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Paper 50
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.

IPR2021-00926
Patent 9,982,248 B2

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

HEANEY, *Administrative Patent Judge*.

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

I. INTRODUCTION

Pfizer Inc. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 2, 4–6, 11–13, 17, and 18 of U.S. Patent No. 9,982,248 B2 (Ex. 1001, "the '248 patent"). Paper 1 ("Petition" or "Pet."). uniQure Biopharma B.V. ("Patent Owner") filed a Preliminary Response. Paper 13. Petitioner also filed a Notice Regarding Multiple Petitions. Paper 2. Patent Owner filed a Response to Petitioner's Notice Regarding Multiple Petitions. Paper 12. With the Board's authorization, Petitioner filed a Reply to Patent Owner's Preliminary Response and Patent Owner filed a Sur-reply to Petitioner's Reply. Paper 14; Paper 15. Taking into account the arguments presented in all of these papers, we determined the information presented in the Petition established that there was a reasonable likelihood that Petitioner would prevail in challenging at least one of claims 2, 4–6, 11–13, 17, and 18 of the '248 patent, and we instituted this *inter partes* review as to all challenged claims. Paper 16 ("Dec. on Inst.").

During the course of trial, Patent Owner filed a Patent Owner Response (Paper 33, "PO Resp."); Petitioner filed a Reply to the Patent Owner Response (Paper 38, "Pet. Reply"); Patent Owner filed a Sur-reply (Paper 44, "PO Sur-reply").

Petitioner filed declarations of Lee Pedersen Ph.D. (Ex. 1094) ("Pedersen Declaration") and Lili Wang Ph.D. (Ex. 1003) ("Wang Declaration") in support of the Petition. Petitioner also filed declarations of Dr. Wang (Ex. 1100) and Dr. Pedersen (Ex. 1101) with its Reply. Patent Owner filed declarations of Christopher Doering Ph.D. (Ex. 2102) and P. Clint Spiegel Ph.D. (Ex. 2101) with its Response. The parties also filed

transcripts of the depositions of Dr. Pedersen (Exs. 2130, 2146), Dr. Wang (Exs. 2114, 2147), Dr. Doering (Ex. 1102), and Dr. Spiegel (Ex.1103).

An oral hearing was held on August 18, 2022, and a transcript of the hearing is included in the record. Paper 49 ("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 2, 4–6, 11–13, 17, and 18 of the '248 patent. For the reasons discussed below, we hold that Petitioner has demonstrated by a preponderance of the evidence that claims 2, 4–6, 11–13, 17, and 18 are unpatentable.

A. 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 6.

B. Related Proceedings and Chain of Priority

Petitioner concurrently challenges a different set of claims of the '248 patent in IPR2021-00925 ("the '925 IPR"). Pet. 4; Paper 6. Petitioner previously challenged claims of related U.S. Patent No. 9,249,405 B2 ("the '405 patent") in IPR2020-00388 ("the '388 IPR"); that proceeding was terminated on March 25, 2021, upon Patent Owner's request for adverse judgment. *See* IPR2020-00388, Paper 52.

Petitioner also filed a petition seeking *inter partes* review of claims of U.S. Patent No. 10,465,180 ("the '180 patent"), which issued from application No. US 2018/0258413 Al, 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). Pet. 4; IPR2020-00928 ("the '928 IPR"), Paper 1. The '180, '248, and '405 patents share substantially the same specification.

Application No. 13/063,898 further claims priority to Italian Applications, filed May 6, 2009 and September 15, 2009 ("the Italian applications"). Ex. 1057, code [30]; Ex. 1010, 5; *see* Ex. 1001, code [30]. Petitioner asserts the '248 patent's earliest claimed priority date of September 15, 2008 applies to Grounds 1 and 2 of the Petition and does "not depend on any adjudication of priority." Pet. 12. Petitioner further asserts none of claims 2, 5, 6, 11–13, 17, and 18 can claim priority to an earlier application and "[a]s such, they only have priority to July 14, 2017, when the '070 application was filed." *Id.*

C. The '248 Patent

The '248 patent, titled "Factor IX Polypeptide Mutant, Its Uses and Method for Its Production," describes a modified Factor IX (FIX)[1] "polypeptide, a nucleotide sequence, a vector comprising said nucleotide sequence and a method for producing the modified FIX polypeptide." Ex. 1001, code [54], 1:25–28. FIX is a vitamin K-dependent glycoprotein, synthesized in the liver, and playing a fundamental role in the coagulation cascade. *Id.* at 1:35–39. A deficiency in FIX can cause a number of coagulation diseases (coagulopathies) including hemophilia B. *Id.* at

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

2:20–22. 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 1:61–2:6. 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 1:39–40, 2:6–14.

The Specification explains that patients with severe hemophilia B "present serious haemorrhagic manifestations which can be 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 2:32–36. According to the '248 patent:

> 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 2:37–44. The Specification further indicates that variants with increased FIX activity are known in the art. *Id.* at 2:56–64. 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 2:64–3:1. According to the Specification, however, there is no evidence of in vivo human testing with "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 3:13–17.

The '248 patent thus discloses preparation of viral vectors comprising a nucleotide sequence for a modified FIX polypeptide and their use in gene therapy for the treatment of hemophilia B. *Id.* at 21:59–63. 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. *See e.g., id.* at Abstract (listing nine amino acid substitutions), 15:53–18:19 (Examples with R338 substituted with leucine ("L")), 18:21–19:23 (Example with R338 substituted with Aspartic Acid ("D")), 19:53–21:52 (Examples with R338 substituted with Glutamine "Q")).

In Example 14, the '248 patent summarizes the results testing R338L, R338D, and R338Q substitution variants. *Id.* at 20:54–21:63. 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 21:46–47, 59–63.

D. The Challenged Claims

Petitioner challenges claims 2, 4–6, 11–13, 17, and 18 ("the challenged claims") of the '248 patent. Pet. 1. Claims 2, 4–6, 11–13, 17, and 18 depend from claim 1. Independent claim 1 is reproduced below:

> 1. A method of treating a coagulopathy in a human patient, comprising administering a vector to the human patient, wherein:
>
> a. the vector is an adeno-associated virus;
>
> b. the vector comprises 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

c. the vector comprises promoter sequences and transcription termination and control elements;

thereby treating the coagulopathy.

Ex. 1001, 45:20–30.

Claims 2 and 5 are illustrative of the subject matter of the challenged claims and are reproduced below:

> 2. The method of claim 1, wherein the modified FIX polypeptide is expressed in the human patient at a level of least five fold less than the level of wild-type FIX of SEQ ID NO: 2 in a healthy human lacking the coagulopathy.

Id. at 45:31–34.

> 5. The method of claim 1, wherein the adeno-associated virus vector is administered at a dose of 1 to 10^{14} particles per kilogram of patient weight.

Id. at 45:40–42.

E. Instituted Grounds of Unpatentability

We instituted *inter partes* review on the following grounds of unpatentability, which are all the grounds presented in the Petition. Pet. 11:

Ground	Challenged Claims	35 U.S.C.[2]	Reference(s)/Basis
1	2, 4–6, 11–13, 17, 18	§ 103	Stafford,[3] Manno[4]
2	2, 4–6, 11–13, 17, 18	§ 103	Stafford, Manno, Schuettrumpf,[5] Hasbrouck[6]
3	2, 5, 6, 11–13	§ 102(a)	Monahan[7]
4	2, 5, 6, 11–13, 17, 18	§ 103	Monahan

II. ANALYSIS

A. Level of Ordinary Skill in the Art

Factors pertinent to a determination of the level of ordinary skill in the art include: "(1) educational level of the inventor; (2) type of problems

[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 we determine the priority date of the challenged claims is the '248 patent's filing date of July 14, 2017 (*see infra* II.E), we apply the 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).

[6] Hasbrouck et al., *AAV-mediated gene transfer for the treatment of hemophilia B: problems and prospect*, 15 GENE THERAPY 870–75, Apr. 24, 2008 (Ex. 1020).

[7] Monahan et al., *Update on a phase 1/2 open-label trial of BAX335, an adeno-associated virus 8 (AAV8) vector-based gene therapy program for hemophilia B*, 13 INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS 87, 2015 (Ex. 1062).

encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of workers active in the field." *Envtl. Designs, Ltd. v. Union Oil Co*., 713 F.2d 693, 696–697 (Fed. Cir. 1983) (citing *Orthopedic Equip. Co. v. All Orthopedic Appliances, Inc.,* 707 F.2d 1376, 1381–82 (Fed. Cir. 1983)). Not all such factors may be present in every case, and one or more of these or other factors may predominate in a particular case. *Id.*

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* 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.

B. Claim Construction

Petitioner proposed construction of five terms: "vector," "treating," "percentage identity," "promoter," and "particles per kilogram." 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. *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))).

In its Response, Patent Owner states it "does not believe any term requires construction for this proceeding." PO Resp. 14. Petitioner, on the other hand, continues to argue that construction of the term "treating" is

necessary to resolve the parties' controversy. Pet. Reply 2. Petitioner contends the '248 patent defines "treat" or "treatment of a pathology" as

> "the prophylaxis and/or therapy and/or cure of this pathology. The term prophylaxis means advantageously to at least partially arrest the development of a potential disease and/or to prevent the worsening of symptoms or progression of a disease. Advantageously, the term therapy means a partial or total alleviation of the disease symptoms."

Pet. 13 (quoting Ex. 1001, 5:19–26). Petitioner further contends the '248 patent does not impose any requirements for the duration of therapeutic efficacy. *Id.* (citing Ex. 1003 ¶¶ 55–56). Having considered the parties' positions, we determine that construction of the term "treating a coagulopathy" may affect the analysis of Petitioner's asserted challenges and assist in resolving the controversy between the parties.

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, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303 at 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).

We agree with Petitioner that the '248 patent provides an express definition of "treat" and "treatment." The Specification states, "[i]n the present text the term 'treat' or 'treatment' of a pathology means the

prophylaxis and/or therapy and/or cure of this pathology." Ex. 1001, 5:19–21. This definition includes "cure" as a separate concept from therapy, and further provides that therapy includes "partial or total" alleviation of symptoms. *Id.* at 5:21–24. The '248 patent does not define or otherwise describe "treating a coagulopathy" as requiring any specific duration of therapeutic efficacy; therefore, a person of ordinary skill in the art would understand that partial alleviation of symptoms and a shorter duration of therapeutic efficacy is encompassed in "treating a coagulopathy" as recited in claim 1.

Claim 16, which depends from claim 1, supports a construction of "treating a coagulopathy" that does not require complete alleviation of symptoms or permanent therapeutic efficacy. Claim 16 recites the "modified FIX polypeptide is expressed at a level that reduces and/or prevents hemorrhages." Ex. 1001, 46:34–36. Because claim 16 depends from claim 1, this means that "treating a coagulopathy" as recited in claim 1 encompasses merely reducing hemorrhages, i.e., partial alleviation of symptoms.

Accordingly, based on the intrinsic evidence, including the express definition of the terms "treat" and "treatment," we construe "treating a coagulopathy" as prophylaxis and/or therapy and/or cure of the coagulopathy which includes partial alleviation of symptoms, for any duration of therapeutic efficacy. We determine that we need not explicitly construe any other claim terms.

C. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103 if "the differences between the subject matter sought to be patented 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. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). 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 ordinary skill in the art; and (4) when available, objective evidence indicating obviousness or non-obviousness, such as commercial success, long felt but unsolved needs, and failure of others. *Graham v. John Deere Co*., 383 U.S. 1, 17–18 (1966); *see KSR*, 550 U.S. at 407 ("While the sequence of these questions might be reordered in any particular case, the [Graham] factors continue to define the inquiry that controls.").

The Supreme Court made clear that we apply "an expansive and flexible approach" to the question of obviousness. *KSR*, 550 U.S. at 415. Whether a patent claiming the combination of prior art elements would have been obvious is determined by whether the improvement is more than the predictable use of prior art elements according to their established functions. *Id*. at 417. Reaching this conclusion, however, requires more than merely showing that the prior art includes separate references covering each separate limitation in a challenged claim. *Unigene Labs., Inc. v. Apotex, Inc*., 655 F.3d 1352, 1360 (Fed. Cir. 2011). Rather, obviousness additionally requires 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*.

D. Overview of the Prior Art

1. Stafford (Ex. 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 still further narrows its selection to two preferred embodiments by specifically claiming a mammalian Factor IX in which

arginine at position 338 is substituted with alanine (R338A) or with leucine (R338L). *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 the "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 2:24–29, 5:29–6:1. In a set of *in vitro* experiments involving the recombinant Factor IX having alanine at position 338 (i.e., R338A), Stafford disclosed that this polypeptide had 2–3 times greater clotting ability than wild-type Factor IX. *See e.g., id.* at 7, 16, 18.

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 7:9–12; *see also id.* at 3, Sequence Listing Sheets 1–10 (disclosing nucleic acid and encoded R338A variant polypeptide SEQ ID NOs:1 and 2, respectively).

2. Manno (Ex. 1017)

Manno is directed to "Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response." Ex. 1017 at 342. 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.* By contrast, Manno discloses 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:

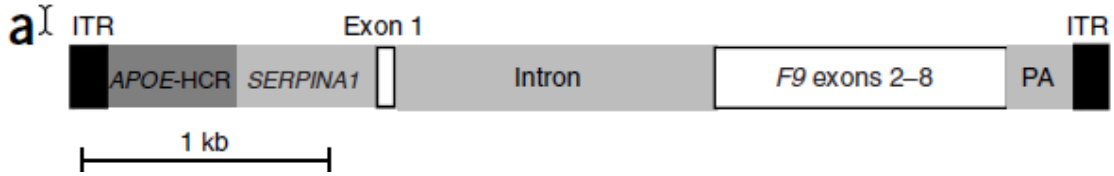

Figure 1a is a schematic of Manno's rAAV-F.IX expression cassette showing the encoding wild-type Factor IX polypeptide and various control elements including an *APOE* enhancer (*APOE*-HCR), a human α1-antitrypsin promoter (*SERPINA-1*), and polyadenylation signal (PA), all of which are flanked by AAV inverted terminal repeat sequences (ITR). *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.* at 343. 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 (Ex. 1005)

Schuettrumpf is titled "Factor IX variants improve gene therapy efficacy for hemophilia B" and 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 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.* at 2317; *see also* Abstract (similar).

Schuettrumpf concludes: "These studies demonstrate that F.IX variants is an attractive alternative to improve phenotypic correction of hemophilia B." *Id.* "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.* at 2322.

4. Hasbrouck (Ex. 1020)

Hasbrouck is titled "AAV-mediated gene transfer for the treatment of hemophilia B: problems and prospects" and discloses "two initial phase I/II AAV clinical trials for hemophilia B, delivering a factor IX cDNA to skeletal muscle or liver." Ex. 1020, Abstract. Hasbrouck discloses that "it is

clear that AAV-2 can transduce human hepatocytes and direct levels of expression adequate to treat hemophilia." *Id.* at 874. Hasbrouck further discloses that "a short course of immunosuppression will be added at the time of vector administration, to blunt the immune response to the transduced cells until the capsid is degraded and cleared from the cells." *Id.* at 873–74.

5. Monahan (Ex. 1062)

Monahan is titled "Update on a phase 1/2 open-label trail of BAX335, an adeno-associated virus 8 (AAV8) vector-based gene therapy program for hemophilia B" and discloses studies with "a gene therapy product BAX335 (AAV8.sc-TTRFIXR338Lopt): a codon optimized hyperactive FIX transgene (FIXR338Lopt), driven by the liver-specific transthyretin (TTR) promoter in an AAV8 capsid." Ex. 1062 at 87. Monahan discloses six subjects in the studies that are "dosed with BAX335: 2 at 2 x 10^{11} vg kg^{-1} (Cohort 1), 3 at 1 x 10^{12} vg kg^{-1} (Cohort 2), and 1 at 3 x 10^{12} vg kg^{-1} (Cohort 3), with follow-up ranging from 7 weeks to 2 years." *Id.* According to Monahan, "[t]herapeutic FIX levels of 3% were achieved in Cohort 1, sustained levels of 0.5 to 20% were observed 6 months post dosing in Cohort 2, and sustained levels above 25% were observed in Cohort 3." *Id.*

E. Grounds 3–4: Alleged Unpatentability Based on Monahan

Petitioner contends the claims challenged in these grounds, i.e., claims 2, 5, 6, 11–13, 17, and 18, cannot claim priority to any of the related applications that preceded the filing of the application for the '248 patent in July 2017. Pet. 53–58; *see supra* I.A. Petitioner further contends "Monahan was published in 2015" and therefore "is prior art under 35 U.S.C. § 102(b)(1) (AIA) to claims with a 2017 priority date." Pet. 21; *see also id.*

at 12 (arguing that "none of claims 2, 5, 6, 11–13, 17, or 18 can claim priority to an earlier application").

Patent Owner contends the claims challenged in these grounds properly claim priority to the '981 application and the '898 application, and therefore Monahan is not prior art. PO Resp. 49–57. Patent Owner does not contest, however, that if the challenged claims have a July 2017 priority date, then the claims are unpatentable under these grounds. *See generally* PO Resp. Further, Patent Owner does not offer objective evidence of nonobviousness premised on a July 2017 priority date. *Id.* at 58–66.

We address the evidence and arguments presented as to priority date for each of the challenged claims below.

1. Applicable Law

To be entitled to the filing date of an earlier provisional application, the earlier application must disclose the claimed invention "in the manner provided by § 112(a) (other than the requirement to disclose the best mode)." 35 U.S.C. §§ 119(e), 120. Section 112(a) requires that the specification contain a written description of the claimed invention. 35 U.S.C. § 112(a). "[T]he hallmark of written description is disclosure." *Ariad Pharm., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The written description requirement is met when the specification "conveys to those skilled in the art that the inventor had possession of" and "actually invented" the claimed subject matter. *Id*. The purpose of the written description requirement is to ensure that a patent's claims "do[] not overreach the scope of the inventor's contribution to the field of art as

described in the patent specification." *Reiffin v. Microsoft* Corp., 214 F.3d 1342, 1345 (Fed. Cir. 2000). The Federal Circuit has stated:

> The question is not whether a claimed invention is an obvious variant of that which is disclosed in the specification. Rather, a prior application itself must describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought.

Lockwood v. Am. Airlines, 107 F.3d 1565, 1572 (Fed. Cir. 1997).

2. Claims 2, 11, 12, 17, and 18

Petitioner contends the '981 and '898 applications do not provide written description support for the limitations directed to particular expression levels of the R338L variant present in each of these claims. Pet. 53–54. Specifically, Petitioner argues both the '981 and '898 applications "stated only that gene therapy has 'low efficiency of expression in man of FIX levels in plasma i.e., around 1%, hence not sufficient to correct the disease," and that neither application discloses any numerical level of expression nor how to obtain it. *Id.* at 54 (citing Ex. 1010, 17, 30; Ex. 1090, 12, 25; Ex. 1003 ¶¶ 227–28). Petitioner further asserts that the Examiner repeatedly noted during prosecution of the '898 application that the applicant never submitted English translations of the Italian applications, and thus could not rely on them for priority. *Id.* at 55 (citing Ex. 1010, 86, 128).

Patent Owner argues the '981 and '898 applications provide written description support because they explain that the "modified FIX polypeptides herein described" "show a gain-of-function of at least ***5 folds higher*** than that of the wild-type FIX molecule" (PO Resp. 51, citing Ex. 1090, 13), and a person of ordinary skill in the art would understand that

a FIX variant having five times the activity of the wild-type could be expressed at one-fifth the quantity of naturally occurring FIX to provide normal levels of FIX activity. *Id.* (citing Ex. 2102 ¶¶ 614–22). Patent Owner further argues a person of ordinary skill in the art would understand from the '981 and '898 applications that less than 100% expression of a hyperactive variant such as FIX-R338L would be desirable in order to avoid thrombotic events, and thus FIX-R338L "can be expressed at a level at least 5 fold less" than wild-type FIX. *Id.* at 52 (citing Ex. 1001, 2:45–55; Ex. 2102 ¶¶ 622–26).

Patent Owner's argument is not persuasive, because it does not address whether a person of ordinary skill in the art would have recognized that the named inventor had invented the claimed subject matter. At most, Patent Owner's assertion that a person of ordinary skill in the art would have *wanted* to have a lower level of expression than wild-type FIX, based on the level of activity of the variant disclosed in the '981 and '898 applications, would support an argument that the expression level would have been obvious. But, to satisfy the written description requirement, the disclosure needs to demonstrate recognition that the inventor was in possession of the invention. *See Lockwood*, 107 F.3d at 1572 ("[i]t is not sufficient for purposes of the written description requirement of §112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose."). Although something may be well known, "[o]bviousness simply is not enough; the subject matter must be disclosed to establish possession." *PowerOasis v. T-Mobile USA*, 522 F.3d 1299, 1310 (Fed. Cir. 2008).

Patent Owner also does not address Petitioner's assertion that the '981 and '898 applications are devoid of any gene therapy examples. *See* Pet. Reply 22 (citing Ex. 1100 ¶¶ 176–184). The absence of any example discussing gene therapy reinforces that the applications do not describe any level of expression. Even though specification disclosures are viewed from the perspective of one of ordinary skill in the art and written description support does not have to be *in haec verba*, nonetheless they must "reasonably convey[] to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co.,* 772 F.2d 1570, 1575 (Fed. Cir. 1985). Here, the '981 and '898 applications do not satisfy that requirement with respect to the limitations directed to particular expression levels of the R338L variant in the challenged claims.

3. Claims 5 and 6

Petitioner contends the '981 and '898 applications do not provide written description support for the limitations requiring administering a dose of adeno-associated virus ("AAV") vector in claims 5 and 6. Pet. 55–56. Petitioner argues that even assuming a person of ordinary skill in the art would understand the dosing described in the '981 and '898 applications as an appropriate dose amount of particles/kg, the applications only describe administering adenovirus, which is a different family of virus from AAV (adeno-*associated* virus). *Id.* at 56 (citing Ex. 1003 ¶¶ 36–39, 235–37; Ex. 1095, 52:14–22).

Patent Owner argues that a person of ordinary skill in the art would understand from the description of particles/kg dose range in the'981 and '898 applications "how many full particles/genome copies to provide during

gene therapy." PO Resp. 54. Patent Owner does not dispute that the'981 and '898 applications describe doses of adenovirus, not AAV, but essentially argues that the doses of adenovirus described in the '981 and '898 applications could be used for AAV because, like the AAV vector doses, they count full particles that contain the vector genome. *Id.* at 54. Patent Owner further argues that Petitioner's argument is inconsistent with Dr. Wang's testimony and her patent application, that describe AAV vector doses in genome copies (i.e., full particles) per kilogram. *Id.* at 54–55 (citing Ex. 1003 ¶ 68; Ex. 2015, 2).

Patent Owner's argument is not persuasive. Patent Owner focuses on the units of dosage of the vector, but does not address whether a person of ordinary skill in the art would understand that administering adenovirus vector as described in the '981 and '898 applications also describes administering AAV. Dr. Wang's testimony, on which Patent Owner relies, only relates to units of dosing AAV vector but not different types of viral vectors such as adenovirus. *See* Ex. 1003 ¶ 68. On the other hand, Dr. Wang's testimony that "[t]he appropriate dose of an adenovirus vector does not inform the appropriate dose of an AAV vector – even if the two vectors were carrying the same transgene" supports Petitioner's contention. *See* Ex. 1003 ¶ 235. Further, Dr. Doering agreed that adenovirus and AAV are different families of viruses, and testified that he would not try to establish dosing of an AAV by starting from adenovirus dosing values. Ex. 1095, 52:14–22, 66:19–22.

4. Claim 13

Petitioner contends the '981 and '898 applications do not provide written description support for claim 13's limitation "the modified FIX

polypeptide is expressed at a daily dosage between 0.1 μg/kg and 400 μg/kg body weight." Pet. 56–58. Petitioner argues that although the '898 and '981 applications disclose a daily dosage of polypeptide, a person of ordinary skill in the art would understand that the dosage is for protein replacement therapy, which "is wholly different from gene therapy." *Id.* at 57 (citing Ex. 1010, 34; Ex. 1090, 28; Ex. 1003 ¶¶ 231–32. Petitioner further argues that the '981 and '898 applications describe only doses of adenovirus (not AAV) that are administered to a human, rather than expressed in the human body as a result of administration. *Id.* at 57–58 (citing Ex. 1010, 35; Ex. 1090, 29; Ex. 1003 ¶¶ 235–37).

Patent Owner does not dispute that protein replacement therapy and gene therapy are different. PO Resp. 55. Patent Owner argues that despite this difference, protein replacement and gene therapy for hemophilia B share the common goal of restoring a patient's FIX activity levels, so that a person of ordinary skill in the art would have sought to achieve the dosage values in the claimed range and the '981 and '898 applications. *Id.* at 55–56 (citing Ex. 1001, 2:20–44; Ex. 1003 ¶ 209; Ex. 2102 ¶¶ 637–41). Patent Owner further argues that Dr. Wang's testimony that a person of ordinary skill in the art would have sought to achieve those dosage values is consistent with their written description argument. *Id.* (citing Ex. 1003 ¶ 209).

Patent Owner's argument is not persuasive. Patent Owner does not explain how sharing "a common goal" would be probative of a person of ordinary skill recognizing that protein replacement therapy, as described in the '981 and '898 applications, also describes the invention of gene therapy claimed in the'248 patent, and thus provide written description support. Further, Patent Owner's argument that Stafford's disclosure of replacement

therapy does not teach anything about gene therapy, in connection with its nonobviousness argument (*see infra* II.F.2), undermines its argument that protein replacement therapy provides written description support for gene therapy as claimed in the'248patent. As to Dr. Wang's obviousness opinion, we are not persuaded by Patent Owner's argument that it is probative of written description support because, on a legal basis, obviousness is not enough to establish written description. *See PowerOasis*, 522 F.3d at 1310.

5. Conclusion

We find that there is inadequate written description support for claims 2, 5, 6, 11–13, 17, and 18 in the '981 and '898 applications, so the priority date of those claims is the '248 patent's filing date of July 14, 2017. Accordingly, Monahan is prior art to those claims under §102(a). As discussed above, Patent Owner does not dispute that claims 2, 5, 6, 11–13, 17, and 18 are unpatentable in view of Monahan, under either ground 3 or 4 of the Petition. We have reviewed Petitioner's contentions and the full record and conclude that Petitioner has proven by a preponderance of the evidence that claims 2, 5, 6, and 11–13 are anticipated by Monahan, for the reasons provided by Petitioner. *See* Pet. 58–60. We also conclude that Petitioner has proven by a preponderance of the evidence that claims 2, 5, 6, 11–13, 17, and 18 would have been obvious over Monahan, for the reasons provided by Petitioner. *See id.* at 61.

F. Ground 1: Alleged Obviousness Based on Stafford and Manno

Petitioner argues claims 2, 4–6, 11–13, 17, and 18 would have been obvious over the combined teachings of Stafford and Manno. Pet. 27–52.

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. v. Apotex, Inc.* 480 F.3d 1348, 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. 58–65. We consider Patent Owner's proffered evidence below.

a) Nexus

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 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. 58), and argues the objective evidence is tied to "the novelty of the claims," i.e., gene therapy using AAV-FIX-R338L to treat hemophilia B. *Id*. at 65 (citing Ex. 2102 ¶ 672). As to long-felt need, Patent Owner asserts Factor IX Padua (the FIX-R338L mutation identified by the inventor) was a "game-changer" for hemophilia gene therapy that improved vector performance and "allow[ed] for higher FIX expression levels at lower, and thus potentially safer, vector doses." *Id.* at 61 (citing Ex. 2002, 14). Patent Owner asserts that treatment with lower doses minimized the risk of cellular immune

responses. *See* Ex. 2103, 505; Ex. 2102 ¶¶ 662–64. 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. 62 (citing Ex. 2102 ¶ 664).

As to industry praise and copying, Patent Owner asserts that scientific papers referring to FIX-R338L as the "Padua" variant widely recognize the invention of the '248 patent, and credit the named inventor, Dr. Simioni, with discovery of FIX-R338L. PO Resp. 62–63 (citing Ex. 2002; Ex. 2015; Ex. 2026; Ex. 2032; Ex. 2039; Ex. 2077; Ex. 2081; Ex. 2102 ¶¶ 665–68; Ex. 2105; Ex. 2115; Ex. 2122. Despite its reliance on copying as an objective indicia, Patent Owner does not identify any specific evidence of copying beyond the adoption of the "Padua" designation. *See* PO Resp. 63 (citing Ex. 2102 ¶ 668); PO Resp. *generally*. In this respect, Petitioner's counsel asserts: "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.

As to unexpected results, 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, but Stafford taught R-338A is only 2–3 fold more active and Schuettrumpf taught 2–6 fold more activity than wild-type FIX. *Id.* at 64 (citing Ex. 1001, 21:15–17, 21:24–30; Ex. 2102 ¶¶ 669–70; Ex. 2101 ¶¶ 145–51; Ex. 2130, 102:4–9; Ex. 1094 ¶ 104).

Petitioner argues that Patent Owner cannot provide evidence of nexus because the asserted novelty of the claims—gene therapy using the R338L

variant to treat hemophilia B—was in the prior art. Pet. 51 (citing *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015)); Pet. Reply 17–18 (citing Ex. 1004, 1). 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. 52 (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 or more.'" Pet. Reply 18 (citing Ex. 1095, 180:14–181:6); *see also id.* (noting that "the Challenged Claims permit any promoter, and Dr. Doering estimated that there are 'at least 10,000 promoters.'" (citing Ex. 1002, 30:15–31:11)). Moreover, Petitioner contends, all of the Challenged Claims "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." *Id*.

Petitioner also argues that Patent Owner does not show coextensiveness, because the references it relies upon as showing praise for AMT-061 focus on praise for FIX-R338L itself, which is in the prior art. *Id.* Similarly, Petitioner argues that Patent Owner's evidence of unexpected results is directed to FIX-R338L itself and thus lacks nexus. Pet. Reply. 20 (citing Ex. 1100 ¶¶ 253–54).

In response, Patent Owner argues that the objective evidence is commensurate with the claims because, although the claims encompass multiple AAV types and FIX sequences, the invention as a whole is directed to a combination that provides treatment of hemophilia B, "not non-

functional variants or vectors." PO Sur-Reply 22–23 (citing Ex. 1102, 26:9–27:4); *see also* PO Resp. 65 (citing Ex. 2102 ¶ 672). Patent Owner argues that Manno did not disclose hemophilia B gene therapy as Petitioner contends (PO Sur-Reply 23 (citing Ex. 1033, 9)) and that "positive results from ongoing clinical trials—in contrast to discontinuing Manno's trial" confirm long-felt need. *Id.* (citing Ex. 1017, 7; Ex. 2102 ¶¶ 421–24; Ex. 2079). 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. 65 (citing Ex. 2102 ¶ 671); *see also* PO Sur-Reply 24 (asserting that "the only mutant [in the prior art] with data (apart from those causing hemophilia) was FIX-R338A). Patent Owner further argues "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. 66.

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 claim 1.[8] 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. 1091, 276:6–278:1. Further, Patent Owner's evidence notes that different outcomes between AAV trials incorporating FIX-R338L-

[8] The recited subject matter of the dependent claims does not change the nexus determination here.

Padua may be due to differences in vector configuration, expression cassette design, promoter used, and the capsid itself. *Id.* at 15. 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* Ex. 2002, 15 (compare rAAV5 to AAV8-FIX-R338L-Padua and AAV-Spark100). Claim 1 is not limited to the specific AAV in AMT-061, and therefore, Patent Owner's objective evidence is not commensurate in scope with claim 1.

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 claim 1. Further, Petitioner has shown that FIX-R338L was already known in the prior art as discussed *infra* II.F.2. And, Patent Owner's argument that FIX-R338L was not in the prior art is inconsistent with the adverse judgment entered in the '388 IPR as to claims directed to gene therapy with FIX-R338L. Because FIX-R338L was available 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.

Patent Owner's argument that wild-type FIX is the closest prior art for the purpose of comparing unexpected results is not persuasive because it is unsupported (*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, 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* PO Resp. 64, citing 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. Patent Owner argues that it "need not rely on such presumption [of nexus]" under the *Polaris* and *Fox Factory* analysis. PO Resp. 66. Although Patent Owner does not fully explain its position, we note that *Fox Factory* provides, "[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)). Here, we find that Patent Owner 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. *See* PO Resp. 65–66; PO Sur-reply 22–24. 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 & Cie*, 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 is fatal to 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 each of the challenged claims.

2. Claim 1

Because all of the challenged claims depend from claim 1, we first analyze the limitations of claim 1.

a) Petitioner's Contentions

Petitioner contends Stafford discloses a method of treating a coagulopathy in humans comprising administering a vector to the patient, because it teaches administration of vectors in gene therapy to produce Factor IX in the patient. Pet. 30–31 (citing Ex. 1004, 1, 7–9; Ex. 1003 ¶¶ 75–76, 129). Petitioner further contends Stafford's disclosure of administering Factor IX protein "in an amount sufficient to facilitate or enhance blood clotting in said patient" (Ex. 1004, 5) and that "vectors may be used to produce recombinant Factor IX, or may be used in gene therapy to ... produce the Factor IX in the patient" (*id.* at 9) disclose treating a coagulopathy in humans, because the express purpose of generating FIX and

enhancing clotting activity in a patient is to treat a coagulopathy such as hemophilia B. Pet. 36–37. Petitioner further contends Manno discloses methods of treating a coagulopathy in humans by administering an AAV2 vector encoding wild-type FIX to humans with hemophilia B. *Id.* at 31–32 (citing Ex. 1017, 1, 5; Ex. 1003 ¶¶ 129–132). Petitioner contends Manno's description of a clinical trial involving Subject E, who exhibited FIX activity levels as high as 11.8% and experienced absence of any bleeding episodes for ten weeks, discloses treatment of a coagulopathy. *Id.* at 37 (citing Ex. 1017, 2; Ex. 1003 ¶ 55, 136).

Petitioner contends Stafford discloses an adeno-associated virus vector comprising a nucleic acid encoding a FIX polypeptide with at least 70% identity to SEQ ID NO:2 and a leucine instead of an arginine at position 338, as recited in claim 1. *Id.* at 31–33 (citing, e.g., Ex. 1004, 1, 3, 5, 9, claims 1, 5, 11, 14; Ex. 1003 ¶¶ 77–80; Ex. 1094 ¶¶ 71–73). Petitioner contends a person of ordinary skill in the art would have understood from Stafford that the same sequence in SEQ ID NO:1 that encodes for R338A would encode the R338L variant by using one of the six DNA codons disclosed in Stafford to encode for leucine at position 338. *Id.* at 33–34 (citing, e.g., Ex. 1094 ¶¶ 35–37, 69, 73–77, 104). Petitioner further contends Stafford's disclosure of an expression cassette containing a nucleic acid that encodes for one of Stafford's three preferred variants (including the leucine variant) in claim 17, and disclosure of only four DNA viral vectors (including adeno-associated virus) and a DNA virus vector containing an expression cassette in claim 19, amounts to a disclosure of only twelve combinations, from which a person of ordinary skill in the art would at once

envisage an AAV vector containing a nucleic acid that encodes for the R338L variant. *Id.* at 24 (citing Ex. 1004, 21–22; Ex. 1003 ¶¶ 85–88).

Petitioner contends Stafford and Manno each disclose a vector comprising "promoter sequences and transcription termination and control elements" as recited in claim 1. *Id.* at 34–36 (citing, e.g., Ex. 1003 ¶¶ 81–82, 134–135; Ex. 1004, 8; Ex. 1017, 2).

Petitioner contends a person of ordinary skill in the art would have been motivated to combine Stafford and Manno, to improve upon Manno's results of treating hemophilia B with AAV-2 vectors encoding wild-type FIX. *Id.* at 37–38 (citing Ex. 1003 ¶¶ 137–141; Ex. 1004, 9; Ex. 1005, 7; Ex. 1094 ¶ 104). Petitioner contends a person of ordinary skill would have sought to improve existing gene therapy methods by using the more active R338L variant, and that the advantages of gene therapy with improved clotting FIX variants were known. *Id.* Petitioner further contends that a person of ordinary skill would have reasonably expected that given Manno's success in treating hemophilia B using AAV-based gene therapy encoding for wild-type FIX, that gene therapy using AAV vectors encoding Stafford's more active R338L variant would also be successful in treating hemophilia. *Id.*

b) Patent Owner's Contentions

Patent Owner contends Stafford includes no single embodiment of AAV-FIX-R338L for human gene therapy, but rather includes hundreds of combinations from which a person of ordinary skill in the art would need to pick and choose. PO Resp. 18–22; PO Sur-reply 5–7. Patent Owner further contends Stafford would have provided no motivation to pursue AAV-FIX-R338L for gene therapy with a reasonable expectation of success. PO Resp.

24–27; PO Sur-reply 5–7. Patent Owner contends Manno does not remedy the deficiencies in Stafford because Manno's study only involved wild-type FIX, and had no therapeutic window; the single subject who experienced elevated FIX levels also experienced an immune response—a "catch-22." PO Resp. 23; PO Sur-reply 1–3. Patent Owner contends the combination of Stafford and Manno is based on hindsight because of the catch-22. PO Resp. 15, 27, 29; PO Sur-reply 9–10. Patent Owner contends a person of ordinary skill in the art would not have reasonably expected successful treatment with AAV-FIX-R338L based on either Stafford or Manno. PO Resp. 34–39; PO Sur-reply 18–20.

c) Analysis

Having reviewed Petitioner's evidence and argument, we find that Petitioner has shown by a preponderance of the evidence that the combination of Stafford and Manno teaches the limitations of claim 1 of the '248 patent and that a person of ordinary skill would have been motivated to combine the references in the manner suggested with a reasonable expectation of success. We address Patent Owner's evidence and argument below.

Stafford

Patent Owner contends Stafford does not disclose gene therapy, except for a single sentence stating that vectors may be used to produce recombinant FIX or for gene therapy, and not including any reference to a specific sequence, vector, or subject. PO Resp. 18 (citing Ex. 1004, 9; Ex. 2102 ¶¶ 89–91); PO Sur-reply 6. Patent Owner contends Stafford describes one example, comparing only FIX-R338A to wild-type FIX, and based on results showing increased activity of FIX-R338A *in vitro*,

"includes a series of aspirational passages and purports to claim every non-naturally occurring mutation to FIX-338." *Id.* Patent Owner contends Stafford does not include any data for FIX-R338L, and that the leucine substitution R338L is one of ten substitutions identified, in a menu of options including eight categories of replicable vectors, treatment of humans or three types of animals, and protein replacement or gene therapy. PO Resp. 18–20 (citing Ex. 1004, 7–9; Ex. 2102 ¶¶ 89–91, 119–36). Patent Owner contends a person of ordinary skill could construct hundreds of separate combinations from this menu. *Id.* at 20.

We do not find Patent Owner's arguments persuasive, because they do not fairly characterize all that Stafford discloses. FIX-R338L is one of three expressly preferred variants, and only one of two individually claimed in Stafford, and Stafford teaches that specific point mutations at position 338 of the FIX polypeptide provide "increased clotting activity as compared to the corresponding wild-type molecule" for treating hemophilia B. Ex. 1004, 1, 4, 20. Stafford's express preference for FIX variants—specifically, the two variants individually claimed, R338A and R338L—and its statement that "the present invention is primarily contemplated to be for the treatment of human subjects" (*id.* at 8) do not support Patent Owner's contention that a person of ordinary skill would construct hundreds of separate combinations based on Stafford's disclosure. Further, Dr. Wang's testimony that AAV was the most common vector for hemophilia B gene therapy (Ex. 1003 ¶ 39; Ex. 1100 ¶¶ 15, 95–97) supports Petitioner's contention that a person of ordinary skill in the art would have understood Stafford as teaching the combination of an AAV vector with one of the preferred FIX variants it discloses. Dr. Doering also acknowledges that scientists focused on AAV

vectors in gene therapy development in the 2000s. Ex. 2102 ¶ 88; *see also* Ex. 1043, 27. 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 by claim 1.

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 would have recognized that in hemophilia B treatment as Stafford discloses, 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 discloses. *In re Mouttet*, 686 F.3d 1322, 1331 (Fed. Cir. 2012).

Manno

Patent Owner contends Manno does not fill the gaps in Stafford because it describes a study involving wild-type FIX, and only one of the seven subjects in the study, Subject E, experienced elevated FIX levels but no therapeutic window. PO Resp. 23 (citing Ex. 1017, 1–2; Ex. 2102 ¶ 100), 29–30 (citing Ex. 2102 ¶¶ 371–82); PO Sur-reply 2. Patent Owner contends Manno discloses that Subject E experienced an immune response and FDA subsequently required lower dosing for later patients which resulted in no efficacy and transaminitis. PO Resp. 23 (citing Ex. 1017; Ex. 2102 ¶¶ 277–86). Patent Owner contends Manno thus demonstrates "the catch-22" in

gene therapy for hemophilia B that existed prior to the invention of the '248 patent: doses of viral vector that might be effective caused immunogenic responses to the viral vector, and lower doses of viral vector did not lead to sufficient expression to cure the disease. PO Resp. 1, 23 (citing Ex. 2102 ¶¶ 277–86). Patent Owner relies on Dr. Wang's statement in a 2007 reference as recognition that Manno would not have provided a reasonable expectation of successful treatment with AAV-FIX-R338L. PO Resp. 29–30 (citing Ex. 1033, 9).

We disagree with Patent Owner that Manno's study involving AAV-wild-type FIX would not have provided a basis for a person of ordinary skill in the art to pursue AAV-FIX-R338L. Prior art, as explained by Dr. Wang, in fact taught that FIX-R338L would express similarly to wild-type FIX. *See* Ex. 1005, 2 (R338A with an AAV vector in mice was expected to express at similar levels as wild-type); Ex. 1012, 4 (no difference in expression levels of AAV-wild-type FIX and AAV-FIX-R338A); Ex. 1100 ¶ 116.

We do not find persuasive Patent Owner's arguments that Manno failed at treating hemophilia B, because we adopted Petitioner's proposed construction of "treating" as discussed above. Under that construction, "treating" a coagulopathy includes partial alleviation of symptoms, for any duration of therapeutic efficacy. Manno's study demonstrated "treating" a coagulopathy because it reported (1) Subject E achieved expression of FIX at therapeutic levels and "an absence of any bleeding episodes" for ten weeks "despite trauma which would ordinarily have required" replacement therapy (Ex. 1017, 2); (2) vector infusion at the tested doses "was not associated with acute or long-lasting toxicity," and (3) immune-mediated

reduction in Factor IX expression may be addressed with "a short-term immunomodulatory regimen that blocks the response to capsid" and, thus, "permit long-term expression of the donated gene." *Id.* at 2–3. Other references recognized Manno's result. For example, Hasbrouck concluded "it is clear that AAV-2 can transduce human hepatocytes and direct levels of expression adequate to treat hemophilia." Ex. 1020, 5. Thus, Hasbrouck highlights the success of Manno and would have suggested to a person of ordinary skill to modify Manno by using a more active variant and with a short course of immunosuppressants to address the anti-AAV capsid-directed immune response that limited the duration of efficacy in Manno. *Id.* at 4–5; *see* Ex. 1003 ¶ 221.

Similarly, we do not find persuasive Dr. Doering's opinions that are based on characterizing Manno's studies as a failure. *See, e.g.* Ex. 2102 ¶¶ 373–80. Patent Owner's arguments based on the catch-22 assume claim limitations related to duration of treatment and efficacy that we have determined are not present in the claims.

We do not agree with Patent Owner that Dr. Wang's statement in a 2007 paper that it was "difficult ... to develop strategies to overcome" the immune response (Ex. 1033, 9) suggests that a person of ordinary skill would not have recognized Manno as providing a reasonable expectation of treatment with AAV-FIX-R338L. Patent Owner does not fairly characterize Dr. Wang's statement, which recognizes that using immunosuppression is not inconsistent with using FIX-R338L; in the same paper, Dr. Wang recommends immunosuppression. *Id.*; Ex. 1100 ¶¶ 138, 175. As discussed in Manno, mitigating an immune response is not incompatible with

exploration of a FIX mutant using a more active variant. *See* Ex. 1100 ¶ 100.

Motivation to Combine

Patent Owner contends that Petitioner's combination of Stafford and Manno is based on hindsight. PO Resp. 24. Patent Owner contends Stafford at most would have motivated further study of FIX-R338A *in vitro*, and that is in fact what happened in practice (*id.* at 24–26 (citing Ex. 2102 ¶¶ 319–60)): following Stafford's publication, Schuettrumpf studied FIX-R338A in mice (Ex. 1005); Stafford published again on R338A (Ex. 2004); and Huazhong published on AAV-FIX-R338A in mice (Ex. 1012). Patent Owner further contends that because Stafford is primarily directed to protein replacement therapy, it would not have motivated a person of ordinary skill to use AAV for gene therapy. *Id.* at 26–27 (citing Ex. 1004, 7, 8, 18, 20; Ex. 2102 ¶¶ 324–26, 261–70; Ex. 2114, 130:2–131:5). Patent Owner further contends that because Manno's patients experienced safety issues, Manno at most would have motivated further study of wild-type FIX to generate efficacy while addressing immunosuppression; it would not have motivated a person of ordinary skill to study a FIX mutation. *Id.* at 27 (citing Ex. 1017, 5; Ex. 1033, 9; Ex. 2102 ¶¶ 100–03, 462–70).

Patent Owner contends Petitioner's argument that a person of ordinary skill would have been motivated to pursue AAV-FIX-R338L based on Stafford and Manno's teachings is wrong for several reasons: (1) Stafford does not state why it identifies FIX-R338L as preferred, and Dr. Wang agreed a person of ordinary skill would need to test FIX-R338L in Stafford (PO Resp. 31, citing Ex. 1004; Ex. 2102 ¶¶ 321–25; Ex. 2032, 102:15–103:16, 105:9–19); (2) Stafford's *in vitro* results in a specific cell culture

would not necessarily indicate to a person of ordinary skill that FIX-R338L would express, based on prior art mutations' impaired expression and Drs. Pedersen and Wang's failure to explain why (*id.* at 32–33, citing Ex. 2029; Ex. 2101 ¶¶ 97–111, 133–35; Ex. 2102 ¶¶ 84–86, 320–36, 380–98; Ex. 2130, 47:19–48:6; Ex. 2114, 47:6–48:14); (3) a person of ordinary skill would not have expected a surface exposed alanine as in Stafford's variant could be substituted by leucine without losing expression or activity, contrary to Dr. Pedersen's testimony (*id.* at 33–34, citing Ex. 1094 ¶¶ 58, 104; Ex. 2130, 74:13–19, 79:9–80:24; Ex. 2101 ¶¶ 41–57; Ex. 2102 ¶¶ 96–99, 112, 340–60); (4) hemophilia B gene therapy was unpredictable, had experienced multiple setbacks, and there was no data on AAV-FIX-R338L *in vivo* as of 2008, such that a person of ordinary skill would not have had a reasonable basis to expect from Stafford or Manno that R338L would express or have sufficient activity *in vivo* (*id.* at 34–36); and (5) Manno's study using AAV vector had problems with immunogenicity and did not evidence safe and effective treatment, but rather, unsolved problems (*id.* at 37–38, citing Ex. 1017, 5; Ex. 1020, 1; Ex. 2126, 27; Ex. 2102 ¶¶ 317–409).

We disagree with Patent Owner that Petitioner used impermissible hindsight in combining Stafford and Manno. Contrary to Patent Owner's arguments, Petitioner has shown a motivation to combine supported by rational underpinnings in the evidentiary record.

As discussed above, the evidence supports that a person of ordinary skill in the art would have been motivated to use Stafford's disclosure of a DNA sequence encoding one of Stafford's preferred variants, FIX-R338L, for gene therapy *in vivo*, because Stafford discloses FIX-R338L has improved clotting activity. Dr. Pedersen explains why a person of ordinary

skill would have expected to be able to substitute leucine in Stafford's R338A-FIX example, without losing activity, because detailed structural information regarding FIX was available in 2008, including the effect of a substitution at position 38. Ex. 1101 ¶¶ 16, 21. Dr. Pedersen further explains that a person of ordinary skill in the art would have understood that alanine and leucine are both uncharged, non-polar, aliphatic, and hydrophobic amino acids—different from charged, polar, highly hydrophilic arginine—such that a person of ordinary skill would have considered a substitution of leucine for alanine to be a conservative amino acid substitution that would improve clotting activity relative to arginine at position 338 of FIX. *Id.* ¶¶ 23–28, 52; Ex. 1094 ¶¶ 56–59.

We also find Dr. Pedersen's opinion with regard to a leucine substitution in FIX-R338 more credible than Dr. Spiegel's, who states "there is no such thing as 'conservative amino acid substitutions' in the sense Dr. Pedersen asserts." Ex. 2101 ¶ 72. The '248 patent itself refers to "conservative amino acid substitutions" and states "[i]t is expected that substitutions between these homologous amino acids [including alanine and leucine] would not change the phenotype of the proteins." Ex. 1001, 4:48–61. Although Dr. Spiegel notes that substitution is context dependent and "the specification recognizes ... various properties of each unique amino acid all contribute to the amino acid's interactions" (Ex. 2101 ¶ 75, citing Ex. 1001, 4:48–61; Ex. 1002, 4:45–58; Ex. 1039, 51), his opinions do not account for the knowledge of a person of ordinary skill in the art as to the properties of alanine and leucine and the structure of FIX. *See* Ex. 1101 ¶¶ 36–39.

We also do not find persuasive Patent Owner's argument that a person of ordinary skill in the art would have had serious concerns whether R338L would be expressed, based on Stafford. As discussed above, Stafford discloses successful expression of R338A *in vitro*, and as Dr. Wang explains, the understanding of a person of ordinary skill of similarities between R338A and R338L would have supported the understanding that R338L would express at a similar level to R338A, given Stafford's disclosure that only R338P showed reduced expression, and unlike leucine, "proline is a known 'helix breaker.'" Ex. 1004, 14–15; Ex. 1100 ¶¶ 113–116. Stafford's disclosure that mutations at 330–337 cause severe hemophilia due to loss of FIX activity (Ex. 1004, 19:16–20) does not support Patent Owner's argument, because 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. As such, we agree with Dr. Wang that a person of ordinary skill in the art would not have expected difficulties in expression of R338L.

We also do not find persuasive Patent Owner's argument that a person of ordinary skill would not have expected expression of FIX-R338L at similar levels to 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. Ex. 1005, 2; Ex. 1012, 4. 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. Further, 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 that "F.IX variants provide a promising strategy to improve the efficacy for a variety of gene-based therapies for hemophilia B" as also reflected by 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 pursue hemophilia B gene therapy using the R338L variant (*see* Ex. 1003 ¶ 219), based on Dr. Pedersen's testimony regarding similarities between the R338L and R338A variants. *See* Ex. 1094 ¶¶ 104.

Patent Owner's argument that Dr. Wang fails to explain why a person of ordinary skill would have expected sufficient expression of FIX-R338L based on Manno's results does not fairly characterize the record. *See* PO Sur-reply 9–10. Patent Owner's argument is based on Dr. Wang's 2005 publication which referred to a preliminary report of Manno's results[9] as showing "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 in 2008 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 ¶¶ 136–37. Therefore, we are not persuaded by Patent Owner's argument that Dr. Wang's opinion demonstrates hindsight.

[9] Manno was published in 2006.

Reasonable Expectation of Success

Patent Owner contends a person of ordinary skill would not have had a reasonable expectation of success in modifying Stafford, for the reasons described above, such as structural differences between alanine and leucine. PO Resp. 28–29 (citing Ex. 2108 ¶ 73; Ex. 2101 ¶¶ 31–76, 85–86, 135; Ex. 2102 ¶¶ 340–60). Patent Owner contends a person of ordinary skill would have been uncertain as to whether to try immunosuppression to solve safety issues in Manno. PO Resp. 38–39 (citing Ex. 2118; Ex. 1033, 9; Ex. 2102 ¶¶ 415–31). Patent Owner again relies on Dr. Wang's publication "acknowledg[ing] the cause of Manno's immune response was difficult to verify" (*id.* at 39, citing Ex. 1033, 9), and her testimony concerning risk and uncertainty around immunosuppression. *Id.* at 38–39 (citing Ex. 2114, 99:14–101:9, 116:19–117:1, 118:18–119:7, 120:2–7, 121:5–124:5). Patent Owner contends that in view of the highly unpredictable field of gene therapy, Manno's failure, and no AAV-FIX-R338L-specific data, there is no support for a finding of a reasonable expectation of success under *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1384–85 (Fed. Cir. 2019). PO Resp. 3, 39.

We disagree with Patent Owner's assertion of no reasonable expectation of success, for reasons discussed above, in addition to those we highlight below. As to structural differences between alanine and leucine, the '248 patent itself states "It is expected that substitutions between these homologous amino acids would not change the phenotype of the proteins ...." Ex. 1001, 4:48–61. Thus, Patent Owner's specification is evidence that a person of ordinary skill would have expected to substitute alanine with leucine without losing activity, because of their similar properties. *See*

Koninlijke Philips NV v. Google LLC, 948 F.3d 1330, 1339 (Fed. Cir. 2020) ("[I]t is appropriate to rely on admissions in a patent's specification when assessing whether that patent's claims would have been obvious.").

Regarding a person of ordinary skill's purported uncertainty as to whether to try immunosuppression following Manno's results, to the extent Patent Owner's arguments are based on duration of efficacy or therapeutic response, they are inconsistent with our construction of "treating" and therefore not persuasive. Further, Patent Owner's arguments do not adequately credit Hasbrouck's teaching, based on Manno's results, that "it is clear that AAV-2 can transduce human hepatocytes and direct levels of expression adequate to treat hemophilia." Ex. 1020, 5. We have reviewed Dr. Wang's deposition testimony (Ex. 2114, 124:13–126:17) and do not agree with Patent Owner that it undermines this evidence. Therefore, Hasbrouck's conclusion does not support Patent Owner's argument that a person of ordinary skill would not have a reasonable expectation of success in light of Manno's results. *See* Ex. 1100 ¶ 124.

As to Patent Owner's argument concerning the unpredictability of gene therapy, and a lack of efficacy data specifically for AAV-FIX-R338L, we have considered the evidence submitted by both parties. Although we acknowledge that Dr. Doering presents credible testimony concerning the unpredictability of certain aspects of gene therapy (e.g., Ex. 2102 ¶¶ 505–506), we do not agree that the evidence as a whole supports a finding of no reasonable expectation of success, for reasons discussed above. As Petitioner asserts, and Dr. Wang credibly testifies, FIX levels correlate well with clinical symptomology, such that a person of ordinary skill in the art would reasonably expect a small increase in FIX activity would succeed in

"treating" symptoms within the meaning of the '248 patent. Pet. Reply 15 (citing Ex. 1020, 2; Ex. 1100 ¶ 135). Thus, unlike *OSI Pharms.*, which found "a complete absence of an indicator or mechanism on which a person of ordinary skill could rely" to reasonably expect success in treating non-small cell lung cancer (*OSI Pharms.* at 1384–85), Petitioner has shown a person of ordinary skill in the art would have understood the use of FIX variants with AAV vectors for gene therapy, and that using a slightly more active FIX variant would treat hemophilia B. Further, *OSI Pharms.* recognizes that efficacy data is not always required for a reasonable expectation of success. *Id.* at 1385. *University of Strathclyde v. Clear-Vu Lighting LLC.,* on which Patent Owner relies, is also distinguishable because there, the court found lack of any "reliable indicator of success" that MRSA bacteria could be inactivated when exposed to a particular wavelength of light without using a photosensitizer. 17 F.4th 155, 165 (Fed. Cir. 2021). In any event, a finding of obviousness does not require absolute certainty; 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.").

d) Conclusion as to Claim 1

Having reviewed Petitioner's and Patent Owner's evidence and arguments, we find that Petitioner has shown by a preponderance of the evidence that the combination of Stafford and Manno accounts for all of the limitations of claim 1 and that there was a motivation to combine the references in the manner suggested with a reasonable expectation of success.

3. Claim 2

Claim 2 additionally recites that "the modified FIX polypeptide is expressed in the human patient at a level at least five fold less than the level of wild-type FIX of SEQ ID NO:2 in a healthy human lacking the coagulopathy." Petitioner contends Manno discloses that Subject E's FIX expression levels ranged from 8.73 to 12.95 % of normal, which is below the recited upper limit of at least five-fold less, i.e. no more than 20% of normal. Pet. 38–39 (citing Ex. 1003 ¶¶ 177–179; Ex. 1017, 1–2; Ex. 1083, Supp. Table 4). Petitioner contends Manno also discloses an immune reaction to the AAV2 vector that limited the duration of the therapeutic effect. *Id.* at 39 (citing Ex. 1003 ¶ 179; Ex. 10107, 1). Petitioner contends a person of ordinary skill in the art would have been motivated not to increase the dose in Manno, and would have had a reasonable expectation of success in at least preserving efficacy when using the R338L variant, and that if a person of ordinary skill in the art were to reduce the dose, it would have been expected to further reduce the resulting FIX expression levels and keep them under five-fold less than normal. *Id.* (citing Ex. 1003 ¶¶ 179–180; Ex. 1083).

Patent Owner's argument with regard to claim 2 essentially is the same as its argument with regard to claim 1. *See* PO Resp. 40–42. Patent Owner contends Manno does not disclose the limitation of claim 2 because Subject E was treated with wild-type FIX, no dose in Manno was safe and effective, and nothing in Stafford or Manno would give a person of ordinary skill a reasonable expectation that FIX-R338L would be expressed, let alone at any particular level. *Id.* As discussed above for claim 1, we do not find these arguments persuasive. Accordingly, for the reasons discussed above,

we determine Petitioner has shown by a preponderance of the evidence that claim 2 would have been obvious over Stafford and Manno.

4. Claim 4

Claim 4 depends from claim 1 and additionally recites "wherein the nucleic acid integrates stably into the human patient's genome." Petitioner contends the claim requires integration of the nucleic acid that encodes the R338L variant. Pet. 40. Petitioner provides further analysis detailing where it contends this limitation is disclosed in Stafford and Manno.

Patent Owner does not offer any additional argument with respect to the patentability of claim 4.

We have reviewed Petitioner's evidence and argument, and find that Petitioner has shown the combination of Stafford and Manno teaches the limitations of claim 4. Accordingly, for the reasons discussed above, we determine Petitioner has shown by a preponderance of the evidence that claim 4 would have been obvious over Stafford and Manno.

5. Claims 5 and 6

Claims 5 and 6 depend from claim 1; claim 6 additionally recites "wherein the adeno-associated virus vector is administered at a dose of 10^{14} to 10^{12} particles per kilogram of patient weight." Petitioner provides further analysis detailing where it contends these limitations are disclosed in Stafford and Manno. Pet. 41–45.

Patent Owner does not offer any additional argument with respect to the patentability of claims 5 and 6.

We have reviewed Petitioner's evidence and argument, and find that Petitioner has shown the combination of Stafford and Manno teaches the limitations of claims 5 and 6. Accordingly, for the reasons discussed above,

we determine Petitioner has shown by a preponderance of the evidence that claims 5 and 6 would have been obvious over Stafford and Manno.

6. Claims 11 and 12

Claim 11 depends from claim 2 and additionally recites "the healthy human expresses 5 μg/ml of wild-type FIX." Claim 12 depends from claim 11 and additionally recites "the 5 μg/ml of wild-type FIX is measured in plasma from the healthy human." Petitioner provides further analysis detailing where it contends each additional limitation of claims 11 and 12 are disclosed in Stafford and Manno. Pet. 45–46. We have reviewed Petitioner's evidence and argument, and find that Petitioner has shown by a preponderance of the evidence that Stafford and Manno teach each of these limitations.

Patent Owner does not offer any additional argument with respect to the patentability of claims 11 and 12. PO Resp. 42–43.

We have reviewed Petitioner's evidence and argument, and find that Petitioner has shown the combination of Stafford and Manno teaches the limitations of claims 11 and 12. Accordingly, for the reasons discussed above, we determine Petitioner has shown by a preponderance of the evidence that claims 11 and 12 would have been obvious over Stafford and Manno.

7. Claim 13

Claim 13 depends from claim 1 and additionally recites "wherein the modified FIX polypeptide is expressed at a daily dosage between 0.1 μg/kg and 400 μg/kg body weight." Petitioner provides further analysis detailing where it contends this additional limitation is disclosed in Stafford and Manno. Pet. 46–47. Specifically, Petitioner contends the claimed range of

FIX expression encompasses the levels achieved by Subject E in Manno at weeks two and five post-therapy, and even if the dose of AAV in Manno were lowered, a person of ordinary skill in the art would expect FIX expression within the claimed range. *Id.* (citing Ex. 1003 ¶¶ 206–211; Ex. 1083).

Patent Owner does not offer any additional argument with respect to the patentability of claim 13.

We have reviewed Petitioner's evidence and argument and find that Petitioner has shown the combination of Stafford and Manno teaches the limitations of claim 13. Accordingly, for the reasons discussed above, we determine Petitioner has shown by a preponderance of the evidence that claim 13 would have been obvious over Stafford and Manno.

8. Claims 17 and 18

Claims 17 and 18 depend from claim 2 and additionally recite that "the modified FIX polypeptide is expressed at a level of seven to nine fold less than the level of wild-type FIX of SEQ ID NO:2 in the healthy human" (claim 17) and "the modified FIX polypeptide is expressed at a level of eight to nine fold less than the level of wild-type FIX of SEQ ID NO:2 in the healthy human" (claim 18). Petitioner contends, as with claim 2, that it would have been obvious to a person of ordinary skill in the art to lower the vector doses used in Manno in order to limit any immune reaction, or to maintain Manno's dose and use immunosuppression to treat a possible immune reaction. Pet. 48–49 (citing Ex. 1003 ¶¶ 213–217; Ex. 1072 ¶ 118; Ex. 1020, 4–5). Petitioner contends that under either option, a person of ordinary skill would have expected to obtain expression levels in the range disclosed in Manno, 8.73 to 12.95%. *Id.* (citing Ex. 1083). Petitioner

explains that those ranges overlap with the claimed ranges of 11.11–14.29% (translation of seven to nine fold less) and 11.11–12.5% (translation of eight to nine fold less), respectively. *Id.* at 50. Petitioner further contends that in the absence of evidence that the claimed ranges are critical, evidence of an overlapping range renders the claims obvious. *Id.,* citing *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003).

Patent Owner contends the highest expression level measured in Subject E in Manno was 10.84%, which is below the claimed ranges of 11.11–14.29% and 11.11–12.5%. PO Resp. 43 (citing Ex. 1083; Ex. 2102 ¶¶ 583–93). Patent Owner further contends that the standard deviation of Manno's activity range, on which Petitioner relies, is not an appropriate measure of whether Manno discloses the claimed limitation. *Id.* at 44. Patent Owner further contends that a person of ordinary skill in the art would not have been motivated to use Manno's dose of AAV with FIX-R338L with a reasonable expectation of success, for the reasons discussed above for claim 1. *Id.* at 45.

Petitioner responds that Dr. Doering's testimony that Manno discloses FIX antigen levels of "3–12% of normal" contradicts Patent Owner's assertion that Manno's antigen levels do not overlap with the claimed ranges. Pet. Reply 16 (citing Ex. 1072 ¶ 34); Ex. 1100 ¶¶ 160–167.

Patent Owner's argument that Petitioner inappropriately relied on standard deviation of Manno's expression levels is not persuasive, because Manno's table of results for Subject E states expression levels in terms of "% of Normal Mean +/- SD." Ex. 1083. Further, Dr. Doering's testimony in the '388 IPR that Manno achieved expression levels up to 12% is consistent with Petitioner's position as to how a person of ordinary skill

would understand Manno's disclosure of results for Subject E. Ex. 1072 ¶ 34. Moreover, Patent Owner fails to adduce evidence that the expression level ranges of claims 17 and 18 are critical or carry patent weight. *See* PO Resp. 43–45; PO Sur-reply 21–22.

Having reviewed the parties' evidence and argument, we determine Petitioner has shown by a preponderance of the evidence that the combination of Stafford and Manno teaches the limitation of claims 17 and 18. Accordingly, for the reasons discussed above, we determine Petitioner has shown by a preponderance of the evidence that claims 17 and 18 would have been obvious over Stafford and Manno.

G. Ground 2: Alleged Obviousness Based on Stafford, Manno, Schuettrumpf, and Hasbrouck

For the reasons discussed above, Petitioner has shown in Grounds 1, 3, and 4 that claims 2, 4–6, 11–13, 17, and 18 of the '248 patent are unpatentable, by a preponderance of the evidence. In addressing these grounds, we have addressed all of the challenged claims. *See* 35 U.S.C. § 318(a) (requiring the Board to "issue a final written decision with respect to the patentability of any patent claim challenged by the petitioner and any new claim added under section 316(d)"); *see also SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding that a petitioner "is entitled to a final written decision addressing all of the claims it has challenged"). Accordingly, we need not and do not decide whether Petitioner has shown by a preponderance of the evidence that claims 2, 4–6, 11–13, 17, and 18 are unpatentable over the combination of Stafford, Manno, Schuettrumpf, and Hasbrouck. *Cf. In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009) (not reaching other grounds of unpatentability after affirming the anticipation

ground); *see also Beloit Corp. v. Valmet Oy*, 742 F.2d 1421, 1423 (Fed. Cir. 1984) (holding that once a dispositive issue is decided, there is no need to decide other issues).

III. CONCLUSION

Petitioner has shown, by a preponderance of the evidence, that claims 2, 4–6, 11–13, 17, and 18 are unpatentable over the combination of Stafford and Manno; and claims 2, 5, 6, 11–13, 17, and 18 are unpatentable over Monahan,[10] as summarized below:

[10] 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)/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
2, 4–6, 11–13, 17, 18	103	Stafford and Manno	2, 4–6, 11–13, 17, 18	
2, 4–6, 11–13, 17, 18	103[11]	Stafford, Manno, Schuettrumpf, Hasbrouck		
2, 5, 6, 11–13	102(a)	Monahan	2, 5, 6, 11–13	
2, 5, 6, 11–13, 17, 18	103	Monahan	2, 5, 6, 11–13, 17, 18	
Overall Outcome			2, 4–6, 11–13, 17, 18	

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 2, 4–6, 11–13, 17, and 18 of the '248 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.

[11] As explained in the previous section, we need not and do not decide whether Petitioner has shown by a preponderance of the evidence that the combination of references in this ground renders obvious the challenged claims.

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