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Paper 47
Entered: November 15, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

UNIQURE BIOPHARMA B.V.,
Patent Owner.

IPR2021-00928
Patent 10,465,180 B2

Before ERICA A. FRANKLIN, ROBERT A. POLLOCK, and JULIA HEANEY, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

A. Procedural Background

Pfizer, Inc. ("Petitioner" or "Pfizer") filed a Petition for an inter partes review of claims 1–6 of U.S. Patent No. 10,465,180 B2 ("the '180 Patent," Ex. 1002). Paper 1 ("Pet."). uniQure Biopharma B.V. ("Patent Owner" or "uniQure") timely filed a Preliminary Response. Paper 10. Petitioner further filed an authorized Reply to the Preliminary Response (Paper 11); Patent Owner filed a responsive Sur-Reply (Paper 12). Taking into account the arguments and evidence presented, we determined the information presented in the Petition established that there was a reasonable likelihood that Petitioner would prevail in challenging at least one challenged claim of the '180 patent, and instituted this *inter partes* review as to all challenged claims. Paper 13 ("DI").

After institution, Patent Owner filed a Patent Owner Response (Paper 30, "PO Resp."); Petitioner filed a Reply to the Patent Owner Response (Paper 35, "Reply"); Patent Owner filed a Sur-reply (Paper 41, "Sur-reply").

An oral hearing was held on August 18, 2022, and a transcript of the hearing is included in the record. Paper 46 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. This decision is a Final Written Decision under 35 U.S.C. § 318(a) as to the patentability of claims 1–6 of the '180 patent. For the reasons discussed below, we hold that Petitioner has demonstrated by a preponderance of the evidence that claims 1–6 are unpatentable.

B. Real Parties-in-Interest

Petitioner identifies itself, Pfizer Inc., as the real party-in-interest. Pet. 4. Patent Owner, identifies itself, uniQure Biopharma B.V. and its exclusive

licensee, CSL Behring LLC (a division of CSL Limited), as real parties-in-interest. Paper 5.

C. Related Proceedings and Chain of Priority

Petitioner concurrently challenges claims of US Patent No. 9,982,248 ("the '248 patent") in IPR2021-00925 ("the '925 IPR") and IPR2021-00926. Pet. 4; Paper 6. Petitioner previously challenged claims of related U.S. Patent No. 9,249,405 B2 ("the '405 patent") in IPR2020-00338 ("the 338 IPR"); that proceeding was terminated on March 25, 2021, upon Patent Owner's request for adverse judgment. *See* IPR2020-00338, Paper 52.[1]

The '180 patent, at issue in this proceeding, issued from application No. 15/989,665, which is a continuation of application No. 15/650,070 (which issued as the '248 patent), which is a continuation of application No. 14/981,981 ("the '981 application"), which is a continuation of application No. 13/063,898 ("the '898 application"), filed as application No. PCT/EP2009/061935 on Sep. 15, 2009 (which issued as the '405 patent). Ex. 1002, code [21], [22], [63]. Accordingly, the '180, '248, and '405 patents share substantially the same specification.

[1] Petitioner argues that the challenged claims differ from those at issue in the '338 IPR only in further reciting "transcription, termination, and control elements." Pet. 28. Petitioner notes that the Board instituted trial in the '338 IPR on similar grounds, including anticipation by Stafford, and argues that Stafford discloses those additional, well-known features. *See id*. at 26–28 (citing, e.g., '338 IPR Paper 9 at 19–23, 23). Although Petitioner appears to urge that we rely on alleged "concessions" arising from the disposition of the '338 IPR, we consider the merits of the parties' arguments and evidence on the instant record. *See* Pet. 1–2; Reply 4–5; Ex. 1003 ¶ 316.

The '898 application further claims priority to Italian Applications, filed May 6, 2009 and September 15, 2008 ("the Italian applications"). Ex. 1057, code [30]; Ex. 1010, 5; *see* Ex. 1002, code [30]; Pet 7. For the purpose of this proceeding "Petitioner assumes the earliest claimed priority date of September 15, 2008 for the Challenged Claims." Pet. 6. Patent Owner does not contest this assumption. Reply 9.

D. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 12):

Ground	Claims Challenged	35 U.S.C §[2]	Reference(s)/Basis
1	1–6	§ 102	Stafford[3]
2	1–6	§ 103	Stafford
3	1–6	§ 103	Stafford, Manno,[4] Schuettrumpf[5]

In support of its patentability challenge, Petitioner relies on, *inter alia*, the Declarations of Lili Wang, Ph.D. (Ex. 1003; Ex. 1100), and the Declarations of Lee Pedersen, Ph.D. (Ex. 1094; Ex. 1101). Patent Owner

[2] The Leahy-Smith America Invents Act ("AIA") included revisions to 35 U.S.C. §§ 102 and 103 that became effective on March 16, 2013. Because the '180 patent issued from an application that is a continuation of an application filed before March 16, 2013, we apply the pre-AIA versions of the statutory bases for unpatentability.

[3] WO 99/03496 A1 to Stafford et al., published Jan. 28, 1999. Ex. 1004.

[4] Manno et al., *Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response*, 12 NATURE MEDICINE 3:342–47, Feb. 12, 2006. Ex. 1017.

[5] Schuettrumpf et al., *Factor IX variants improve gene therapy efficacy for hemophilia B*, 105 BLOOD 6:2316–23, Mar. 15, 2005. Ex. 1005.

relies on, *inter alia*, the Declarations of Christopher Doering, Ph.D. (Ex. 1072; Ex. 2102) and P. Clint Spiegel, Ph.D. (Ex. 2101). The parties also filed transcripts of the depositions of Dr. Pedersen (Exs. 2033, 2130, 2146), Dr. Wang (Exs. 2147, 2032, 2114, 2099, 2032), Dr. Doering (Ex. 1102, 1095), and Dr. Spiegel (Ex. 1103) from this, and other, proceedings.

E. The '180 Patent

The '180 patent is titled "Factor IX Polypeptide Mutant, Its Uses and Method for its Production" and describes a modified Factor IX (FIX)[6] "polypeptide, a nucleotide sequence, a vector comprising said nucleotide sequence and a method for producing the modified FIX polypeptide." Ex. 1002, code [54], [57]; 1:20–23. According to the Specification, Factor IX is a vitamin K-dependent glycoprotein, synthesized in the liver, and plays a fundamental role in the coagulation cascade. *Id.* at 1:30–34. In humans, the mRNA encoding Factor IX encodes the synthesis of a 461 amino acid precursor (SEQ ID NO:1), which includes N-terminal signal peptide and propeptide domains. *Id.* at 1:57–2:2. Upon cleavage of these N-terminal domains, the mature form of Factor IX, represented by SEQ ID NO:2, "circulates in plasma as a single chain zymogen composed of 415 amino acids." *Id.* at 1:34–35, 2:2–15.

The Specification explains that "[a] genetic deficiency in FIX can cause a number of coagulation diseases (coagulopathies), for example the haemorrhagic disease known as haemophilia B." *Id.* at 2:16–19. Patients with severe haemophilia B (characterized by plasma FIX activity below 1% of normal), "present serious haemorrhagic manifestations which can be

[6] "Factor IX," "FIX," and "F.IX" are used interchangeably in the record.

controlled or avoided by administering FIX concentrates of extractive (from human plasma) or of recombinant origin, currently only available in a single commercial formulation." *Id.* at 2:19–32. According to the Specification, however:

> Attempts to correct the genetic defect by means of gene therapy have so far been fruitless because of various problems. These include firstly those connected to the low efficiency of expression in man of FIX levels in plasma i.e. around 1%, hence not sufficient to correct the disease; those connected to the immunogenicity of treatment with viral vectors; finally those connected to the side effects of gene therapy itself which include hepatitis, myositis and others.

Id. at 2:33–40.

The Specification further indicates that variants with increased FIX activity are known in the art. *Id.* at 2:52–67. In particular, the Specification cites WO 99/03496 (Stafford) as disclosing a "recombinant FIX arginine 338 alanine mutant which resulted in a gain-of-function whose activity levels are 2-3 folds higher than that found in wild type FIX." *Id.* at 2:60–64. However, the Specification asserts, there is no evidence of in vivo human testing of "modified recombinant FIX with gain-of-function for the prophylaxis and treatment of patients affected by haemophilia," or "tests conducted in vivo in man with administrations of modified recombinant FIX which show the absence of side effects." *Id.* at 3:1–13.

The '180 patent further discloses Factor IX variants, viral vectors comprising the nucleotide sequence for modified FIX polypeptides, and their use in gene therapy for the treatment of hemophilia B. *See generally, id.* at 2:20–26, 22:23–24:20. With respect to Factor IX variants, the '180 patent discloses Factor IX polypeptides wherein the arginine ("R") that normally occurs at position 338 of mature factor IX is replaced by another amino acid

such as leucine (L), aspartic acid (D), or glutamine (Q). *See e.g., id.* at Abstract (listing nine amino acid substitutions), 15:60–18:36 (Examples with R338 substituted with leucine ("R338L")), 18:39–19:46 (Example with R338 substituted with aspartic acid ("R338D")), 19:48–21:9 (Examples with R338 substituted with glutamine "R338Q")).

In Example 14, the '180 patent summarizes the results of testing R338L, R338D, and R338Q substitution variants. *Id.* at 21:9–22:22. The Specification states that the R338L variant "shows 8 to 9 folds increased functional activity as compared to" wild-type Factor IX and, in light of its "efficiency and yield" is "the best choice for the use of FIX mutants in gene therapy by using viral vectors." *Id.* at 22:1–22.

F. The Challenged Claims

Petitioner challenges claims 1–6 of the '180 patent, of which only claim 1 is independent. Claim 1 recites:

> 1. An adeno-associated virus vector compromising:
>
> a. a nucleic acid encoding a modified FIX polypeptide, the modified FIX polypeptide comprising at least 70% identity to SEQ ID NO: 2 and a leucine in position 338 of SEQ ID NO: 2; and
>
> b. promoter sequences, transcription termination, and control elements.

Among the dependent claims, claim 2 recites "[a] pharmaceutical composition comprising the adeno-associated virus vector of claim 1," claim 3 recites "a modified FIX polypeptide identical to SEQ ID NO:2 except for the leucine at position 338," and claim 5 requires 70% homology with the exon regions of GenBank sequence K02402.

II. ANALYSIS

A. Legal Standards

"In an IPR, 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 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).

To anticipate a claim under 35 U.S.C. § 102, "a single prior art reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Grp., Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). That "single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002). A finding based on inherency "requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present" in the anticipating reference. *Trindec Indus., Inc. v. Top-USA Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002) (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). It is, however, "proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). Accordingly, the dispositive question is whether one skilled in the art would have reasonably understood or inferred from a prior art reference that every claim element is disclosed in that

reference. *Eli Lilly & Co. v. Los Angeles Biomedical Research Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017).

Regarding obviousness, the Supreme Court in *KSR International 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). The *KSR* Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and (4) considering objective evidence indicating obviousness or non-obviousness, if present. *KSR*, 550 U.S. at 406.

The Supreme Court made clear that we apply "an expansive and flexible approach" to the question of obviousness. *Id.* at 415. For example, "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *Id.* at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)). But in analyzing the obviousness of a combination of prior art elements, it can also be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *Id.* at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that

petitions the Board for a determination of unpatentability based on obviousness must show that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so. *In re Magnum Oil Tools International, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted). Under the proper inquiry, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

B. Level of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the "type of problems encountered in the art, [the] prior art solutions to those problems, [the] rapidity with which innovations are made, [the] sophistication of the technology, and the educational level of active workers in the field." *See Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *see also Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

Petitioner argues a person of ordinary skill in the art at the time of the invention "can possess the skills and experience of multiple individuals working together as a team" and that "[r]esearch teams working to develop protein variants for gene therapy generally included at least (i) one or more clinicians or clinical researchers with experience in gene therapy, working together with (ii) one or more individuals with experience in protein engineering." Pet. 14–15 (citing Ex. 1094 ¶ 19; Ex. 1003 ¶¶ 47–49). According to Petitioner, a person of ordinary skill in the art, therefore,

"would have had at least the relevant skills of those team members, in addition to knowledge of the literature concerning protein structure generally, factor IX in particular, and gene therapy." *Id.* at 15.

Patent Owner argues that a person of ordinary skill "has the skills of a person or team of persons with at least three years of experience studying the treatment of coagulopathy, as well as at least three years of experience in protein engineering or gene therapy." PO Resp. 13.

In our Decision on Institution, although we agreed with Patent Owner that the ordinarily skilled artisan would have experience in the treatment of coagulopathy, we applied a broader definition of a person of ordinary skill in the art, as articulated by Drs. Wang and Pedersen. *See* DI 11 (citing Ex. 1003 ¶ 48; Ex. 1094 ¶ 19). We determined a person of ordinary skill in the art would have the skill of a research team working to develop factor IX variants and gene therapies, where that team would include "(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; and where the individuals working on the team have an advanced degree and several years of experience in a relevant discipline. *See id.*

Patent Owner states its positions on patentability of the challenged claims "would not change under that construction or Petitioner's proposed definition ...." PO Resp. 13. Accordingly, we apply the definition of a person of ordinary skill in the art set forth *supra* and in our Decision on Institution.

C. Claim Construction

We apply 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). Under that standard, the "words of a claim 'are generally given their ordinary and customary meaning,'" which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). "In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17).

In the Petition, Petitioner proposed constructions for five terms: "vector," "percentage identity," "promoter," and "percentage homology," and "polypeptide precursor." Pet. 12–14. In our Decision on Institution, we determined that we did not need to explicitly construe any claim terms at that stage of the proceeding. DI 12.

Patent Owner "does not believe any term requires construction for this proceeding." PO Resp. 13. Considering the arguments and evidence of record, we agree with Patent Owner and apply the plain and ordinary meaning to all claim terms. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("we 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))).

D. Overview of Asserted References

1) Stafford (Exhibit 1004)

Stafford is titled "Factor IX Antihemophilic Factor with Increased Clotting Activity" and relates to "Factor IX containing a mutation that enhances the clotting activity thereof" and "DNA constructs encoding such Factor IX, along with vectors containing such constructs." Ex. 1004 at [54], 1:18–21. Stafford discloses a non-naturally occurring Factor IX protein having an amino acid substitution at amino acid position 338 in which the naturally-occurring arginine is substituted with one of 10 possible amino acids. In particular, Stafford states that "[s]ubstitutions 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." *Id.* at 5:8–11; *see also id.* at claims 1–2, 8–9.

Stafford further narrows this list to three preferred embodiments, stating that, "[i]n 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. *Id.* at 5:11–14. These preferred embodiments are expressly recited in Stafford's claims 3–5 (directed to alanine, leucine, and/or valine Factor IX protein variants); claim 10 (methods of facilitating blood clotting using the preferred variants); claim 14 (isolated nucleic acids encoding the preferred variants); and claim 17 (expression cassettes containing nucleic acids encoding the preferred variants).

Stafford appears to still further narrow its selection to two preferred embodiments by specifically claiming a mammalian Factor IX in which

arginine at position 338 is substituted with either alanine or leucine (R338A and R338L, respectively). *Id.* at claims 4, 5. In particular, Stafford discloses:

> 4. A mammalian Factor IX according to claim 1, wherein said substitution is a substitution of an arginine residue for an alanine residue.
>
> 5. A mammalian Factor IX according to claim 1, wherein said substitution is a substitution of an arginine residue for a leucine residue.

Id. As discussed below, Stafford discloses actual embodiments relating to the R338A substitution of claim 4.

According to Stafford, Factor IX molecules within the scope of its "invention advantageously have increased clotting activity as compared to the corresponding wild-type molecule," and "preferably have two or three [ ] more coagulant activity than the corresponding wild type or plasma FIX." *Id.* at 2, 5–6. In a set of in vitro experiments involving the recombinant Factor IX having a substitution of alanine for arginine at position 338, Stafford disclosed that the R338A polypeptide had 2–3 times greater clotting ability than wild-type Factor IX. *See e.g., id.* at 8 ("Examples"), 12–16 ("Results"); *see also id*. at Sequence Listing Sheets 1–10 (disclosing nucleic acid and encoded R338A variant polypeptide as SEQ ID NOs: 1 and 2, respectively).

Stafford defines a vector as "a replicable DNA or RNA construct," which "typically comprise plasmids, viruses (*e.g.,* papillomavirus, adenovirus, adeno-associated virus, cytomegalovirus), phage, retroviruses and integratable DNA fragments." *Id.* at 7. Stafford further defines an expression vector as "a replicable nucleic acid construct in which a nucleic acid sequence encoding the protein of the invention is operably linked to suitable control sequences capable of effecting the expression of proteins of

the invention in a suitable host." *Id.* at 6. According to Stafford, these control sequences generally comprise "a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation." *Id.* at 6–7.

Stafford further discloses vectors that "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; *see also id.* at 3 ("A third aspect of the present invention is a method of facilitating blood clotting in a subject in need of such treatment, comprising administering to the subject a mammalian Factor IX protein as described above, in an amount sufficient to facilitate or enhance blood clotting in said patient.").

2) Manno (Exhibit 1017)

Manno is directed to the "successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response." Ex. 1017, Title (capitalization normalized). By way of background, Manno discloses that prior administration of a recombinant adeno-associated viral vector (rAAV) expressing wild-type Factor IX "to skeletal muscle of individuals with severe hemophilia B was safe, but circulating levels were generally not sufficient to improve disease phenotype." *Id.* at 342. By contrast, Manno reports that studies showing "a single portal vein infusion of a recombinant adeno-associated viral vector (rAAV) expressing canine Factor IX (F.IX) resulted in long-term expression of therapeutic levels of F.IX in dogs with severe hemophilia B1." *Id.* at Abstract.

"Based on the safety studies of rAAV-F.IX delivered to muscle in humans and the efficacy studies of rAAV-F.IX delivered to liver in dogs with severe hemophilia B, [Manno] undertook an open-label, dose-escalation study of rAAV-F.IX . . . delivered through the hepatic artery in humans with severe hemophilia B." *Id.* at 342. The AAV-based expression cassette used in Manno's study is illustrated in Figure 1a, reproduced below:

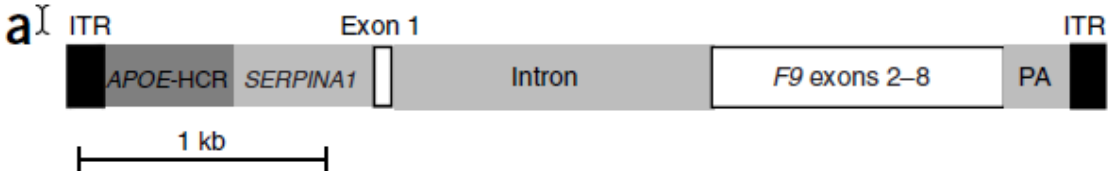

Figure 1a is a schematic of Manno's rAAV-F.IX expression cassette showing regions encoding wild-type Factor IX polypeptide and various control elements including an *APOE* enhancer (*APOE*-HCR), a human α1-antitrypsin promoter (*SERPINA-1*), and polyadenylation signal (PA)—all of which are flanked by a pair of AAV inverted terminal repeat sequences (ITRs). *Id.* at 343.

Manno's study involved seven subjects, including Subject E, who "reported an absence of any bleeding episodes" for 10 weeks of follow-up and required "no infusion of clotting factor, despite trauma which would ordinarily have required factor infusion." *Id.* Manno further reports:

> i) vector infusion at doses up to 2 x 10^{12} vg/kg was not associated with acute or long-lasting toxicity; (ii) therapeutic levels of F.IX were achieved at the highest dose tested; (iii) duration of expression at therapeutic levels was limited to a period of ~8 weeks; (iv) a gradual decline in F.IX was accompanied by a transient asymptomatic elevation of liver transaminases that resolved without treatment.

Id. at Abstract.

Summarizing the results of the study, Manno states that, "rAAV-2 vectors can transduce human hepatocytes *in vivo* to result in therapeutically relevant levels of FIX," however, "in contrast to long-lasting expression in hemophilic dogs and nonhuman primates, expression at therapeutic levels in humans was short lived." *Id.* Manno hypothesizes that "the difference in outcome of AAV-mediated gene transfer to liver in humans compared to experimental animals," derives from stimulation of AAV-specific memory T cells in human subjects. *Id.* at 346. In particular, Manno suggests that because humans are naturally infected with AAV-2 in childhood, exposure to AAV-based vectors triggers the cellular immune response against AAV capsid protein, resulting in the elimination of hepatic cells transduced with the AAV-based vector. *Id.* Noting that the capsid is required only for delivery of the Factor IX gene, and "present only transiently in the transduced cell," Manno suggests that administration of a "short-term immunomodulatory regimen that blocks the response to capsid until these sequences are completely cleared from the rAAV-2–transduced cells may permit long-term expression of the donated gene." *Id.*

3) Schuettrumpf (Exhibit 1005)

Schuettrumpf, titled "Factor IX variants improve gene therapy efficacy for hemophilia B," discloses that, "[i]ntramuscular injection of adeno-associated viral (AAV) vector to skeletal muscle of humans with hemophilia B is safe, but higher doses are required to achieve therapeutic factor IX (F.IX) levels." Ex. 1005, Abstract. Accordingly, "it is fundamental to develop strategies that improve gene transfer efficacy without simply increasing the vector dose." *Id.* at 2316.

Noting that "[p]revious studies demonstrated that the substitution R338A in the F.IX catalytic domain resulted in a molecule with 3-fold higher specific activity than F.IX–wild type (WT)," Schuettrumpf "constructed AAV vectors encoding F.IX variants for muscle- or liver directed expression in hemophilia B mice." *Id.* at 2316, Abstract; *see also id.* at 2318, Figure 1 (illustrating design of rAAV-based expression cassettes). Among these, Schuettrumpf reports that "variant F.IX-R338A generates a protein with 2- or 6-fold higher specific activity than F.IX-WT, when delivered to skeletal muscle or liver, respectively." *Id.* at 2316. Moreover, the "muscle-synthesized F.IX variants presented correction of the hemophilia B phenotype upon in vivo challenges by tail-clipping assay." *Id.* at 2322. "Importantly, intramuscular injection of AAV-F.IX variants does not trigger antibody formation to F.IX in mice tolerant to F.IX-WT." *Id.*; *see also id.* at Abstract (similar).

Schuettrumpf concludes: "These studies demonstrate that [ ] F.IX variants is an attractive alternative to improve phenotypic correction of hemophilia B." *Id.* at 2317 "In the development of a gene-based therapy for the treatment of hemophilia, the use of clotting factors with advantageous biologic properties, as demonstrated here, offers an attractive alternative to enhance the efficacy of several distinct strategies to treat hemophilia B." *Id.*

E. Ground 1: Anticipation by Stafford

In Ground 1, Petitioner contends that claims 1–6 are unpatentable for anticipation by Stafford. Pet. 25–41; Reply 5–9. In support, Petitioner details where in Stafford each limitation of claims 1–6 is disclosed. *See e.g.,* Pet. 28–39 (citing Ex. 1004; 1, 3–5, 8, 9, 21, 22, 28–34 (SEQ ID NO:1), 28–37 (SEQ ID NO:2), claims 18, 19). Patent Owner opposes. PO Resp. 15–39;

Sur-reply 5–16. Patent Owner argues claims 1–6 together, and separately argues the "pharmaceutical composition" element of claim 2. *See* PO Resp.; Sur-reply 16.

1) Claim 1 (and dependent claims 3–6)

Petitioner contends that Stafford discloses all elements of claim 1 including: a nucleic acid sequence encoding a Factor IX variant in which the arginine at position 338 of the mature polypeptide is replaced with leucine (Pet. 29–31 (citing, e.g., Ex. 1004, claims 1, 5, 11, 14); the use of AVV viral vectors to produce recombinant Factor IX for the treatment of hemophilia (*id.* at 28–29 (citing, e.g., Ex. 1004, 9); and suitable "promoter sequences, transcription termination elements, and control elements . . . in as much, if not greater detail than the '180 patent" (*id.* at 31–32 (citing, e.g., Ex. 1004, 8–9; Ex. 1003 ¶ 319)).

Addressing claim 1, in particular, Patent Owner contends that Ground 1 fails because Stafford does not disclose the identified limitations as arranged in the claims, nor permit one of ordinary skill to "at once envisage" the claimed combinations and, further, that Stafford is not enabled. PO Resp. 15–37.

Patent Owner first argues that Stafford discloses only one complete example. PO Resp. 18. In this respect, Patent Owner cites Stafford's disclosure that: "We have found ***one*** mutation, R338A-FIX, whose clotting activity is two and one half to three times that of wild type FIX," based on *in vitro* study of man-made FIX-R338A produced using a plasmid." *Id.* (citing Ex. 1004, 10–11). With respect to any other combination, Patent Owner contends that one of ordinary skill in the art would have to choose from "menus of exemplary, but unrelated options," comprising ten non-naturally

occurring mutations at position 338, eight possible vectors, and two uses for constructs based on those vectors (recombinant protein production for replacement therapy or gene therapy). *See id.* at 18–19. Given the scope of Stafford's disclosure, Patent Owner contends that the ordinarily skilled artisan "would need to pick and choose from Stafford's lists, with hundreds of combinations" to arrive at the claimed invention. Sur-reply 5. We do not find Patent Owner's arguments persuasive.

With respect to the selection of leucine at position 338, we note that Stafford discloses FIX-R338L as one of two or three preferred variants disclosed and individually claimed, and as having "increased clotting activity as compared to the corresponding wild-type molecule" for treating hemophilia B. Ex. 1004, 2, 7. Stafford expressly states for example that, "[i]n 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." *Id.* 7. Stafford's claims similarly disclose the same three preferred variants: claims 3–5 are directed to a mammalian Factor IX having a substitution of R338 for alanine, leucine, or valine; claim 10 to method of facilitating blood clotting using mammalian Factor IX having a substitution of R338 for alanine, leucine, or valine; claim 14 to isolated nucleic acids encoding mammalian Factor IX having a substitution of R338 for alanine, leucine, or valine; and claim 17 to an expression cassette containing nucleic acids encoding mammalian Factor IX having a substitution of R338 for alanine, leucine, or valine. And as further discussed in Section II.D.1, above, Stafford further narrows these embodiments to R338A and R338L by specifically identifying mammalian Factor IX having those substitutions in claims 4 and 5, respectively.

Patent Owner also argues that one of ordinary skill in the art reading Stafford would not envisage the claimed invention because each amino acid in Stafford has different properties. *See* PO Resp. 22–26 (citing e.g., *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381-83 (Fed. Cir. 2015). Given Stafford's focus on the limited class of two or three preferred substitutions at R338—at most, alanine, leucine, and valine—we agree with Petitioner that Patent Owner's reliance on *Kennametal* is inapposite. *See* Reply 6. Moreover, and despite Patent Owner's extensive discussion of potential ways to categorize Stafford's preferred substitutions, the '180 patent itself discloses that alanine, leucine, and valine were known to reflect conservative (aliphatic) substitutions. Ex. 1002, 4:43–59. The '180 patent explains that

> It is expected that substitutions between these homologous amino acids would not change the phenotype of the proteins (conservative amino acid substitutions). Specific examples of conservative substitutions are known in this technical field and are described in the various literature (e.g., Bowie et al., Science, 247:1306–1310 (1990).

Id. at 4:53–59; *see also*; Ex. 1094 ¶¶ 41–45 (Dr. Pederson's testimony that one of ordinary skill in the art would have considered alanine and leucine functionally similar, and used "groupings of amino acid structures to make small-scale, qualitative predictions about the effect of swapping one amino acid for another on protein structure or inter-protein interactions, and therefore function"); Ex. 1100 ¶¶ 23–36.

With respect to the selection of vectors, Patent Owner argues that: "In one sentence [Stafford] states vectors 'may be' used for gene therapy, though the replicable vectors it defines are inappropriate for that purpose."

PO Resp. 16 (citing Ex. 1004, 7; Ex. 2102 ¶¶ 89–91); Sur-reply 7. Stafford discloses that

> control sequences are operably associated with a nucleic acid to be expressed on a common nucleic acid to provide a recombinant expression cassette (on a nucleic acid molecule) which is carried by the vector into the target cell of interest. . . . **Vectors typically comprise** plasmids, viruses *(e.g.,* papillomavirus, adenovirus, **adeno-associated virus**, cytomegalovirus), phage, retroviruses and integratable DNA fragments. **The vectors** 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.**

Ex. 1004, 7 (emphasis added).

Although Patent Owner minimizes Stafford's disclosure of gene therapy, Stafford's larger focus on protein replacement therapy does not negate its teaching of gene therapy; Stafford is relevant "for all that it teaches." *In re Mouttet*, 686 F.3d 1322, 1331 (Fed. Cir. 2012). As such, and considering the record as a whole, we credit Dr. Wang's testimony that one of ordinary skill in the art "reading Stafford would have envisaged AAV-R338L as a combination to use in gene therapy, not protein replacement therapy." Ex. 1100 ¶ 29.

Pointing to Stafford's statement that "[a] vector is a replicable DNA or RNA construct," Patent Owner further extends its "common properties" argument to the vectors described in Stafford. PO Resp. 26–27; Ex. 1004, 8. According to Patent Owner,

> Stafford defines: "[a] vector is a replicable DNA or RNA construct" (Ex. 1004, 8), which is DNA or RNA that self-replicates, i.e., makes copies of itself. POR 32-33; Ex. 2102, ¶94. The replicable vectors disclosed and exemplified in Stafford are intended for amplification and expression in vitro.

> Ex. 1004, 8-9. These DNA constructs differ from AAV particles (recombinant AAV genomes packaged in capsid proteins). Ex. 2147, 33:4-34:3 ("recombinant AAV viral vector produced contains the AAV viral genome and the AAV capsid.").

Sur-reply 11 (citing Ex. 1004, 6).

In short, we do not read the statement that "[a] vector is [] replicable" to exclude Stafford's expressly disclosed AAV vectors for gene therapy. As an initial matter, we credit Dr. Wang's testimony that AAV was the most commonly used vector for gene therapy as of the date of the invention and "were being used routinely in the hemophilia B field." *See* Ex. 1003 ¶¶ 39, 88, 323; Ex. 1100 ¶¶ 15, 95–97); *see* also Ex. 2102 ¶ 88 (Dr. Doering discussing the widespread interest in AAV vectors); Ex. 1043,[7] 5–6, 8, 64–69 (reviewing the use of AAV vectors for gene therapy including for treatment of Factor IX deficiency). Given that Stafford expressly discloses that "[v]ectors typically comprise . . . adeno-associated virus" and, ***in the next sentence***, states that "[t]he vectors . . . may be used in gene therapy to . . . produce the Factor IX in the patient," we find Patent Owner's interpretation implausible. *See* Ex. 1004, 7.

Patent Owner's argument is also unavailing for the reasons set forth at pages 7–8 of Petitioner's Reply. As articulated by Petitioner:

> PO confuses whether a vector is *replicable in vitro—i.e.*, whether it is capable of being replicated, which is necessary to manufacture it—with whether a vector is *self-replicable in vivo*. *E.g.*, Ex. 2102, ¶94 (equating "replicable" with "self-

[7] "*Adeno-Associated Viral Vectors for Gene Therapy*," and "*Gene therapy for hemophilia*," in LABORATORY TECHNIQUES IN BIOCHEMISTRY AND MOLECULAR BIOLOGY, Chapters 1 and 3, (Flotte & Berns, eds. 2005) ("Flotte and Berns").

> replicate"). Stafford points to the vector AAV, which the POSA would recognize must be replicated as part of manufacture; however, the POSA would further recognize that AAV is not self-replicating, even when it has rep and cap genes, as it requires another virus (a helper virus) in order to replicate. Ex. 1100, ¶¶51-59, 198; Ex. 2114, 147:12-148:22; Ex. 1035, 16; Ex. 1040, 2.

Id.

Patent Owner further argues that Ground 1 fails because Stafford does not enable the claimed invention. PO Resp. 31–39; Sur-reply 13–15. Patent Owner contends that given the unpredictability of expression and activity, Stafford provides insufficient guidance or working examples to produce the claimed vector absent undue experimentation. PO Resp. 31–37; Sur-reply 13–15. Patent Owner's argument is premised on construction that the challenged claims incorporate certain functional limitations—i.e., that the claimed "vector is used to introduce a nucleic acid into a cell for "***expression,***" includes a promoter that "***controls (activates) the transcription***" of the nucleotide sequence," and "is capable of instructing target cells to ***express*** the FIX-R338L protein." PO Resp. 32–33 (citing Ex. 1002, 5:8:11, 5:24-26; Ex. 1003, ¶¶ 64–65). But the challenged claims are product claims generally directed to an adeno-associated virus vector containing a nucleic acid encoding FIX-R338L and do not recite functional limitations. Patent Owner's arguments merely attempt to import intended use limitations into a product claim, and are unavailing for the reasons set forth at pages 8–9 of the Reply.

Contrary to Patent Owner's assertions, the record provides adequate indications that Stafford is enabling. Stafford discloses the use of vectors, including those derived from adeno-associated virus, for "use[] in gene

therapy to administer the expression cassette to targetted [sic] cells within the patient and produce the Factor IX in the patient." *See* Ex. 1004, 6–7; Ex. 1003 ¶ 346. These AAV vectors were well-known, and had been programmed to produce wild-type Factor IX in animal models and clinical trials. Ex. 1003 ¶¶ 345 (citing e.g., Ex. 1005; Ex. 1017; Ex. 1012; Ex. 1017). Stafford discloses Factor IX amino acid and nucleotide sequences having leucine at position 338, and notes that "[t]he production of cloned genes, isolated DNA, recombinant DNA, vectors, transformed host cells, proteins and protein fragments of the present invention may be carried out by well known genetic engineering techniques." Ex. 1004, 6:16–20 (citations omitted), SEQ ID Nos: 1, 2; Ex. 1003 ¶ 65.

To the extent Stafford does not exemplify the nucleotide sequence of the leucine variant, it was well within the skill of the POSA to create a nucleotide sequence that encoded a specified protein sequence. Ex. 1004, 7, 11 (discussing the introduction of missense mutations using site-directed mutagenesis and other methods for introducing mutations "as is known in the art"); Ex. 1003 ¶¶ 37–38; Ex. 1094 ¶¶ 69, 93–94, 105; *In re Wallach*, 378 F.3d 1330, 1334 (Fed. Cir. 2004) (it is a "routine matter" to convert between sequence of protein and sequence of nucleotide encoding it). Accordingly, to be enabling with respect to the claims at issue here, Stafford need not have actually made or tested a nucleotide sequence encoding the R338L variant—it is sufficient for Stafford to disclose it, because making it would have been well within the skill of one of ordinary skill in the art. *See* Ex. 1094 ¶¶ 38–39, 69, 76, 80, 93, 94, 97, 101; *see also* Ex. 1003 ¶¶ 342–347 (Dr. Wang's discussion of enablement); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368. 1379 (Fed. Cir. 2001) ("although he

did not actually premedicate the patients himself, anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art."); *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985) ("It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement."). Accordingly, and considering the entirety of the record, we do not find Patent Owner's enablement argument availing.

In sum, Stafford discloses (and claims) preferred Factor IX variants for the treatment of hemophilia B, wherein arginine 338 is replaced with, at most, one of three amino acids having similar properties: alanine, leucine, or valine. Ex. 1004, 5, claims 3–5, 10, 14; Ex. 1094 ¶ 104. Stafford further discloses vectors and associated control elements that "may be used in gene therapy to administer the expression cassette to targeted [sic] cells within the patient and produce the Factor IX in the patient." Ex. 1004, 6–7. In addition to listing various general classes of potential expression vectors, Stafford specifically names four DNA-based viruses including AAV for the construction of vectors: "papillomavirus, adenovirus, adeno-associated virus, [and] cytomegalovirus." *Id.*; Ex. 1003 ¶¶ 41, 77–78, 315.

Because Stafford's claims 15 and 17–19 describe a DNA viral vector encoding a FIX variant (of which Stafford names four), and because Stafford specifies three (if not two) preferred amino acid variants, "a POSA would have faced twelve possible combinations of DNA vector and preferred FIX variant for gene therapy." *See* Ex. 1003 ¶¶ 321–323.[8] Moreover, crediting

[8] As previously noted, Dr. Wang misstates, in part, the dependency of Stafford's claims. *See* DI 27 (citing Ex. 1003 ¶ 323). Although Stafford's

Dr. Wang's testimony that, as of the time of the invention, "AAV vectors were considered the leading candidate for useful human gene therapy vectors, and were being used routinely in the hemophilia B field" (Ex. 1003 ¶ 39; *see also id.* at ¶¶ 32–36, 88, 323), we find that one of ordinary skill in the art would read Stafford as disclosing all elements of claim 1, "arranged as in the claim." *See Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008).

As noted above, Patent Owner does not separately argue dependent claims 3–6. We have reviewed Petitioner's evidence and argument, and agree with Petitioner that Stafford discloses all limitations of claims 3–6.

In view of the argument and evidence of record, Petitioner has shown by a preponderance of the evidence that claims 1 and 3–6 are unpatentable as anticipated by Stafford.

2) Claim 2

Claim 2 recites "[a] pharmaceutical composition comprising the adeno-associated virus vector of claim 1." Patent Owner further contends that claim 2 is not anticipated because Petitioner has failed to establish that Stafford discloses a pharmaceutical composition for gene therapy. PO Resp. 37–39 (citing Ex. 2102 ¶¶ 756–757); Sur-reply 16. According to Patent Owner, despite disclosing pharmaceutical compositions comprising mammalian Factor IV ***protein***, "Stafford does not disclose a pharmaceutical composition comprising a ***vector***." *Id.* at 38 (emphasis modified).

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preferred variants are expressly recited in connection with the expression cassette of claim 17, Stafford's claim 19—directed to a DNA-based gene transfer vector—more broadly recites "mammalian Factor IX protein having an amino acid substitution at amino acid position 338."

Petitioner appears to argue that Stafford inherently discloses the pharmaceutical composition limitation of claim 2. *See* Pet. 32–34; Reply 9. Relying on the testimony of Dr. Wang, Petitioner argues that Stafford discloses the administration of a pharmaceutical composition of claim 2 because Stafford discloses administering AAV vectors to patients, Ex. 1004, 9, and the POSA would understand that such vectors must be administered in a pharmaceutical composition, Pet. 34; Ex. 1003, ¶¶ 324–325, 347; *see* Ex. 1100, ¶¶ 212–213.

Petitioner has the better argument. "In an anticipation analysis, the dispositive question is whether a skilled artisan would "reasonably understand or infer" from a prior art reference that every claim limitation is disclosed in that single reference. Expert testimony may shed light on what a skilled artisan would reasonably understand or infer from a prior art reference. *Acoustic Tech., Inc. v. Itron Networked Sols., Inc.*, 949 F.3d 1366, 1373 (Fed. Cir. 2020) (internal citation omitted).

Considering the argument and evidence adduced at trial, including the high level of skill in the art and the testimony of the parties' experts, we find that because Stafford discloses administering the vector of claim 1 to patients, one of ordinary skill would have immediately recognized that the vector would necessarily be administered in a pharmaceutical composition, as recited in claim 2.[9] Accordingly, Petitioner has shown by a preponderance of the evidence that claim 2 is unpatentable as anticipated by Stafford.

[9] To the extent Stafford does not inherently disclose the pharmaceutical composition of claim 2, the evidence of record makes clear that one of ordinary skill in the art would find this element obvious under Grounds 2 and 3. *See e.g.*, Ex. 1003 ¶¶ 324–328, 347, 355–360, 387–338.

F. Grounds 2 and 3: Obviousness in view of Stafford or further in view of Manno and Schuettrumpf

Petitioner contends that claims 1–6 are invalid as obvious in view of Stafford (Ground 2), and further in view of Manno and Scheuttrumpf (Ground 3). Pet. 41–58; Reply 10–25. In support, and with reference to its arguments for Ground 1, Petitioner details where in Stafford each limitation of claims 1–6 is disclosed. *See e.g.,* Pet. 43–49, 53–58. Patent Owner opposes. PO Resp. 39–63; Sur-reply 16–27. Because the parties' arguments with respect to Grounds 2 and 3 are somewhat overlapping and intertwined, we addressed them in the same section. And as Patent Owner does not separately address the dependent claims, we focus on independent claim 1.

1) Objective Indicia of Nonobviousness

We make our determination of patentability based on the entirety of the evidence before us, both for and against obviousness. Notwithstanding what the teachings of the prior art would have suggested to a person of ordinary skill in the art, objective evidence of non-obviousness may lead to a conclusion that the challenged claims would not have been obvious. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Objective evidence of non-obviousness "may often be the most probative and cogent evidence in the record" and "may often establish that an invention appearing to have been obvious in light of the prior art was not." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)). Such evidence, however, does not necessarily control the obviousness conclusion. *See, e.g., Pfizer, Inc.,* 480 F.3d at 1372 (Fed. Cir. 2007). ("Here, the record establishes such a strong case of

obviousness that Pfizer's alleged unexpectedly superior results are ultimately insufficient.").

Patent Owner alleges there is evidence of record supporting the objective indicia of nonobviousness of long-felt need, praise and copying by others, and unexpected results. PO Resp. 55–63. We consider Patent Owner's proffered evidence below.

For us to give substantial weight to objective indicia of obviousness or nonobviousness, a patentee must establish a nexus between the evidence and the merits of the claimed invention. *ClassCo, Inc., v. Apple, Inc.*, 838 F.3d 1214, 1220 (Fed. Cir. 2016). Patent Owner bears the burden of establishing that a nexus exists between the objective evidence and the claimed invention. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). Nexus is a legally and factually sufficient connection between the objective evidence and the claimed invention, such that the objective evidence should be considered in determining non-obviousness. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). "A nexus may not exist where, for example, the merits of the claimed invention were 'readily available in the prior art.'" *ClassCo,* 838 F.3d at 1220 (quoting *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983)). Further, "there is no nexus unless the evidence presented is 'reasonably commensurate with the scope of the claims.'" *Id.* (quoting *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013)).

A patentee is entitled to a presumption of nexus "when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'embodies the claimed features, and is coextensive with them.'" *Fox Factory*, 944 F.3d at 1373 (quoting *Polaris Indus., Inc. v. Arctic Cat,*

Inc., 882 F.3d 1056, 1072 (Fed. Cir. 2018)). "[I]f the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). Coextensive "mean[s] that the product is the invention disclosed and claimed. . . . A product is essentially the claimed invention when, for example, the unclaimed features amount to nothing more than additional insignificant features." *Campbell Soup Co. v. Gamon Plus, Inc.*, 10 F.4th 1268, 1276–77 (Fed. Cir. 2021) (emphasis and internal quotations omitted, citation omitted). Recently, the Federal Circuit indicated that *Fox Factory's* "coextensiveness" requirement is the same as the "commensurate in scope" standard regarding the "presumption of nexus." Specifically, the court held that "the Board determined that Zaxcom's evidence of industry praise and long-felt need was entitled to *a presumption of nexus*, *noting that these indicia were commensurate in scope with the claims as now narrowed*, . . . a determination that comports with the legal standards for a presumption." *Zaxcom, Inc. v. Lectrosonics, Inc.*, 2022 WL 499843, at *2 (Fed. Cir. Feb. 18, 2022) (published only in Westlaw) (citing *Fox Factory,* 944 F.3d at 1373). "Ultimately, the fact finder must weigh the [objective indicia] evidence presented in the context of whether the claimed invention as a whole would have been obvious to a skilled artisan." *See Lectrosonics, Inc. v. Zaxcom, Inc.*, IPR2018-01129, Paper 33 at 33 (PTAB Jan. 24, 2020) (precedential) (citing *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1331–32 (Fed. Cir. 2016)).

Patent Owner relies on objective evidence of "(1) long-felt need for an effective gene therapy for hemophilia B and failure of others; (2) industry praise and copying; and (3) unexpectedly superior efficacy" (PO Resp. 55), and argues the objective evidence is tied to "the novelty of the claims," i.e., AAV-FIX-R338L. *Id*. at 63 (citing Ex. 2102 ¶ 870); Tr. 55:13–24. As to long-felt need, Patent Owner asserts that the named inventor's identification of the Factor IX "Padua variant" (the FIX-R338L mutation identified in Padua, Italy) was a "game-changer" for hemophilia gene therapy because it permitted the development of "a vector to be used in safe and efficacious gene therapy of hemophilia B," that "allow[ed] 'for higher FIX expression levels, and thus potentially safer, vector doses.'" PO Resp. 12, 58 (citing Ex. 2002, 14–15).

Patent Owner asserts that treatment with lower doses minimized the risk of cellular immune responses. *See* Ex. 2103, 505; Ex. 2102 ¶¶ 860–862. Patent Owner asserts that industry adoption, including ongoing clinical trials of AAV-FIX-R338L by Petitioner, Patent Owner, and a third party, is evidence of satisfying the long-felt need. PO Resp. 59–60 (citing Ex. 2102 ¶¶ 862, 865; Ex. 2002, 1; Ex. 2077, 34). Patent Owner argues that "positive results from ongoing clinical trials—in contrast to discontinuing Manno's trial" confirm long-felt need. Sur-reply 25–26 (citing Ex. 1017, 7; Ex. 2102 ¶¶ 421–24; Ex. 2079).

Addressing "Praise of and Copying by Others," Patent Owner asserts that scientific papers referring to FIX-R338L as the "Padua" variant widely recognize the invention of the '180 patent, and credit the named inventor, Dr. Simioni, with discovery of FIX-R338L. PO Resp. 59–61 (citing Ex. 2002; Ex. 2015; Ex. 2026; Ex. 2032; Ex. 2039; Ex. 2077; Ex. 2081;

Ex. 2102 ¶¶ 863–866; Ex. 2105; Ex. 2115; Ex. 2122. Despite its reliance on copying as an objective indicia Patent Owner focuses on industry praise and does not identify any specific evidence of copying beyond adoption of the "Padua" designation. (*see e.g.,* PO Resp. 61 (citing Ex. 2102 ¶ 866); Sur-reply 26.

As to unexpected results, Patent Owner argues FIX-R338L is not the closest prior art and that it "need not establish unexpected results compared to AAV-FIX-R338L." PO Resp. 62 (citing Ex. 2102 ¶ 869); *see also* PO Sur-reply 26–27 (asserting that, in the prior art, "the only mutant with data (apart from those causing hemophilia) was FIX-R338A"). Patent Owner asserts that the 9-fold increased activity of FIX-R338L as compared to wild-type FIX was surprising because, according to Dr. Pedersen, a person of ordinary skill in the art "would have expected R338A and R338L to have ***similar*** activity." PO Resp. at 61 (citing Ex. 1001, 21:15–17, 21:24–30; Ex. 2102 ¶¶ 867–868; Ex. 2101 ¶¶ 145–51; Ex. 2130, 102:4–9; Ex. 1094 ¶ 104). Yet, Patent Owner asserts, Stafford taught R338A is only 2–3 fold more active and Schuettrumpf taught 2–6 fold more activity than wild-type FIX. *Id.* Petitioner argues that Patent Owner cannot provide evidence of nexus because the asserted novelty of the challenged claims—and, moreover, gene therapy using the R338L variant to treat hemophilia B—was in the prior art. Pet. 50 (citing *Merck & Cie v. Gnosis S.P.A*, 808 F.3d at 837 (Fed. Cir. 2015)); Reply 21.

Petitioner argues that Patent Owner's evidence of unexpected results is similarly directed to FIX-R338L itself and, thus, also lacks nexus. Reply. 24 (citing Ex. 1100 ¶¶ 253–254). Petitioner similarly argues that Patent Owner does not show coextensiveness, because the references it relies upon

as showing praise for its clinical candidate, AMT-061, focus on praise for FIX-R338L itself, which is in the prior art and, indeed, claimed and disclosed in Stafford as a preferred embodiment. Pet. 50–51; *see* Section II.D.1, above. Summarizing its position at oral argument, Petitioner's counsel stated that, "the fact that the leucine variant [R338L] may now commonly be referred to as Padua doesn't somehow erase or negate the disclosure in Stafford of the leucine variant itself." Tr. 26:23–27:11. Patent Owner takes the position that, "Petitioner cannot circumvent non-obviousness evidence by circularly arguing no objective indicia are possible because the claimed invention was in the prior art." PO Resp. 63.

Petitioner further argues Patent Owner's "clinical candidate AMT-061 cannot provide evidence of objective indicia," because it is not coextensive with the challenged claims and "because it reflects the implementation of Stafford's disclosure rather than a distinction from it." Pet. 50 (citing Ex. 1003 ¶¶ 304–08). Specifically, Petitioner asserts "AMT-061 uses a specific AAV capsid (AAV5), while the claims cover the use of *any* AAV capsid"— "of which there are 'thousands more.'" *Id.* (citing Ex. 1003 ¶ 308); Reply 23 (citing Ex. 1095, 180:14–181:6); *see also* Reply 22 (noting that "the Challenged Claims permit any promoter, and Dr. Doering estimated that there are 'at least 10,000 promoters' Ex. 1002, 30:15–31:11"). Moreover, Petitioner contends, claims 1, 2 and 4–6 "permit a massive number of changes to FIX—as little as 70% identity. But PO's evidence is limited to a single change, R338L, and for that reason as well is nowhere near reasonably commensurate with the claims." Reply 22. Responding to these arguments, Patent Owner argues that the objective evidence is commensurate with the claims because, although the claims encompass

"multiple AAV types and FIX sequences, the claim combinations that are ***functional*** vectors or variants for gene therapy." Sur-reply 25; *see also* PO Resp. 54 (citing Ex. 2102 ¶ 830–835).

We find that Patent Owner's evidence of long-felt need and failure of others, industry praise, and unexpectedly superior efficacy is not coextensive or commensurate in scope with the challenged claims. As to long-felt need, Patent Owner's evidence appears to praise the R338L variant as the "game-changing" aspect, and not AAV-FIX-R338L as a whole. *See* Ex. 2002, 14 ("The improvement in vector performance in this recent clinical trial can be ascribed mainly to the use of a modified FIX transgene encoding a hyperactive mutant FIX protein containing just a single point-mutation (i.e., R338L)."); Ex. 1095, 276:6–278:1. Dr. Wang, for example, points to an article describing "the R338L variant as '[a] Game-Changer for Hemophilia Gene Therapy,'" but explains that the "'game-changer language' . . . referred to the R338L variant itself." Ex. 1003 ¶ 401 (citing Ex. 1048[10], 1).

Further, Patent Owner's evidence notes that different outcomes between AAV trials incorporating FIX-R338L-Padua may be due to differences in vector configuration, expression cassette design, promoter used, and the capsid itself. Ex. 2002, 15 ("As is often the case in gene therapy, the devil is in the details, and an apparent subtle change in vector design and/or manufacturing could potentially yield divergent results in patients."). Moreover, Patent Owner's clinical candidate, AMT-061, includes a specific AAV, i.e., rAAV5, which is not used in the other clinical candidates. *See id.* (comparing rAAV5 to AAV8-FIX-R338L-Padua and

[10] VandenDriessche & Chuah, *Hyperactive Factor IX Padua: A Game-Changer for Hemophilia Gene Therapy*, 26 Molecular Therapy 14 (2018).

AAV-Spark100). The challenged claims are not limited to the specific AAV in AMT-061, and therefore, Patent Owner's objective evidence is not commensurate in scope with the claims.

As to industry praise, we agree with Petitioner that the praise in the references Patent Owner relies on was primarily directed to FIX-R338L, which is not commensurate with the challenged claims. Further, Petitioner has shown that FIX-R338L was already known in the prior art as discussed *infra* II.D.1 and II.E. Because FIX-R338L—and its predicted improved activity—was known in the prior art, it cannot be the basis for finding a nexus with the claimed invention; this is settled law and not a circular argument as Patent Owner contends. *See ClassCo,* 838 F.3d at 1220. Patent Owner's evidence of unexpected results is also directed to FIX-R338L and lacks nexus for the same reason. Further, Patent Owner's argument that wild-type FIX is the closest prior art for the purpose of comparing unexpected results is unsupported and, thus, not persuasive. *See* Ex. 1102, 130:7–16. Patent Owner's assertion of 9-fold increased activity with FIX-R338L compared to wild-type FIX, versus 6-fold increased activity with R338A as described in Schuettrumpf, is also unpersuasive because the 9-fold results are from a recombinant study as described in the '248 patent (*see* Ex. 1102, 132:8–133:13), while Schuettrumpf's are from a gene therapy study in mice. Ex. 1005, Abstract. Lacking a head-to-head comparison, or other means of normalizing the results, Patent Owner's evidence does not outweigh Dr. Pedersen's testimony that a person of ordinary skill would have expected R338A and R338L to have similar activity. *See* Ex. 1094 ¶ 104; Ex. 2130, 102:4–9.

Accordingly, Patent Owner has failed to show that it is entitled to a presumption of a nexus between the objective evidence and the claimed invention. Citing *Polaris*, Patent Owner argues that it "need not rely a presumption of nexus." PO Resp. 63. Although Patent Owner does not fully explain its position, we note that the court in *Fox Factory* instructs that, "[a] finding that a presumption of nexus is inappropriate does not end the inquiry into secondary considerations"; rather, "the patent owner is still afforded an opportunity to prove nexus by showing that the evidence of secondary considerations is the 'direct result of the unique characteristics of the claimed invention.'" *Fox Factory*, 994 F.3d at 1374 (quoting *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996)). Patent Owner here, however, presents insufficient evidence to establish a nexus by this alternative route. Patent Owner does not present argument as to the "unique characteristics" of the claimed invention, or provide evidence to support such an analysis. In addition, as discussed above, Patent Owner's evidence is broadly directed to FIX-R338L, which was in the prior art and does not suggest non-obviousness of the claimed invention as a whole.

In summary, Patent Owner does not meet its burden to show a presumption of nexus or show a nexus to the alleged long-felt need for an effective gene therapy for hemophilia B, industry praise, and unexpectedly superior efficacy of AAV-FIX-R338L. Weighing the evidence and arguments presented, we determine that even if there is some nexus, it is weak. *See Merck*, 808 F.3d at 837 (Where objective indicia "result[ ] from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention."). The failure to show a nexus undermines Patent Owner's contentions regarding objective indicia.

With these determinations in mind, we turn to the evidence and argument regarding the remaining *Graham* factors in evaluating Petitioner's obviousness contentions as to the challenged claims.

2) The Parties' Arguments

According to Petitioner, one of ordinary skill in the art would have found it obvious to construct the vector described in claim 1 because, as discussed in the context of Ground 1, Stafford discloses all limitations of the claim "including an AAV vector encoding the improved-clotting R338L variant." *See* Pet. 41–45 (citing e.g., Ex. 1003 ¶¶ 33–35, 105, 319, 325, 326, 334–336, 350–370; Ex. 1094 ¶¶ 38, 39, 76, 86–90, 97, 104, 105). Petitioner further contends that one of ordinary skill in the art would have been

> motivated to use Stafford's preferred, improved clotting variants such as the R338L variant in an AAV vector, and to use that vector for gene therapy for the treatment of hemophilia B. EX1003, ¶¶ 351-53. As of the priority date, the POSA would have been aware of gene therapy trials using AAV vectors for the treatment of hemophilia B, and would have been motivated to use pro-coagulant variants such as the R338L variant to provide improved efficacy. *Id.*, ¶ 354.

Id. at 41. Petitioner further points to Stafford's teaching that its claimed nucleic acids can be placed into expression cassettes, which can in turn be placed into gene transfer vectors, and that such vectors include adeno-associated virus. *Id.* at 44 (citing Ex. 1003 ¶ 351); *see, e.g.*, Ex. 1004, 7:4–13, claims 17–19. According to Petitioner, one of ordinary skill in the art "would have been motivated to create such a vector to transduce the nucleic acid of claim 1 into patient's cells in gene therapy . . . [and t]his motivation would have been especially strong in light of the available literature and clinical trials for hemophilia B gene therapy, which used AAV

vectors." *Id.* (citing Ex. 1004, 9; Ex. 1003 ¶ 34–35, 351; Ex. 1017; Ex. 1018; Ex. 1020, 4).

With respect to a reasonable expectation of success, Petitioner asserts that "[i]t would have been routine to modify Stafford's nucleic acid of SEQ ID NO:1 encoding the R338A variant to encode a leucine at position 338," and constructing the claimed nucleic acid was well within the ordinary skill in the art as of the time of the invention. *Id.* at 43–44 (citing Ex. 1004, 5, 28–29; Ex. 1094 ¶ 38–39, 105; Ex. 1003 ¶ 354). Noting that AAV vectors encoding for FIX had been used in various prior art studies, Petitioner contends that the ordinarily skilled artisan "would have been familiar with how to construct such vectors." *Id.* at 45 (citing Ex. 1003 ¶¶ 34–35, 346, 354; Ex. 1094 ¶¶ 38–39, 105).

For Ground 3, Petitioner points to Manno and Schuettrumpf as additional support for its position that one of ordinary skill in the art would have been motivated to prepare AAV vectors encoding Stafford's R338L variant with a reasonable expectation of success. Pet. 51–58; Reply 10–20. Briefly, Petitioner asserts that "Manno reports a successful hemophilia B gene therapy clinical trial using an AAV vector encoding the wild-type FIX protein, but also observed a dose-dependent immune response to the AAV2 capsid that limited the duration of efficacy." Pet. 51 (citing Ex. 1017, 1). In light of Manno, Petitioner contends that one of ordinary skill in the art "would have been motivated to improve upon the results in Manno by using the more active R338L variant." *Id.* (citing Ex. 1003 ¶¶ 372–733).

Petitioner further points to Schuettrumpf's demonstration that AAV vectors encoding FIX R338A "resulted in FIX proteins that had 6-times greater specific activity than wild-type FIX when administered via liver-

directed gene therapy," and the reference's conclusion that "F.IX variants provide a promising strategy to improve the efficacy for a variety of gene-based therapies for hemophilia B." *Id.* at 52 (citing Ex. 1005, 1; Ex. 1003 ¶ 372). According to Petitioner, Schuettrumpf thus "provides additional support for the notion that the POSA would have been motivated to prepare AAV vectors encoding Stafford's R338L variant and use them in gene therapy to treat a coagulopathy, with a reasonable expectation of success." *Id.*

In response, Patent Owner first argues that Ground 2 and 3 fail because Stafford is not enabled (PO Resp. 39, 51)—a contention we reject in Section II.E.1, above.

Patent Owner further argues that Petitioner has failed to show sufficient motivation to arrive at the claimed invention with a reasonable expectation of success. PO Resp. 39–61.

Patent Owner contends one of ordinary skill in the art would not have been motivated to pursue an AAV vector encoding FIX-R338L based on Stafford's general focus on protein manufacture and a "single sentence referenced to gene therapy [which] provides no direction, and no expectation that a specific vector with a specific mutant would work." PO Resp. 40; *see id.* at 41–42 (citing Ex. 1004, 7–8, 18, 20, claims 1–8, 21–22); Ex. 2114, 56:20–57:6; Ex. 2102 ¶¶ 772–807. According to Patent Owner, "Stafford has broad aspirational language surrounding a single example: FIX-R338A produced using a plasmid *in vitro*," and "at most would have motivated study of FIX-R338A." *Id.* at 39–40. Patent Owner argues that the only testing data in Stafford and other prior art references was based on FIX-R338A. *Id.* at 40 (citing Ex. 1004, 11–12; Ex. 1003 ¶121; Ex. 2041;

Ex. 1005; Ex. 1012; Ex. 2114, 87:16–88:3, 90:18–91:8; Ex. 1005, 1; Ex. 2093, 479; Ex. 2084, 1772. As we understand Patent Owner's argument, given the art's focus on R338A and the purported expectation that R338L would have had "similar activity," one of ordinary skill in the art would not have been motivated to pursue an untested variant such as R338L. *See id.* at 40–41 (further citing Ex. 2102 ¶¶ 769–771; Ex. 2130, 102:4–9, 102:16–103:14; Pet. 16–17); Sur-reply 18–19; *see also* Ex. 2130 ¶ 768 (Dr. Doering's testimony that if one of ordinary skill in the art "assumed that a leucine substitution would have had similar or the same activity as FIXR338A . . .[they] would not have been motivated to pursue FIX-R338L, and particularly not in an untested vector in the complex field of gene therapy.").

Patent Owner further argues that one of ordinary skill in the art would not have had a reasonable expectation of success because "[e]very other known mutation in FIX helix 330–338 caused hemophilia due to reduced expression, reduced activity, or both."[11] PO Resp. 42 (citing Ex. 1004, 8, 19; Ex. 1009, 2; Ex. 2029, 4054–4057; Ex. 2102 ¶¶ 82–95, 115–132; Ex. 2102 ¶¶ 327–339, 763–782); Sur-reply 19–23. In support of this contention, Patent Owner argues that alanine and leucine have different structures and, absent data, one of ordinary skill in the art "would have had concerns that a large, surface-exposed hydrophobic amino acid like leucine could make the

[11] To the extent Patent Owner directs this argument to reasonable expectation of success as opposed to motivation, we note in section II.E.1, above, that the challenged claims are product claims that do not incorporate certain functional limitations as implied by Patent Owner. As such, obviousness only requires that the skilled artisan would have had motivation and a reasonable expectation of success in constructing the claimed vectors.

protein unstable and poorly expressed, and reduce solubility, possibly leading to aggregation." PO Resp. 43–44 (citing, Ex. 2102 ¶¶ 62, 85–86, 135; Ex. 2102 ¶¶ 787–807; Ex. 2108, 73); Sur-reply 20–22.

With respect to Ground 3, Patent Owner further argues that Manno provides no motivation to arrive at the claimed invention because it "did not evidence safe and effective treatment" and "to the extent Manno motivated a POSA to 'improve upon its results, it would have motivated study of wildtype-FIX" and the investigation of an immunosuppression regime rather than the R338L variant for there was no prior art data. PO. Resp. 52–53 (citing e.g., Ex. 1017, 5; Ex. 1033, 9; Ex. 2102 ¶¶ 825–835, 839–850; Ex. 2126, 27; Ex. 2124, 80; Ex. 2020, 1); Sur-reply 17, 23–24; Ex. 1017, 343, 346 (Manno proposing the addition of "a short-term immuno-modulatory regimen that blocks the response to capsid" to "permit long-term expression of the donated gene").

Patent Owner also argues that rather than provide an independent motivation to arrive at the claimed variant with a reasonable expectation of success, the addition of Schuettrumpf "at most confirms a POSA's motivation to pursue FIX-R338A." PO Resp. 54 (citing Ex. 2102 ¶¶ 98–99, 836–850; Ex. 1005, 1).

3) Analysis

For essentially the same reasons discussed in Section II.E, above, with respect to Ground 1, we do not find Patent Owner's arguments persuasive. In short, Stafford discloses FIX-R338L as one of only three preferred variants—and moreover, one of only two variants individually claimed—having "increased clotting activity as compared to the corresponding wild-type molecule" for treating hemophilia B. Ex. 1004, 1,

4, 20, claims 3–5, 10, 14, 17. Stafford's focus on two individually claimed variants, R338A and R338L, and its statement that "the present invention is primarily contemplated to be for the treatment of human subjects" do not support Patent Owner's contention that a person of ordinary skill would construct hundreds of separate combinations based on Stafford's disclosure. *See id.* at 6, claims 3–4.

We also disagree with Patent Owner's assertion that Stafford does not disclose AAV as a vector for gene therapy. Stafford in fact connects its disclosures of AAV and gene therapy; they appear in adjacent sentences. Ex. 1004, 9:9–14. We also find persuasive Dr. Wang's testimony that a person of ordinary skill reading Stafford would have recognized that in hemophilia B treatment, AAV is used for gene therapy, not protein replacement therapy. Ex. 1100 ¶ 29. Although Patent Owner minimizes Stafford's disclosure of gene therapy, Stafford's teaching of protein replacement therapy does not negate its teaching of gene therapy; a person of ordinary skill in the art would have considered Stafford "for all that it teaches." *See In re Mouttet*, 686 F.3d 1331.

One of ordinary skill in the art reading Stafford would also have found the use of AAV vectors obvious as evidenced by Dr. Wang's testimony that AAV was the most common vector for hemophilia B gene therapy. S*ee* Ex. 1003 ¶¶ 39, 88, 323; Ex. 1100 ¶¶ 15, 201, 218–220. The testimony of Dr. Doering and the prior art review of Flotte and Burns similarly underscore the prior art focus on AAV vectors in gene therapy. *See* Ex. 2102 ¶ 88; Ex. 1043. This further supports Petitioner's contention that a person of ordinary skill in the art would have found it obvious to combine one of Stafford's most preferred variants, R338L, with an AAV vector as

recited in the challenged claims. In sum, considering the record as a whole, we agree with Dr. Wang's testimony that one of ordinary skill in the art would have found the challenged claims obvious in view of Stafford. Ex. 1003 ¶¶ 348–370.

We also do not find persuasive Patent Owner's argument that a person of ordinary skill in the art reading Stafford would have had serious concerns regarding whether R338L would be expressed. As discussed above, Stafford discloses successful expression of R338A *in vitro*. As Dr. Wang explains, given that Stafford demonstrated in vitro expression for numerous other variants in the 330–338 helix region of FIX, only R338P showed reduced expression, and unlike leucine, "proline [P] is a known 'helix breaker.'" Ex. 1004, 14–15; Ex. 1100 ¶¶ 113–116, 225; *see also* Ex. 1100 ¶¶ 117–121. As such, we agree with Dr. Wang that one of ordinary skill in the art would not have expected difficulties in the expression of R338L.

We also find unavailing Patent Owner's argument that a person of ordinary skill would not have expected *in vivo* expression of FIX-R338L at levels similar to that of wild-type FIX. To the contrary, Schuettrumpf supports a conclusion that a person of ordinary skill would have expected that gene therapy with FIX-R338A expressed *in vivo* from liver cells at levels similar to wild-type FIX. *See* Reply 13 (citing Ex. 1005, 2, 4; Ex. 2114, 53:13–55:14; Ex. 1100 ¶¶ 113–116, 225). As Dr. Wang testified, this would have suggested to a person of ordinary skill that FIX-R338L would express at a similar level. Ex. 2114, 53:13–55:14; Ex. 1100 ¶¶ 113–16; *see also* Ex. 1001, 4:45–58 ('180 patent's teaching that it was expected that conservative amino acid substitutions (e.g. alanine and leucine) "would not change phenotype of the proteins").

We do not find persuasive Patent Owner's argument that a person of ordinary skill in the art reading Stafford would have had serious concerns regarding whether R338L would be active. To the contrary, we credit Dr. Wang's testimony that one of ordinary skill in the art would have expected the R338L variant to exhibit higher activity than wild-type Fix based, for example, on Stafford and Schuettrumpf showing that R338A exhibited higher activity in vitro and in vivo, respectively, and the similarities between alanine and leucine. *See,* e.g., Ex. 1003 ¶¶ 40, 42, 158, 219, 383, Ex. 1100 ¶¶ 101–112; *see also* Ex. 1094 ¶¶ 41–45, Ex. 1100 ¶¶ 23–36 (Dr. Pederson's explanation of why one of ordinary skill would have expected replacing arginine 338 with leucine would have a similar effect as replacing it with alanine).

Stafford's disclosure that numerous mutations in the FIX 330–337 region cause severe hemophilia due to loss of FIX activity (Ex. 1004, 19:16–20) also does not support Patent Owner's argument. In particular, Patent Owner's experts do not persuasively explain why the risk of severe hemophilia from single amino acid substitutions at positions 330–337 would be predictive of a similar risk at position 338. *See* Ex. 1100 ¶¶ 115–119; Ex. 1101 ¶¶ 48–51. Indeed, Patent Owner's argument is undercut by Stafford's (and Schuettrumpf's) teaching that the alanine variant at position 338 exhibited *increased* activity as compared to wild-type. Patent Owner's surface-exposure argument is also undercut by Petitioner's evidence that the 330–338 region of wild-type FIX contains *two* solvent-exposed leucines.

Reply 13 (citing Ex. 1004, 19; Ex. 1101 ¶ 41);[12] *see also* Reply 17 (citing Ex. 1004, 9; Ex. 1101 ¶ 58 (noting that the 330-338 helix is stabilized by a disulfide bond). In any event, a finding of obviousness does not require absolute certainty and some level of unpredictability in the art cannot defeat a showing of a reasonable expectation of success. *See, e.g.*, *Pfizer, Inc.,* 480 F.3d at 1364 ("the expectation of success need only be reasonable, not absolute.").

Patent Owner's selective use of Schuettrumpf as evidence that a person of ordinary skill would have been motivated to study FIX-R338A rather than FIX-R338L, fails to credit Schuettrumpf's broader teaching. *See* Ex. 1003 ¶ 220. In particular, Schuettrumpf discloses that "F.IX variants provide a promising strategy to improve the efficacy for a variety of gene-based therapies for hemophilia B," a teaching similarly reflected in its title: "Factor IX variants improve gene therapy efficacy for hemophilia B." Ex. 1005, 1. We find more persuasive Dr. Wang's opinion that Schuettrumpf's disclosure of R338A's high activity levels would have further motivated a person of ordinary skill "to prepare AAV vectors that encode for the R338L variant based on the results of the hemophilia B gene therapy trial disclosed in Manno." Ex. 1003 ¶¶ 372–373; *see also* Ex. 1094 ¶ 104 (Dr. Pedersen's testimony regarding similarities between the R338L and R338A variants).

We also do not find persuasive Patent Owner's argument that one of ordinary skill in the art would have had no motivation to modify

[12] We also find no credible support for Patent Owner's aggregation/ solubility argument, and accord little weight to this speculative theory. *See* Reply 17 (citing Ex. 1103, 78:15–18, 80:8–15; Ex. 1101 ¶ 60).

Schuettrumpf's FIX-R338A construct to express R338L because they would expect the two variants to have "similar activity." *See* PO Resp. 40–41; Sur-reply 18–19. The prior art need not suggest that the component recited in a claim would have been the *best* option in order to make it an obvious choice. *See In re Mouttet*, 686 F.3d at 1334 ("[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.").

Patent Owner's argument that Manno's trials present a "catch-22" between safety and lack of efficacy, and that Dr. Wang fails to explain why a person of ordinary skill would have expected sufficient expression of FIX-R338L based on Manno, does not fairly characterize the record. *See* Sur-reply 1–2. Patent Owner's argument is based on Dr. Wang's 2005 publication referring to preliminary report of Manno's testing,[13] and Patent Owner's focus on the preliminary report's finding of "no gene transfer" at low dose using an AAV2 vector. Ex. 2138, 1. Following publication of the full results in Manno, Dr. Wang explains that, as of the effective filing date of the '180 patent, a person of ordinary skill in the art would have been motivated to use the higher activity R338L variant of Stafford in order to lower the dose and decrease the immune response reported by Manno. Ex. 1100 ¶¶ 136–137; *see also id.* ¶¶ 137–139 (Dr. Wang's testimony that one of ordinary skill in the art would understand that lowering the dose would "decrease the immune reaction to" AAV capsids, and "[f]ollowing Manno's suggestion to use immunosuppression," a later clinical trial used steroids to address the anti-capsid immune response). Therefore, we are not

[13] Manno was published in 2006.

persuaded by Patent Owner's argument that Dr. Wang's opinion demonstrates hindsight.

4) Conclusion as to Grounds 2 and 3

Considering the arguments and evidence adduced at trial, including the limited weight afforded Patent Owner's evidence of objective indicia of non-obviousness, Petitioner has shown by a preponderance of the evidence that claim 1 is unpatentable as obvious in view of Stafford, or Stafford in view of Manno and Schuettrumpf. Patent Owner does not separately argue dependent claims 2–6. We have reviewed Petitioner's evidence and argument with respect to the dependent claims, and find that Petitioner has similarly shown that claims 2–6 would have been obvious in view of the cited references.

III. CONCLUSION

Petitioner has shown, by a preponderance of the evidence, that claims 1–6 are unpatentable under § 102 as anticipated by Stafford, or under § 103 as obvious in view of Stafford, with or without Manno and Scheuttrumpf[14] as summarized below:

[14] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this Decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

Claims	35 U.S.C. §	Reference(s)	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–6	102	Stafford	1–6	
1–6	103	Stafford	1–6	
1–6	103	Stafford, Manno, Schuettrumpf	1–6	
Overall Outcome			1–6	

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–6 of the '180 patent are held to be unpatentable; and

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

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