

NOTE: This disposition is nonprecedential.

**United States Court of Appeals  
for the Federal Circuit**

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**UNIQUE BIOPHARMA B.V.,**  
*Appellant*

**v.**

**PFIZER INC.,**  
*Appellee*

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2023-1404, 2023-1405, 2023-1406

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Appeals from the United States Patent and Trademark  
Office, Patent Trial and Appeal Board in Nos. IPR2021-  
00925, IPR2021-00926, IPR2021-00928.

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Decided: May 22, 2025

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Before DYK, CHEN, and STARK, *Circuit Judges*.

STARK, *Circuit Judge*.

Appellant uniQure Biopharma B.V. (“uniQure”) appeals from Final Written Decisions (“FWD”) of the Patent Trademark and Appeal Board (“Board”) finding that all challenged claims of uniQure’s U.S. Patent Nos. 9,982,248 (“248 patent”) and 10,465,180 (“180 patent”) are unpatentable. Because the Board did not commit any legal error and its factual findings are supported by substantial evidence, we affirm.

## I

### A

Hemophilia B is a serious bleeding disorder caused by a single-gene mutation that leads to decreased or absent production of Factor IX (“FIX”), a protein critical to the body’s blood coagulation process. Traditional treatment for hemophilia B involves protein replacement therapy, by which recombinantly (artificially) made FIX is administered to a patient through frequent infusions. Given that hemophilia B is caused by a single genetic mutation, the disease is an ideal candidate for treatment via gene therapy. In this context, gene therapy involves dosing a patient with a viral vector containing genetic information coding for the production of FIX. Gene therapy thereby allows the patient to continuously produce her own FIX protein, reducing or even eliminating reliance on protein replacement therapy for treatment.

Gene therapy requires the use of a viral vector to deliver genetic material into a patient’s cells. These viral vectors elicit an immune response – a response that in this context is undesirable – which may be exacerbated by higher viral vector doses. This presented an obstacle to the development of successful hemophilia B gene therapy, since the high viral vector doses that may be necessary to

achieve efficacious results may also cause patients to experience serious adverse immune responses.

uniQure's '248 and '180 patents purport to tackle this problem by utilizing a mutated version of the wild-type FIX gene<sup>1</sup> in gene therapy. The specific mutation utilized by the uniQure process is called "FIX-R338L" and consists of an amino acid substitution of leucine for the wild-type arginine at position 338 of the FIX protein. FIX-R338L is eight to nine times more active than wild-type FIX. This higher activity of the FIX protein allows for lower viral vector dosing and, thus, reduced patient immune activation in the context of gene therapy. Utilizing FIX-R338L, uniQure developed HEMGENIX®, an FDA-approved gene therapy for the treatment of hemophilia B.

Representative claims 1 of uniQure's '248 and '180 patents are reproduced below:

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.

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<sup>1</sup> "Wild-type FIX" is also known as "non-mutant" FIX. A wild-type protein is one that is naturally occurring, commonly found in a population, and can be used as a standard against which mutations are measured.

J.A. 186.

An adeno-associated virus vector comprising:

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

J.A. 212.

## B

Pfizer, Inc. (“Pfizer”) filed three petitions for *inter partes* review (“IPR”) of the ’248 and ’180 patents and the Board instituted IPR for all three. As pertinent to this appeal, the petitions set out the following grounds for unpatentability: (i) all claims of the ’248 patent are unpatentable as obvious over Stafford and Manno or, alternatively, over Stafford, Manno, and Schuettrumpf; and (ii) all claims of the ’180 patent are invalid as anticipated by Stafford.<sup>2</sup>

WO 99/03496 (“Stafford”) is an international patent application published on January 28, 1999, entitled “Factor IX Antihemophilic Factor with Increased Clotting Activity.” J.A. 1283. Stafford discloses a “recombinant FIX arginine 338 alanine mutant” (“FIX-R338A”) “which result[s] in a gain-of-function whose activity levels are 2-3 folds

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<sup>2</sup> Specifically, IPR2021-00925 determined claims 1, 3, 7-10, 14-16, 19, and 20 of the ’248 patent unpatentable as obvious; IPR2021-00926 determined claims 2, 5, 6, 11-13, 17, and 18 of the ’248 patent unpatentable as obvious; and IPR 2021-00928 determined claims 1-6 of the ’180 patent unpatentable as anticipated and obvious. uniQure’s appeals from the three FWDs were consolidated.

higher than that found in wild type FIX.” J.A. 5; *see also* J.A. 1286. Stafford claims all non-naturally occurring mammalian FIX proteins having an amino acid substitution at position 338, including dependent claims directed to preferred embodiments: “said substitution is a substitution of an arginine residue for an amino acid residue selected from the group consisting of alanine, *leucine*, and valine.” J.A. 1302 ¶ 3 (emphasis added). Stafford further narrows its three preferred embodiments by specifically claiming a FIX protein in which the arginine at position 338 is substituted with leucine, i.e., FIX-R338L, *see* J.A. 1302 ¶5, and explains that this variant had improved clotting activity, *see* J.A. 1286. Stafford teaches that the mutations it discloses “advantageously have increased clotting activity,” by as much as two to three times “as compared to the corresponding wild-type molecule.” J.A. 1286.

Manno is an article published in *Nature Medicine* in 2006. *See* Catherine S. Manno et al., *Successful Transduction of Liver in Hemophilia AAV-Factor IX and Limitations Imposed by the Host Immune Response*, 12 NATURE MED. 342 (2006). Manno reports the results of a clinical trial that involved treating seven patients with severe hemophilia B by delivering wild-type FIX with an adeno-associated virus vector (“AAV”). Manno reported that this “AAV-FIX-wild type” gene therapy was “[s]uccessful,” resulting in “therapeutic levels” of FIX over a period of approximately eight weeks. J.A. 1570-1573. Manno acknowledges that “therapeutic levels [of FIX] in humans [were] short lived,” due to immune responses triggered by and against the AAV vector she used, but nonetheless discloses short-term treatment of hemophilia B utilizing AAV-FIX-wild type. J.A. 1570.

Schuettrumpf is a 2004 academic article. *See* Joerg Schuettrumpf et al., *Factor IX Variants Improve Gene Therapy Efficacy for Hemophilia B*, 105 BLOOD 2316 (2005). Schuettrumpf “constructed AAV vectors encoding FLX variants for . . . hemophilia B mice.” J.A. 1321. Schuettrumpf noted that “[p]revious studies demonstrated that the

substitution R338A in [FIX] result[s] in a molecule with 3-fold higher” activity than wild-type FIX. J.A. 1321. Schuettrumpf found that intramuscular injection of AAV-FIX-R338A<sup>3</sup> in mice results in two-to-six-fold greater activity than that resulting from FIX-wild type.

## II

“Obviousness is a question of law that we review de novo,” although it is based on “underlying findings of fact” that we review for substantial evidence. *Liqwd, Inc. v. L’Oreal USA, Inc.*, 941 F.3d 1133, 1136 (Fed. Cir. 2019). “An obviousness determination requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so.” *Regents of Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1291 (Fed. Cir. 2018). “Whether a person of ordinary skill in the art would have been motivated to modify or combine teachings in the prior art, and whether he would have had a reasonable expectation of success, are questions of fact.” *Id.* “Anticipation is a question of fact reviewed for substantial evidence in an appeal from the Board.” *In re Antor Media Corp.*, 689 F.3d 1282, 1287 (Fed. Cir. 2012). “A finding is supported by substantial evidence if a reasonable mind might accept the evidence as adequate to support the finding.” *Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1347 (Fed. Cir. 2024) (citing *Consol. Edison Co. v. NLRB*, 35 U.S. 197, 229 (1938)).

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<sup>3</sup> “AAV-FIX-R338A” is the scientific shorthand for a gene therapy system that delivers, via an adeno-associated virus vector, a mutated form of the FIX protein wherein the naturally-occurring arginine at position 338 of the protein is replaced with an alanine.

### III

uniQure raises a number of challenges to the Board's decisions and we have carefully considered them all. Given the Board's thorough analysis, stretched out across three opinions comprising more than 150 pages, and our determination that the Board committed no legal error and had substantial evidence for its findings, we confine our discussion to the most significant of uniQure's concerns: (i) the Board's determination that the claims of the '248 patent were obvious over Stafford, Manno, and/or Schuettrumpf; (ii) the Board's treatment of uniQure's objective evidence of nonobviousness; and (iii) the Board's finding that Stafford anticipates the claims of the '180 patent.

#### A

With respect to the Board's conclusion that Pfizer succeeded in proving the challenged claims of the '248 patent would have been obvious, uniQure first attacks the Board's findings that a person of ordinary skill in the art ("POSA") would have had a reasonable expectation of success in utilizing an AAV-FIX-R338L vector to treat hemophilia B via gene therapy. It is undisputed that the prior art cited in the petitions collectively discloses each of the limitations of the challenged independent claim (claim 1): Stafford teaches leucine is a preferred substitution for arginine at position 338 in FIX-R338A, *see* J.A. 1302, Manno teaches gene therapy "treatment" (as construed here) of hemophilia B by generating therapeutic FIX levels, *see* J.A. 1321, and Schuettrumpf teaches AAV-FIX-R338A produces proteins with six-fold greater activity than wildtype-FIX when administered to mice and that FIX-R338L is a "promising" variant, *see* J.A. 1573. On appeal, uniQure further concedes that a POSA would have had a motivation to combine these references. uniQure's principal dispute is with the Board's findings that a POSA would have had a reasonable expectation of success in doing so.

The '248 patent's independent claims require (among other components not relevant to this appeal) "treating a coagulopathy" by "administering a vector to the human patient," wherein such vector "is an adeno-associated virus," comprising "a nucleic acid encoding a modified FIX polypeptide" with "a leucine in position 338." '248 patent at 45:20-29. The Board construed "treating" as requiring at least "a partial alleviation of symptoms, for any duration of therapeutic efficacy." J.A. 11. Applying this construction, substantial evidence supports the Board's finding that a POSA would have had a reasonable expectation of success in combining the references to achieve the claimed alleviation of a coagulopathy, for some duration of therapeutic efficacy, by administering an AAV-FIX-R338L vector.

The Board read Stafford as demonstrating to a POSA that the results achieved by use of FIX-R338A can also be expected to be achieved by use of FIX-R338L. J.A. 40-43. It noted: "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." J.A. 31 (internal quotation marks omitted). The Board further read Manno and Schuettrumpf as establishing successful AAV vector gene therapy for treating hemophilia B. To the Board, then, the combination of either Stafford and Manno or Stafford, Manno, and Schuettrumpf would have given a POSA a reasonable expectation of success that hemophilia B could be treated utilizing an AAV-FIX-R338L vector.

The Board was also persuaded that uniQure's own '248 patent would have contributed to a skilled artisan's expectation of success, as the patent indicated a POSA would understand that alanine and leucine are "homologous amino acids" and that substitutions between them "would not change the phenotype of the proteins." J.A. 41. The Board considered "Patent Owner's argument concerning the



unpredictability of gene therapy, and a lack of efficacy data specifically for AAV-FIX-R338L,” and after evaluating “evidence submitted by both parties” found Pfizer had met its burden. J.A. 42. We have not required such data as a prerequisite to a finding of reasonable expectation of success, even in an unpredictable art. *See Eli Lilly & Co. v. Teva Pharms. Int’l GmBH*, 8 F.4th 1331, 1346 (Fed. Cir. 2021) (“[O]ur case law makes clear that a showing of a reasonable expectation of success in a method of treatment claim need not rely on clinical data . . . nor must it include a demonstration of certainty that the treatment would be successful in every instance.”). Moreover, while the Board “acknowledge[d] that [uniQure’s expert witness] Dr. Doering present[ed] credible testimony concerning the unpredictability of certain aspects of gene therapy,” it was (as is permissible) more persuaded by Pfizer’s expert, Dr. Wang, who “credibly testifie[d] [that] FIX levels correlate well with clinical symptomology.” J.A. 42 (citing J.A. 11084).

The Board was likewise persuaded by another Pfizer expert, Dr. Pedersen, who expressed the view that a POSA would have expected to be able to substitute leucine for alanine at FIX-R338, without losing clotting activity, based on structural similarities between the two amino acids. J.A. 38. The Board credited Dr. Pedersen’s testimony that a POSA would have viewed the substitution of leucine for alanine to be “conservative” and, hence, likely to “improve clotting activity relative to arginine at position 338 of FIX.” *Id.*; *see also* J.A. 10580 (Dr. Pedersen testifying that: “[A] POSA would . . . have expected that substituting leucine for arginine at position 338 of FIX would have had a similar effect on the resulting protein’s clotting activity as substituting alanine for arginine did”). Further, as the Board observed, J.A. 48, the ’248 patent itself characterizes alanine and leucine as conservative substitutions for one another, based on their structural similarities. J.A. 165 (’248 patent at 4:51-58) (“It is expected that substitutions between

[leucine and alanine,] homologous amino acids[,] would not change the phenotype of the proteins.”).

We find no merit in uniQure’s contention that the evidence on which the Board relied is tainted by impermissible hindsight. uniQure emphasizes that Stafford provides no explanation for its featuring of three embodiments as preferred and for dependently claiming just two of those, including the leucine embodiment. The Board considered this point and credited Dr. Pedersen’s opinion that a POSA “would have understood that alanine and leucine are both uncharged, non-polar, aliphatic, and hydrophobic amino acids” and, further, that “detailed structural information about FIX was available in 2008, including the effect of a substitution at position 38.” J.A. 38 (citing J.A. 11196-97).

uniQure additionally contends that the Board violated the Administrative Procedure Act (“APA”) by crediting Dr. Pedersen without, purportedly, fully considering contrary evidence from its expert, Dr. Spiegel. Dr. Spiegel testified, for instance, that “no two amino acids are so similar that the substitution of one for another protein produces a mutant with predictable structure and function,” J.A. 13360 ¶ 118, such that “there is no such thing as ‘conservative amino acid substitutions,’” J.A. 13335 ¶ 72. In finding that Dr. Spiegel’s “opinions do not account for the knowledge of a person of ordinary skill in the art,” J.A. 39, the Board credited Dr. Pedersen’s reply to Dr. Spiegel, J.A. 38 (citing J.A. 11196-200), which was reasonable to do. *See also* J.A. 38 (“We also find Dr. Pedersen’s opinion with regard to a leucine substitution in FIX-R338 more credible than Dr. Spiegel’s . . .”). While “the Board may not short-cut its consideration of the factual record before it,” there is no indication that this is what happened here. *Princeton Vanguard, LLC v. Frito-Lay N. Am., Inc.*, 786 F.3d 960, 970 (Fed. Cir. 2015).

uniQure’s citation to *OSI Pharmaceuticals, LLC v. Apotex Inc.*, 939 F.3d 1375 (Fed. Cir. 2019), does not lead

to a different conclusion. We agree with the Board that whereas *OSI* involved evidence that “*in vitro* . . . effectiveness of a drug . . . [is] a poor proxy for how effective that drug actually was in treating cancer *in vivo*,” 939 F.3d at 1377, here the Board credited testimony from Pfizer’s expert, Dr. Wang, that “FIX levels correlate well with clinical symptomology,” making such levels adequate proxies for effectiveness. J.A. 42. It is also worth noting that in *OSI*, 939 F.3d at 1385, we explained that efficacy data is not always required in order to prove a reasonable expectation of success.

uniQure directs additional criticisms at the Board’s analyses of several of the dependent claims of the ’248 patent. Claim 14 depends from claim 1 and additionally requires that “the modified FIX polypeptide is expressed at a level that does not cause thrombotic complications.” J.A. 186. As the Board noted, the ’248 patent teaches that “risk of thrombosis only increases when wild-type FIX levels exceed 120% of normal,” and Dr. Wang testified that “Manno’s highest vector dose resulted in wild-type FIX activity of 11.8%,” which is well below the danger level identified by the patent. J.A. 45. There is also no indication in Manno that any patient participating in the study experienced thrombotic complications. The Board’s finding that a POSA would agree with Dr. Wang that mouse models showing little risk of thrombotic complications are “predictive of human response” is grounded in the record, including expert declarations. J.A. 45 (citing declarations of Drs. Wang and Doering).

Claim 15, too, depends from claim 1 and further requires that the “modified FIX polypeptide is expressed at a level that does not lead to neutralizing antibody generation.” J.A. 186. The Board found that, given the results reported in Manno and Schuettrumpf – showing that participants receiving FIX-wild type and FIX-R338A, respectively, did not generate such antibodies – a POSA would have understood that the structurally-similar FIX-R338L

would likewise not lead to production of such antibodies. The Board additionally credited testimony from Dr. Wang that patients with a history of not producing such neutralizing antibodies would continue not to produce such antibodies, while subjects with a history of antibody formation would not receive the claimed gene therapy treatment.

## B

uniQure's other principal challenge to the Board's obviousness determinations relates to its handling of uniQure's objective evidence of nonobviousness, particularly "long-felt need, praise and copying by others, and unexpected results." J.A. 19. The Board found that uniQure failed to demonstrate the required nexus between its objective evidence and the challenged claims, and, alternatively, that "even if there is some nexus, it is weak." J.A. 27. "We give deference to [the Board's] factual findings regarding evidence of secondary considerations." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 978 (Fed. Cir. 2014).

uniQure argues that the Board committed legal error by: (i) imposing too strenuous of a nexus requirement, essentially requiring that the evidence be entirely commensurate with the claims; and (ii) failing to recognize that uniQure's evidence relates to AAV-FIX-R338L and not just FIX-R338L.

"[T]here is no nexus unless the evidence presented is reasonably commensurate with the scope of the claims." *ClassCo, Inc. v. Apple, Inc.*, 838 F.3d 1214, 1220 (Fed. Cir. 2016) (internal quotation marks omitted). The Board found that uniQure's objective evidence of nonobviousness lacked a sufficient nexus to the claims because that evidence was directed to FIX-R338L, which was disclosed in Stafford, while the purported innovation of uniQure's claims was AAV-FIX-R338L as a whole, to which none of uniQure's evidence was specifically directed. J.A. 24-26 ("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.”).

uniQure makes much of the fact that the Board also discussed the legal standard for obtaining a *presumption* of nexus, which applies “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,” J.A. 20 (internal quotation marks omitted). But the Board did not hold uniQure to that heightened standard. The Board’s discussion of presumption of nexus appears to have been the result of the parties’ arguments about whether the presumption should apply. The Board expressly found “the 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,” thereby applying the standards applicable to presumptive nexus and non-presumptive nexus disputes. J.A. 24 (emphasis added); *see also* J.A. 25 (“Patent Owner’s objective evidence is not commensurate in scope with claim 1.”). After finding uniQure is not “entitled to a presumption of a nexus,” the Board continued by examining if uniQure proved a nexus, and then found uniQure “presents insufficient evidence to establish a nexus by this alternative route.” J.A. 26.

In sum, we discern no legal error in any aspect of the Board’s obviousness analysis. The Board’s underlying factual findings are supported by substantial evidence.

### C

Finally, uniQure argues that the Board erred in finding that Stafford anticipated the claims of the ’180 patent. We are not persuaded.

Substantial evidence supports the Board’s finding that Stafford discloses an AAV vector encoding a FIX-R338L polypeptide for use in gene therapy. *See* J.A. 131-33 (citing J.A. 1285). Stafford expressly discloses a vector, which it

describes as “a replicable DNA or RNA construct” that “typically comprise[s] plasmids, viruses (e.g., papillomavirus, adenovirus, adeno-associated virus, cytomegalovirus), phage, retroviruses and integratable DNA fragments.” J.A. 1291. Stafford further discloses 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.” J.A. 1291. As we have noted above, the Board also found Stafford’s preferred embodiments of leucine and alanine, combined with a viral vector (including AAV) in gene therapy, disclosed all of the elements as they are arranged in the claims of the ’180 patent. J.A. 130.

While “[a] prior art reference can only anticipate a claim if it discloses all the claimed limitations arranged or combined in the same way as the claim . . . a reference can anticipate even if it d[oes] not expressly spell out all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would at once envisage the claimed invention or arrangement or combination.” *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (cleaned up). The Board reasonably relied on Stafford’s preferred embodiments and dependent claims as evidence that a POSA would know of the similarities between leucine and alanine. J.A. 131 (finding POSA would understand Stafford discloses a “limited class of two or three preferred substitutions at R338 – at most, alanine, leucine and valine”).

uniQure counters the Board’s findings by arguing that Stafford is not enabled. “[E]nablement is ultimately a question of law subject to *de novo* review, [that] is based on underlying factual findings . . . reviewed for clear error.” *Bruning v. Hirose*, 161 F.3d 681, 686 (Fed. Cir. 1998). While “[a] prior art reference cannot anticipate a claimed invention ‘if the allegedly anticipatory disclosures cited by the prior art are not enabled,’ ‘claimed and unclaimed materials disclosed in a patent’ and ‘prior art publications’ ‘are presumptively enabled.’” *In re Antor Media Corp.*, 689

F.3d 1282, 1287 (Fed. Cir. 2012). Thus, Stafford’s AAV-FIX-R338L embodiment, despite not being claimed, is presumed enabled. The Board had substantial evidence for finding that this presumption has not been rebutted, including uniQure’s concession that Stafford discloses only “eight categories of vectors,” Open. Br. at 67, and three preferred mutation embodiments, resulting in at most 24 potential embodiments, a number consistent with what we have previously presumed may be enabled in an anticipatory reference. *See Kennametal*, 780 F.3d at 1382-83 (finding enablement of class of five metals in combination with one of three potential coatings); *see also Antor Media*, 689 F.3d at 1289 (“[A]n examiner is entitled to reject claims as anticipated by a prior art publication or patent without conducting an inquiry into whether or not that prior art reference is enabling. As long as an examiner makes a proper prima facie case of anticipation . . . the burden shifts to the applicant to submit rebuttal evidence of nonenablement.”).

uniQure additionally argues that Stafford does not disclose a pharmaceutical composition, as claimed in claim 2 of the ’180 patent. The Board had substantial evidence for its contrary finding. The Board found that a pharmaceutical composition is inherent in Stafford’s disclosure of “vectors . . . used in gene therapy to administer the expression cassette,” citing testimony from Pfizer’s expert, Dr. Wang, that a POSA would understand such vectors must be administered in a pharmaceutical composition. J.A. 135-38.

#### IV

We have considered uniQure’s remaining arguments and find they lack merit. Accordingly, we affirm the Board’s judgments that the challenged claims are unpatentable.

**AFFIRMED**