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Paper 9
Date: July 13, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER INC.,
Petitioner,

v.

UNIQURE BIOPHARMA B.V.,
Patent Owner.

IPR2020-00388
Patent 9,249,405 B2

Before ERICA A. FRANKLIN, TINA E. HULSE, and JOHN E. SCHNEIDER, *Administrative Patent Judges.*

SCHNEIDER, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314, 37 C.F.R. § 42.4

I. INTRODUCTION

Pfizer Inc. ("Petitioner") filed a Petition (Paper 2, "Pet.") requesting *inter partes* review of claims 6 and 9–15 of U.S. Patent No. 9,249,405 B2 ("the '405 Patent", Ex. 1001). uniQure Biopharma B.V. ("Patent Owner") filed a Preliminary Response. (Paper 8, "Prelim. Resp.").

To institute *inter partes* review, we must determine that the information presented in the Petition shows "there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a) (2018). For the reasons discussed below, after considering the parties' submissions and the evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood of prevailing with respect to at least one claim of the '405 patent. Thus, we institute *inter partes* review.

A. Real Parties in Interest

Petitioner has identified the real party in interest as Pfizer Inc. Pet. 4. uniQure states that it is the sole real party in interest with respect to Patent Owner. Paper 4, 2

B. Related Matters

Petitioner states that there are "no judicial or administrative matters that would affect, or be affected by, a decision in an IPR for the '405 patent." Pet. 4. uniQure states that it "is not aware of any judicial or administrative matters that would affect or be affected by a decision in IPR2020-00388." Paper 4, 2.

C. The '405 Patent

The '405 Patent relates to a modified Factor IX ("FIX") "polypeptide, a nucleotide sequence, a vector comprising said nucleotide sequence and a method for producing the modified FIX polypeptide." Ex. 1001, col. 1, ll.

16–19. FIX is a vitamin K dependent glycoprotein that plays a role in coagulation. *Id.* at col. 1, ll. 26–30. A deficiency in FIX can cause a number of diseases including haemophilia B. *Id.* at col. 2, ll. 10–13.

The '405 Patent also relates to the preparation of viral vectors comprising the nucleotide sequence for the modified FIX polypeptide and their use in gene therapy for the treatment of hemophilia B. *Id.* at col. 22, ll. 11–16.

D. Illustrative Claims

Claim 6 is the only independent claim challenged in the Petition and reads as follows:

> 6. A sequence of nucleotides encoding a modified FIX (Factor IX) polypeptide comprising at least 70% identity to SEQ ID NO: 2 and a leucine at position 338 of SEQ ID NO: 2.

Ex. 1001, col. 57, ll. 34–37.

Claims 14 and 15, which depend from claim 6, are directed to the use of the nucleotide sequence in gene therapy. Claim 14 reads as follows:

> 14. A method to perform gene therapy, the method comprising
>
> administering to an individual in need thereof the nucleotide sequence according to claim **6** via a vector configured for gene therapy.

Id. at col. 58, ll. 33–37.

E. Evidence

Petitioner relies on the following references:

Stafford et al. WO 99/03496, published January 28, 1999. (Ex. 1004, "Stafford").

Schuettrumpf et al., *Factor IX variants improve gene therapy efficacy for hemophilia B,* 105 Blood 2316 (2005) (Ex. 1005, "Schuettrumpf").

Gao et al., *Novel adeno-associated viruses from rhesus monkey as vectors for human gene therapy,* 99 Proc. Nat'l Acad. Sci. 11854 (2002) (Ex. 1006, "Gao").

Hasbrouck et al., *AAV-mediated gene transfer for the treatment of hemophilia B: Problems and prospects*, 15 Gene Therapy 870 (2008) (Ex. 1020, "Hasbrouck").

F. Prior Art and Asserted Grounds

Petitioner asserts that claims 6 and 9–15 would have been unpatentable on the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
6, 9–15	102	Stafford
6, 9–15	103	Stafford
11–15	103	Stafford, Schuettrumpf, Gao, Hasbrouck

G. Disclaimer

A "patent owner may file a statutory disclaimer under 35 U.S.C. 253(a) in compliance with §1.321(a) of this chapter, disclaiming one or more claims in the patent. No *inter partes* review will be instituted based on disclaimed claims." 37 C.F.R. § 42.107(e) (2019). A disclaimer under 35 U.S.C. § 253(a) is "considered as part of the original patent" as of the date on which it is "recorded" in the Office. 35 U.S.C. § 253(a). For a disclaimer to be "recorded" in the Office, the document filed by the patent owner must:

(1) Be signed by the patentee, or an attorney or agent of record;

(2) Identify the patent and complete claim or claims, or term being disclaimed. A disclaimer that is not a disclaimer of a complete claim or claims, or term will be refused recordation;

(3) State the present extent of patentee's ownership interest in the patent; and

(4) Be accompanied by the fee set forth in [37 C.F.R.] § 1.20(d).

37 C.F.R. § 1.321(a); *see also Vectra Fitness, Inc. v. TNWK Corp*., 162 F.3d 1379, 1382 (Fed. Cir. 1998) (holding that a § 253 disclaimer is immediately "recorded" on the date that the Office receives a disclaimer meeting the requirements of 37 C.F.R. § 1.321(a), and that no further action is required in the Office).

Here, Patent Owner filed a statutory disclaimer of claims 6 and 9–13 of the '405 Patent. Ex. 2001. Based on our review of Exhibit 2001 and Office public records, we conclude that a disclaimer of claims 6 and 9–13 of the '405 Patent under 35 U.S.C. § 253(a) has been recorded in the Office as of April 16, 2020. *Id*. Because claims 6 and 9–13 have been disclaimed under 35 U.S.C. § 253(a) in compliance with 37 C.F.R. § 1.321(a), no *inter partes* review shall be instituted as to those claims. 37 C.F.R. § 42.107(e); *Intuitive Surgical, Inc. v. Ethicon LLC*, IPR2018-01248, Paper 7 at 2 n.1, 9–10 (PTAB Feb. 7, 2019) (discussing interplay of a disclaimed claim, Federal Circuit precedent, and our governing statutes and rules); *Daikin Indus. Ltd. v. The Chemours Co.*, IPR2018-00993, Paper 12 at 5–7 (PTAB Nov. 13, 2018) (noting that adverse judgment following partial disclaimer was not appropriate at least because the nondisclaimed claims "ha[d] yet to be 'decided.'"); *cf. General Electric Co. v. United Techs. Corp.*, IPR2017-00491, Paper 9 (PTAB July 6, 2017) (precedential) (declining to institute *inter partes* review when all challenged claims were disclaimed under 35 U.S.C. § 253(a)).

II. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 325(d)

Patent Owner contends that we should exercise our discretion under 35 U.S.C. § 325(d) and deny the Petition. Patent Owner contends that at least two of the references relied upon in the Petition were considered by the Examiner during prosecution of the '405 Patent. Prelim. Resp. 12–13. Patent Owner contends that the factors set forth in *Becton, Dickinson & Co. v. B. Braun Melsungen AG,* IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (informative), weigh in favor of our exercising our discretion and denying the Petition. *Id.* Patent Owner also contends that applying the two-step test enunciated in *Advanced Bionics* supports denying institution. *Id.* at 19–20 (citing *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 8 (PTAB Feb. 13, 2020) (precedential)).

Under § 325(d), the Board uses the following two-part framework: (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. *Advanced Bionics* at 8.

Advanced Bionics explains how the *Becton, Dickinson* factors are used in applying the two-part framework under § 325(d). The first, second, and fourth factors provide guidance as to whether the art and arguments presented in the petition are the same or substantially the same as those previously presented to the Office, whereas the third, fifth, and sixth factors "relate to whether the petitioner has demonstrated a material error by the Office" in its prior consideration of such. *Id.*

Petitioner contends while Stafford and Schuettrumpf were before the Examiner, that the grounds presented in the Petition are not duplicative of those considered during prosecution. Pet. 31–32. Petitioner contends that the claims addressed during prosecution were directed to the R338L protein and not the nucleotide sequence of claims 6 and 9–13 nor did the Examiner consider method of treatment claims using the nucleotide sequence. *Id.* Petitioner contends that the allowance of claims 6 and 9–15 was a mistake in that the claims were never substantively examined. Pet. 12. Petitioner also contends that while Schuettrumpf was cited on an IDS, the Examiner never relied on Schuettrumpf during examination. Pet. 32, n. 9.

A. Prosecution History of the '405 Patent

Our analysis begins with a review of the prosecution history of the '405 Patent. The '405 Patent arose from Application No. 13/063,898 ("'898 Appl."). As filed the '898 Appl. contained 14 claims with an additional claim added by Preliminary Amendment. Ex. 1010, 9–10.[1]

In the First Office Action, the Examiner found that the claims addressed three separate inventions, namely the modified Factor IX, a polynucleotide encoding for the modified Factor IX, and a method of using the modified Factor. *Id.* at 58. The Examiner required the Patent Owner to elect one of the inventions for examination. *Id.* at 59. The Examiner informed Patent Owner that if the elected claims were deemed allowable, the unelected claims could be rejoined if the withdrawn claims included all the limitations of the allowed claims and met the requirements of 35 U.S.C. §§ 101, 102, 103, and 112. *Id.* at 62. The Examiner also pointed out that

[1] Ex. 1010 is the prosecution history of the '405 Patent. The page citations are to the page numbers added by Petitioner.

any withdrawn claims that were not commensurate with the scope of the allowed claims would not be rejoined. *Id.* (citing MPEP §821.04). Patent Owner was advised that the withdrawn claims should be amended to include the limitations of the allowed claims and that failure to amend the claims would result in no rejoinder. *Id.*

In response to the restriction requirement, Patent Owner elected, with traverse, to prosecute the claims directed to the modified Factor IX. *Id.* at 70. Patent Owner argued that the claims represented a single invention in that there was a unique technical feature common to all the claims. *Id.* at 70–76. Patent Owner also amended the claims to include claims to a method for performing gene therapy. *Id.* at 68.

In the next Office Action, the Examiner found that while the claims did possess a common feature, the feature was not unique and the claimed Factor IX peptides were known in the art. *Id.* at 83–84. The Examiner found the restriction requirement to be proper and stated "Claims 5-11, 16-22, and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 18, 2014." *Id.* at 85.

Examination then proceeded as to the claims directed to the modified Factor IX. *See id.* at 88. The Examiner rejected the elected claims on several grounds including anticipation based on Stafford and obviousness based on Stafford. *Id.* at 90–91. The rejections focused on Stafford's disclosure of a Factor IX having leucine at position 338. *Id.*

Patent Owner then presented both legal and factual arguments urging that Stafford was focused on a modified Factor IX with an alanine at positon 338 and that the leucine substitution recited in the claims produced

surprising and unexpected results. *Id.* at 109–116. The Examiner found these arguments unpersuasive and maintained the rejections based on Stafford. *Id.* at 134–139. The Examiner also maintained the restriction requirement. *Id.* at 125–127. The Action was made final. *Id.* at 124.

Patent Owner then filed an amendment in conjunction with a Request for Continued Examination. *Id.* at 148. The amendment included a requirement that the factor IX polypeptide have at least 70% identity with SEQ ID NO:2 and a leucine at position 338 and that the polypeptide be present in an amount sufficient to provide a daily dosage of from between 0.1 μg/kg and 400μg/kg body weight. *See id.* at 151. Patent Owner also argued that Stafford did not teach the recited amount of the polypeptide or that the recited amounts would produce unexpected results. *Id.* at 159.

The Examiner then issued a Notice of Allowance. *Id.* at 170. The Notice indicated that some of the withdrawn claims were allowed including the gene therapy claims. *Id.* The Notice did not provide an explanation of the Examiner's reasons for allowing the claims. *See id.*at 171.

With this background we now consider whether to exercise our discretion under 35 U.S.C. § 325(d).

B. Analysis

Both Petitioner and Patent Owner acknowledge that Stafford, the primary reference in all three grounds, and Scheuttrumpf, one of the secondary references, were before the Examiner during prosecution of the '405 Patent. Pet. 31; Prelim. Resp. 13. Thus, the first step of the analysis set forth in *Advanced Bionics,* 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, is met.[2] The issue in the present case is whether the second step – whether the Office erred in a material manner – has been satisfied.

Petitioner contends that the Examiner erred in allowing issued claims 14 and 15 as those claims were not subject to substantive examination. Pet. 12–13, 31–32. Petitioner contends that claims 14 and 15 were withdrawn from consideration and were never properly rejoined. *Id.* Petitioner also contends that even if claims 14 and 15 had been rejoined, such rejoinder was improper as the claims are not commensurate in scope with the allowed claims, specifically they do not include the dosing limitation recited in the allowed claims. *Id.*

Patent Owner contends that Petitioner has not shown that there was a material error committed by the Examiner. Prelim. Resp. 17. Patent Owner argues that Stafford was before the Examiner, including Stafford's teachings regarding gene therapy. *Id.* at 19. Patent Owner contends that rejoinder of the withdrawn claims was not unusual. *Id.* at 17. Patent owner argues that there is no evidence to support Petitioner's contention that the claims were allowed because of the dosing limitation and argues that to require the addition of a dosing limitation to the claims would be illogical. *Id.*

We have considered the arguments presented by the parties and the evidence of record and conclude that, for purposes of this decision, Petitioner has shown that there was a material error in the allowance of

[2] Patent Owner contends that Gao and Hasbrouck are cumulative of references already considered. Prelim. Resp. 13–15. Petitioner contends that Gao and Hasbrouck are not cumulative. Pet. 31. We need not resolve this issue at the present time because, as discussed below, we conclude that Petitioner has shown that the Office materially erred during prosecution.

claims 14 and 15. Claims 14 and 15 were withdrawn from examination and were never subjected to substantive examination. *See* Ex. 1010, 85, 127.[3] While we agree with Patent Owner that Stafford teaches using a vector containing nucleotide encoding for a FIX variant gene therapy, Patent Owner does not point to, nor do we discern, any rejection based on this teaching. *See* Prelim Resp. 19; Ex. 1010, 90–91, 134–138. Thus, even if the Examiner had substantively examined claims 14 and 15, the Examiner appears to have overlooked that teaching. *See Advanced Bionics* at 8 n.9 ("An example of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims.").

Moreover, while we agree with Patent Owner that rejoinder of claims is not unusual, in the present case any rejoinder appears to have been improper. To begin, we note that nowhere in the prosecution history did the Examiner state that the restriction requirement was being withdrawn. *See* Ex. 1010, 170–171; MPEP § 821.04 ("Rejoinder involves withdrawal of a restriction requirement between an allowable elected invention and a nonelected invention and examination of the formerly nonelected invention on the merits."). In addition, we discern nothing in the record that shows that the withdrawn claims were fully examined for compliance with 35 U.S.C. §§ 101, 102, 103 and 112. *See* MPEP § 821.04.

Rejoinder also requires that the withdrawn claims must include the same limitations of an allowed claim. *Id.* Failure to include those

[3] The Action mailed April 3, 2014, refers to claims 16–22 as being withdrawn from consideration. Ex, 1010, 127. Issued claim 14 corresponds to claim 20 of the application and issued claim 15 corresponds to claim 22. *See* Ex. 1010, 68.

limitations "**may result in a loss of right to rejoinder.**" MPEP § 821.04 (emphasis in original). Claims 14 and 15 do not include the dosing limitations added to the claims that were substantively examined. *See* Ex. 1010, 151, 158–159.

The parties disagree as to whether the dosing limitation led to the allowance of the claims. Petitioner contends that the dosing limitation was specifically added to the claims to overcome the Examiner's rejection based on Stafford. Pet. 32. Patent Owner contends that there is nothing in the prosecution record to indicate that the Examiner allowed the claims based on the dosing limitations. Prelim. Resp. 17.

While we agree that the Examiner did not state an explicit reason for allowing the FIX variant claims, it is reasonable to conclude that the dosing limitations led to allowance of the FIX variant claims. Prior to the amendment that added the dosing limitation and led to allowance of the FIX variant claims, the Examiner had consistently maintained the rejections based on Stafford. Ex. 1010, 90, 134–139. Only after Patent Owner amended the claims to add the dosing limitations and argued that Stafford did not teach those limitations did the Examiner allow the FIX variant claims. *Id.* at 158–160, 165.

Patent Owner also argues that the addition of a dosing limitation would not make sense as claims 14 and 15 are directed to using gene therapy and not a peptide. Prelim. Resp. 17–18. Patent Owner contends that it would be illogical to call for a daily dose in gene therapy. *Id.* Patent Owner argues that "[t]his significant difference between Claim 1 and challenged Claims 14 and 15 further explains why the daily dosage limitation of Claim 1 was properly omitted from Claims 14 and 15." *Id.*

Patent Owner's argument regarding the logic for not adding a dose limitation to the claims may be correct, however it does not support the positon that the gene therapy claims were properly rejoined. As discussed above, proper rejoinder of non-elected claims requires that the claims must include the same limitations of an allowed claim. It is logical to conclude that the claims were allowed based on the amendment adding the dosing limitation and the arguments relating to the amendment. Absent such a limitation, claims 14 and 15 should not have been rejoined. The illogic of adding such a limitation, as asserted by Patent Owner, also highlights the difference between the FIX variant invention recited in claim 1 and the gene therapy invention recited in claims 14 and 15.

Based on the foregoing we conclude that Petitioner has demonstrated that the Examiner erred in a material manner. Accordingly, we decline to exercise our discretion under 35 U.S.C. § 325(d) to deny the Petition.

III. PATENTABILITY ANALYSIS

A. Legal Standards

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

1. Anticipation

Section 102(a) provides that "[a] person shall be entitled to a patent unless . . . the claimed invention was patented [or] described in a printed publication . . . before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a) (2002).[4] Accordingly, unpatentability by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently. *See Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999); *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994).

"A reference can anticipate a claim even if it does not expressly spell out all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1341 (Fed. Cir. 2016) (quoting *Kennametal, Inc. v. Ingersoll Cutting Tool Co*., 780 F.3d 1376, 1381 (Fed. Cir. 2015)).

2. Obviousness

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art, and (4) where in evidence, so-called secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). If

[4] The provisions of the Leahy-Smith America Invents Act ("AIA") regarding novelty and obviousness apply to patents containing at least one claim having an effective filing date on or after March 16, 2013. Pub L. 112–29, 125 Stat. 284 (2011). The '405 patent has an effective filing date before March 16, 2013. Ex. 1001, (87). Therefore, the pre-AIA provisions of 35 U.S.C. §§ 102 and 103 apply to this decision.

the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains, the claim is unpatentable under 35 U.S.C. § 103(a). *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

A proper § 103 analysis requires "a searching comparison of the claimed invention—including all its limitations—with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995).

"Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). "Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Id.*

B. Level of Ordinary Skill in the Art

The level of ordinary skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner contends,

> The person of ordinary skill in the art ("POSA") is a hypothetical person, and thus can possess the skills and experience of multiple individuals working together as a team. As of the priority date, research teams working to develop protein variants for use in gene therapy typically included at least (1) one or more researchers with experience in the fields of molecular biology and virology and the use of gene therapy

> for treatment of coagulopathies, working together with (2) one or more individuals with experience in protein structure or engineering. EX1002, ¶ 22, EX1003, ¶ 15. The POSA to whom the '405 patent is directed would therefore have had at least the relevant skills of those individuals, with experience and knowledge of the scientific literature in the areas of protein engineering and gene therapy, in particular as they relate to FIX.

Pet. 16. For purposes of this proceeding, Patent Owner has adopted Petitioner's definition of a person of ordinary skill in the art. Prelim. Resp. 10. Because Petitioner's proposed definition is unopposed and not inconsistent with the cited prior art, we adopt it for the purposes of this Decision. *See also Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Claim Construction

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. § 42.100(b) (2018). 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.* Furthermore, at this stage in the proceeding, we need only construe the claims to the extent necessary to determine whether to institute *inter partes* 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))).

For purposes of this decision, we do not find it necessary to construe any of the claim terms.

D. Ground 1 – Anticipation by Stafford

Petitioner contends that claims 14 and 15 are anticipated by Stafford.[5] The claims are directed to a method of gene therapy using vectors containing a polynucleotide sequence which encodes for a polypeptide which as 70% identity to SEQ. ID NO:2 and a leucine at position 338 of SEQ ID NO:2. Ex. 1001, col. 57, ll. 34–37; col. 58, ll. 33–37.

Petitioner contends that Stafford discloses a nucleotide sequence which encodes for modified FIX polypeptides. Pet. 33 (citing Ex. 1004, 1 and 5). Petitioner contends that Stafford discloses that the polypeptide has a substituted amino acid residue at position 338 where the substituted amino acid is selected from the group consisting of alanine, valine and leucine. Pet. 33–34 (citing Ex. 1004, 21).

Petitioner contends that Stafford discloses a polypeptide having at least 70% identity to SEQ. ID NO: 2 in that Stafford's SEQ ID NO:2 is 99% identical to SEQ ID NO:2 of the '405 Patent. Pet. 35 (citing Ex. 1002 ¶¶ 68–69). Petitioner also contends that Stafford discloses the presence of leucine at positon 338. Pet. 36 (citing Ex. 1004, 21).

[5] While the Petition states that claims 6 and 9–15 are anticipated by Stafford, as discussed above, claims 6 and 9–13 have been disclaimed leaving only claims 14 and 15 subject to challenge in the present Petition. We, therefore, focus our analysis on those claims.

With respect to claim 14, Petitioner contends that Stafford discloses that the nucleotide sequence can be placed in a vector that can then be used in gene therapy. Pet. 44–45.

With respect to claim 15, Petitioner contends that Stafford discloses that the invention can be used to treat hemophilia, a coagulopathy. Pet. 45–46.

Patent Owner contends that Stafford does not anticipate claims 14 and 15 as Stafford is not enabling for gene therapy. Prelim. Resp. 21. Patent Owner contends that while Stafford mentions gene therapy as a possible use for the disclosed invention, that mention is merely a direction for further research and does not enable one skilled in the art to actually use the nucleotides in gene therapy. Prelim. Resp. 22–24. Patent Owner contends the *Wands* factors support the conclusion that it would take undue experimentation to practice the claimed invention based on the teachings of Stafford. Prelim. Resp. 25–30.

1. Stafford

Stafford discloses a non-naturally occurring Factor IX protein having an amino acid substitution at positon 338. Ex. 1004, Abstr. Stafford discloses:

> Substitutions of the inventions are, for example, a substitution of an arginine residue for an amino acid residue selected from the group consisting of alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, glycine, serine, and threonine. In preferred embodiments of the invention, the substitution is a substitution of an arginine residue for an amino acid residue selected from the group consisting of alanine, leucine, and valine.

Ex. 1004, 5. Stafford discloses that the "FIX molecules of the present invention preferably have two or three more coagulant activity than the

corresponding wild type or plasma FIX." *Id.* at 5–6. Stafford discloses the sequence listing for both a FIX polypeptide ("Stafford SEQ ID NO:2") and a nucleic acid sequence which encodes for the peptide ("Stafford SEQ ID NO:1"). *Id.* at 3.

Stafford discloses that the FIX molecules may be produced by recombinant means. *Id.* Stafford discloses that vectors such as plasmids, viruses, phages, retroviruses and DNA fragments "may be used to produce recombinant Factor IX, or may be used in gene therapy to administer the expression cassette to targetted [sic] cells within the patient and produce the Factor IX in the patient." *Id.* at 7.

2. Analysis

As discussed above, Petitioner contends that Stafford discloses all of the limitations of claims 14 and 15. Pet. 33–37, 44–46. Petitioner supports these contentions by pointing to the specific portions of Stafford where the limitations are disclosed and citing to the testimony of Drs. Pederson and Wang. Ex. 1004; Ex. 1002 ¶¶ 61–72; Ex. 1003 ¶¶ 105–119.

At this stage of the proceeding Patent Owner does not contend that Stafford does not disclose the limitations of the claims but argues that Stafford does not enable gene therapy using a FIX variant with a leucine substituted at position 388 ("R338L variant"). Prelim. Resp. 21. Patent Owner contends that Stafford provides only "a starting point, a mere direction for further research." *Id.* at 22 (quoting *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997)).

Analyzing the factors set forth in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), Patent Owner contends that undue experimentation would be required to produce the R338L variant and then use it in gene therapy.

Patent Owner summarizes its analysis of the *Wands* factors in the following chart:

Wands Factor	Analysis of Stafford Disclosure
(1) the required quantity of experimentation	Substantial (Ex. 1004, Ex. 1005, 1-2)
(2) the amount of direction or guidance present	None for use of R338L in gene therapy (Ex. 1004)
(3) the presence or absence of working examples	None for use of R338L in gene therapy (Ex. 1004)
(4) the nature of the invention	Gene therapy (Ex. 1001, Claims 14-15)
(5) the state of the prior art	Protein modification is unpredictable (Ex. 1004) Gene therapy is unpredictable (Ex. 1005, 1)
(6) the relative skill of those in the art	High (Pet., 16)
(7) the predictability or unpredictability of the art	Highly unpredictable (Ex. 2016, 46)
(8) the breadth of the claims	Narrow (Ex. 1001, Claims 14-15)

Id. at 29.

Chart listing *Wands* Factors analysis from Patent Owner's Preliminary Response

Petitioner contends that Stafford is enabled. Pet. 38. Petitioner contends that one skilled in the art would have been able to create a nucleotide sequence that would have encoded for a specific protein sequence such as the R338L variant. *Id*. at 38–39. Petitioner supports this contention with the testimony of Dr. Pederson who states that the desired nucleotide sequence could be produced either through site directed mutagenesis or through the use of automated DNA synthesizers. Ex. 1002 ¶¶ 34–35.

We have considered the arguments presented by the parties and the evidence of record and conclude that for purposes of this decision, Petitioner has shown that Stafford anticipates claims 14 and 15. Petitioner has demonstrated through the disclosure of Stafford and the testimony of Dr.

Pederson and Wang that Stafford discloses all of the limitations of the claims.

We also find that the evidence currently of record sufficiently supports Petitioner's contention that the claims are enabled. While we agree with Patent Owner that the disclosure in Stafford is minimal, as our reviewing court has held, "a patent need not teach, and preferably omits, what is well known in the art." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). On this record, Petitioner has shown sufficiently through the testimony of Drs. Pederson and Wang that one skilled in the art would have known how to make and use a nucleotide encoding for the R338L variant. Pet. 38–39; Ex. 1002 ¶¶ 34–35; Ex. 1003 ¶¶ 72–76. Although the guidance given in Stafford may be minimal, the evidence of record supports the conclusion that making and using an R338L variant would have been well known in the art.

Patent Owner contends that a substantial amount of experimentation would have been required to make and use an R338L variant. Prelim. Resp. 26–27. In support of this contention, Patent Owner cites to Schuettrumpf. *Id.* While Scheuttrumpf outlines the steps that might be required to develop and use a nucleotide sequence for gene therapy, we discern nothing in Schuettrumpf to support Patent Owner's contention that this work would involve substantial experimentation that supports a determination that Stafford is not enabled. Patent Owner has offered no testimony or other evidence to support this contention.

Patent Owner contends that the art relating to the present invention is unpredictable. Prelim. Resp. 28–29. In support of this contention, Patent

owner cites to Schuettrumpf, Huazhong[6], and the Office's Examination Policy. *Id.* (citing Exs. 1005, 1012, and 2016). Patent Owner also argues that Stafford supports this contention in that it teaches that a leucine substitution at amino acid 337 causes hemophilia rather than treats it. Patent Owner contends that the unpredictability of the art supports a finding of non-enablement.[7] *Id.*

We have considered Patent Owner's argument and the evidence of record and conclude that this element does not weigh in favor of finding non-enablement. While we agree that the Office Examination policy states generally that gene therapy has not been definitively demonstrated, Petitioner has advanced evidence that supports the conclusion that, at least for the claimed therapy, the results for the specific therapy claimed have met expectations. For example, Huazhong reports that using the vector developed by Stafford, Huazhong was able to induce production of FIX in mice. Ex. 1012, 592. Dr. Pederson has testified that one skilled in the art could readily create the desired nucleotide and Dr. Wang testified that "by the late 1990s, a person of ordinary skill in the art would have understood that factor IX gene therapy using viral vectors was a feasible method of treating a coagulopathy such as hemophilia B." Ex. 1002 ¶¶ 34–35; Ex.

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[6] Huazhong et al., *Gene therapy for hemophilia B mediated by recombinant adeno-associated virus vector hFIXR338A, a high catalytic activity mutation of human coagulation factor IX,* 44 Sci, in Chia 585 (2001) (Ex. 1012 "Huazhong").

[7] We note that at this stage of the proceeding, Patent Owner relies on attorney argument regarding what one skilled in the art would understand from the teachings of the various references. *See, e.g.,* Prelim. Resp. 28–29. "Attorneys' argument is no substitute for evidence." *Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989).

1003 ¶ 73. Dr. Wang has also testified that before the priority date of the present invention, several studies had reported the efficacy of gene therapy to produce Factor IX. Ex. 1003 ¶ 73.

On balance, at this stage of the proceeding we find that it would not require undue experimentation to use the disclosure of Stafford to make and use the R338L variant in gene therapy.

We conclude that, for purposes of this decision, Petitioner has demonstrated a reasonable likelihood that it would prevail in establishing that claims 14 and 15 are anticipated by Stafford.

E. Ground 2 – Obviousness Based on Stafford

Petitioner contends that the subject matter of claims 14 and 15 would have been obvious to one skilled in the art at the time the invention was made over the teachings of Stafford. Pet. 46. Petitioner references its prior arguments that Stafford discloses all of the limitations of the claims. *Id.* Petitioner also contends that one skilled in the art would have been motivated to use the leucine variant with a reasonable expectation of success. *Id.* at 47. Petitioner contends that Stafford teaches that FIX variants such as those disclosed in Stafford "advantageously have increased clotting activity as compared to the corresponding wild-type molecule." *Id.* at 46–47 (quoting Ex. 1004, 4).

In addition to the teachings of Stafford, Petitioner supports its contentions with the testimony of Drs. Pederson and Wang. Pet. 46–53. For example, Dr. Pederson testified that "[t]he POSA would have been motivated to create nucleotide sequences encoding each of Stafford's preferred variants (R338A, R338V, and R338L) because the POSA would have understood that they were likely to be useful for purposes of expressing factor IX protein from vectors, including in gene therapy, as Stafford itself

suggests explicitly." Ex. 1002 ¶ 80. Dr. Pederson goes on to testify that "the POSA would have expected the R338A and R338L variants to behave similarly and advantageously, and would have been particularly optimistic about the R338L variant in light of expectations about helix formation." *Id.* Similarly, Dr. Wang testified that the teachings of Stafford would have motivated one skilled in the art to use the nucleotide sequence R338L in gene therapy and that such therapy would be successful. Ex. 1003 ¶¶ 113–119.

Patent Owner contends that claims 14 and 15 would not have been obvious to one skilled in the art as there would have been no motivation to replace leucine at position 338 for arginine. Prelim. Resp. 31. Patent Owner contends that the art of protein mutation is inherently unpredictable as is expression of a nucleotide for such a sequence. *Id*. at 31–32.

We have considered the arguments advanced by the parties and the evidence of record and conclude that Petitioner has demonstrated a reasonable likelihood of showing that claims 14 and 15 are unpatentable as obvious over Stafford. As discussed above, Petitioner has demonstrated a reasonable likelihood of showing that claims 14 and 15 are anticipated by Stafford. *See* Section III. D. above. "It is well settled that 'anticipation is the epitome of obviousness.'" *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). Thus, we find that Stafford teaches all of the limitations of claims 14 and 15.

We now turn to the issues of whether one skilled in the art would have been motivated to produce the claimed nucleotide and would have had a reasonable expectation of success in using it in a gene therapy to treat hemophilia.

Stafford teaches the preparation of a modified FIX polypeptide having a substitution at position 338 of the polypeptide. Ex. 1004, Abstr. Stafford teaches that the preferred substitution is alanine, leucine or valine for arginine. *Id.* Stafford teaches that the FIX molecules of the invention "have two or three times more coagulant activity than the corresponding wild type or plasma FIX." Ex. 1004, 5–6. Dr. Pederson testified that these teachings in Stafford would have motivated one skilled in the art to make the R338L peptide as well as a nucleotide sequence encoding for that peptide. Ex. 1002 ¶¶ 34–35. Dr. Wang also testified that Stafford's teachings would have motivated one skilled in the art to use a vector encoding for the R338L variant and used that vector in gene therapy to treat hemophilia. Ex. 1003 ¶¶ 104–110. Dr. Wang also testified that given the success using vectors that expressed wild-type FIX polypeptides in gene therapy, one skilled in the art would have had a reasonable expectation of success in using the R338L variant taught by Stafford. *Id.*

Patent Owner contends that studies using the R338A variant disclosed by Stafford did not show "therapeutic results sufficient for gene therapy." Prelim. Resp. 31 (citing Ex. 1005, 1; Ex. 1012, 8). We have reviewed the references cited by Patent Owner and do not discern any teaching in either reference that would lead one skilled in the art to conclude that the R338A or R338L variant would not work. In fact, Schuettrumpf states that "[t]hese studies demonstrate that FIX variants provide a promising strategy to improve the efficacy for a variety of gene-based therapies for hemophilia B." Ex. 1005, Abstr. Huazhong teaches that the gene therapy did work but that the FIX level declined after 4 month. Ex. 1012, 592. Huazhong also teaches that repeated use may make the variant more successful. *Id.* We discern nothing in either of these papers, nor has Patent Owner offered any

evidence, to support the conclusion that one skilled in the art would not have had a reasonable expectation of success.

Patent Owner also contends that those skilled in the art would know that expressing a sequence with an amino acid substitution in vivo is highly unpredictable and that a point mutation might result in severe consequences or no activity. Prelim. Resp. 31–32. We are not persuaded by this argument. While it is generally true that some point mutations can be harmful or ineffective, Stafford expressly teaches that specific point mutations at positon 338 of the FIX polypeptide have a positive effect, namely increasing the coagulation activity of the FIX. Ex. 1004, 4. That Stafford and other references might teach that other mutations at a different location might be harmful does not detract from Stafford's explicit teaching regarding specific substitutions at position 338 of FIX.

Based on the foregoing and for purposes of this decision, we conclude that Petitioner has demonstrated a reasonable likelihood that Petitioner would prevail in establishing that the subject matter of claims 14 and 15 would have been obvious to one of ordinary skill in the art at the time the invention was made over the teachings of Stafford.

F. Ground 3 – Obviousness Based on Stafford, Gao, Hasbrouck and Schuettrumpf

Petitioner contends that the subject matter of claims 14 and 15 would have been obvious over Stafford in light of Gao, Hasbrouck and Schuettrumpf. Pet. 56. Petitioner contends that Stafford teaches R338L FIX variant, nucleotide sequences encoding it, and vectors for gene therapy using such sequences. *Id.* Petitioner argues that "Schuettrumpf, Gao and Hasbrouck provide additional support for the fact that the POSA would have been motivated to prepare AAV vectors encoding Stafford's R338L variant

and to use them in gene therapy to treat a coagulopathy, all with a reasonable expectation of success." *Id.*

Patent Owner begins by contending that Petitioner has failed to state the precise grounds for unpatentability asserted in Ground 3. Prelim. Resp. 35. Patent Owner argues that the headings and text for Ground 3 are inconsistent and lack particularity. *Id.* at 37–38. Patent Owner argues that the use of the term "and/or" in Ground 3 results in voluminous and excessive grounds, which justifies denying the petition. *Id.* at 38–40.

Patent Owner contends that, with respect to Ground 3, Petitioner has failed to present a legally sufficient basis for obviousness. Prelim. Resp. 40. Patent Owner contends that Petitioner has failed to articulate the differences between the claimed invention and the prior art. *Id.* at 41. Patent Owner also contends that Petitioner has not explained why one skilled in the art would modify the teachings of Stafford or combine the teachings of Stafford with the secondary references. *Id.* at 42.

1. Gao

Gao discloses a study of novel adeno-associated virus, AAV8, and its use as a vector in gene therapy for hemophilia B. Ex. 1006, Abstr. Gao reports that the use of AAV8 produced significantly greater gene expression than other adeno-associated viruses. *Id.* at 5. Gao also discloses the successful use of AAV8 to transduce mice with the FIX gene and reported high level of the FIX protein after infusion. *Id.*

2. Hasbrouck

Hasbrouck reports a survey of the progress of gene therapy for treating hemophilia B. Ex. 1020, Abstr. Hasbrouck teaches that several factors make hemophilia B an attractive candidate for gene therapy and describes work to date that has used adeno-associated virus ("AAV")

vectors. *Id.* at 2. Hasbrouck teaches that the use of different vectors such as AAV8 may help overcome some of the deficiencies of other AAVs used. *Id.*

3. Schuettrumpf

Schuettrumpf discloses the results of a study using AAV vectors encoding for FIX variant R338A to treat hemophilia in a mouse model of the human disease. Ex. 1005, 1. Schuettrumpf reports that when the AAV vectors were used to transduce liver cells, the FIX variant produced has 6 times the activity of wild-type FIX and was effective in treating hemophilia. *Id.* Schuettrumpf conclude that the use of "F.IX [sic] variants provide a promising strategy to improve the efficacy for a variety of gene-based therapies for hemophilia B," in part because they have the "potential to correct the phenotype at low vector doses." *Id.* at Abstr., 7.

4. Analysis

We have considered the arguments presented by the parties and the evidence of record and conclude that, for purposes of this decision, Petitioner has demonstrated a reasonable likelihood that it would prevail in showing that claims 14 and 15 are unpatentable for obviousness.

As discussed above, Stafford discloses all of the limitations of the claims. Section III. D., *supra*. In addition to the teachings in Stafford that would lead one skilled in the art to create and use the R338L FIX variant, the additional references cited by Petitioner would have motivated one skilled in the art to use the variants disclosed in Stafford in gene therapy with a reasonable expectation of success. For example, Schuettrumpf teaches that an AAV vector can be used to transduce liver cells in mice such that the FIX variant resulted in a significant increase in activity. Ex. 1005, 1, 7. Schuettrumpf goes on to teach that the results achieved provide a

promising strategy to improve the efficacy of a variety of gene based therapies for hemophilia. *Id.* As Dr. Wang has testified,

> Because vectors that encode wild-type factor IX were successfully used in gene therapy, one would have reasonably expected that vectors encoding the R338L variant would also work in gene therapy because such vectors contain nucleotide sequences that are nearly identical to the nucleotide sequences that encode wild-type factor IX, except for the codon corresponding to residue 338.

Ex. 1003 ¶ 145.

Patent Owner's argument that Ground 3 fails to set forth a ground for unpatentability with particularity is unpersuasive. In its discussion of Ground 3, Petitioner makes it clear that it relies on Stafford for teaching the various limitations of the claims and that the additional references are cited only for the purpose of providing additional evidence regarding motivation to combine and reasonable expectation of success. Pet. 56. Given the detailed discussion of Stafford in the prior Grounds, we find that Petitioner has provided the required explanation of the basis for alleging that the claims are unpatentable. *See* Pet. 33–53.

Patent Owner contends that the use of and/or in Ground 3 could lead to up to 14 different combinations of references that Patent Owner would need to address and that this is excessive. Prelim. Resp. 38–39. Patent Owner contends that the excessive number of reference combinations places an undue burden on Patent Owner in formulating a response to Ground 3 and that for this reason we should not consider Ground 3. *Id.* Patent Owner relies on *Adaptics Ltd. v. Perfect Co.*, IPR2018-01596, Paper 20 at 17–18 (PTAB Mar. 6, 2019) (informative) to support its contention. *Id.* We are

not persuaded that the use of the term "and/or" presents an undue burden on Patent Owner under the facts and circumstances of this case.

In *Adaptics*, the petition recited ten different references that led to at least 17 and possibly hundreds of different combinations. *Adaptics* at 18–19. Additionally, in *Adaptics*, the petition did not specify which elements were missing from the primary references and where they were found in the secondary references. *Id.* at 19–20.

This is in contrast with the present Petition where the citation of four or five references[8] lead to a maximum number of 14 combinations. *See* Prelim. Resp. 39. Moreover, Petitioner has clearly stated that the secondary references are cited only to provide additional evidence regarding motivation to combine and reasonable expectation of success. Pet. 56. The Petition and Dr. Wang's testimony provide an analysis of how each of the secondary references provides the necessary motivation and expectation of success. Pet. 61–63; Ex. 1003 ¶¶ 143–151.

We conclude that the effort required to respond to the arguments and references presented by Petitioner with respect to Ground 3 is not unreasonable. We decline to exercise our discretion to not consider Ground 3 as the Board does not have discretion to not consider individual grounds. *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition").

[8] Patent Owner contends that Manno et al., *Successful Transduction of Liver in Hemophilia by AAV-Factor IX and Limitations Imposed by the Host Immune Response*, 12 Nat. Med. 342 (2006) (Ex. 1017, "Manno") should be considered in the analysis as it was cited by both Petitioner and Dr. Wang in their analysis of claims 14 and 15. Prelim. Resp. 38–40. Our analysis is the same whether we consider Manno or not.

Based on the foregoing we conclude that Petitioner has demonstrated a reasonable likelihood of prevailing in establishing that the subject matter of claims 14 and 15 would have been obvious over Stafford combined with Gao and/or Hasbrouck and Schuettrumpf.

IV. CONCLUSION

After considering the evidence and arguments presented in the Petition and the Preliminary Response, we have determined that Petitioner has shown a reasonable likelihood of prevailing with regard to claims 14 and 15 with respect to Grounds 1, 2, and 3.

We therefore grant the Petition and institute trial as to claims 14 and 15 on all grounds asserted.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 324(a), an *inter partes* review is instituted on all challenges raised in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 324(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of trial commencing on the entry of this Decision.

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