates that position 320 was not identified by Chao as part of the Hyal-EGF domain, was not identified by Stern in the active site, and was not identified by Arming as impacting PH20 activity. *See id.* ¶¶ 98–101 (citing Ex. 1006, 6912; Ex. 1008, 825; Ex. 1011, 811–813).

Indeed, Dr. Hecht states that "[i]ntroducing random amino acids could disrupt that [alpha helical] pattern, which could have a range of effects in this region of the helical structure." Ex. 1003 ¶ 192. And while Dr. Hecht asserts that the '429 patent suggests conservative mutations generally, Petitioner did not point us to any specific teaching by Dr. Hecht to modify position 320 of PH20. *See, e.g.*, *id.* ¶¶ 202–204. Petitioner did not point us 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.

We also are not persuaded by Petitioner's arguments that the "high propensity of lysine to favor (*i.e.*, support) α-helix structures would have made lysine a logical option to incorporate as a substitution for aspartic acid

at position 320 in the α8 helix region of in $PH20_{1-447}$." Pet. 98. This statement is not a reason, but rather a statement. Dr. Park identified seven different amino acids that favor alpha helix formation. *See* Ex. 1004 ¶ 70. Figure 3 of Chao shows a number of different alpha helical regions, α1, α3, η4', α4', α4, α5, α6, α7, and α8, each composed of multiple amino acids, many of which appear to be non-conserved. *See* Ex. 1006, 6916 Table 1. Each of these large number of amino acids found within alpha helices might be subject to substitution by one of the seven preferred amino acids identified by Park, but it is Petitioner's "burden to show that the 'prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention.'" *Amerigen Pharm. Ltd. v. UCB Pharma GmBH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019) (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007)). Petitioner has not satisfied this burden of showing specific reasons to modify position 320 of the PH20 polypeptide.

Accordingly, on the current record, we find that Petitioner has not shown that it is more likely than not to likely to establish that the combination of the '429 patent and Chao with the knowledge and teaching described by Dr. Hecht and Dr. Park demonstrate obviousness for the claims of the '600 patent.

XIII. CONCLUSION

Petitioner has, at this stage, established that it will more likely than not prevail in showing that at least one of the challenged claims is unpatentable. This determination is, however, based on a preliminary record and is not final on any issues of patentability. We will make a final determination on the patentability of the challenged claims, as necessary and

applying the preponderance of the evidence standard, based on a fully developed record through trial.

XIV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 324(a) post grant review of claims 1–4 and 8–21 of the '600 patent is hereby *instituted* on the grounds set forth in the Petition, commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 324(d) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; and

FURTHER ORDERED that the trial will be conducted in accordance with a separately issued Scheduling Order.

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