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Paper 9
Entered: August 22, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SARFPTA THERAPEUTICS, INC.,
Petitioner,

v.

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA,
Patent Owner.

IPR2024-00580
Patent 11,680,274 B2

Before ULRIKE W. JENKS, SUSAN L. C. MITCHELL, and
ROBERT A. POLLOCK, *Administrative Patent Judges*.

MITCHELL, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Sarepta Therapeutics, Inc. ("Petitioner") filed a Petition (Paper 2, "Pet."), seeking *inter partes* review of claims 1, 3–6, and 8 of U.S. Patent No. 11,680,274 B2 (Ex. 1001, "the '274 patent"). The Trustees of the University of Pennsylvania ("Patent Owner") filed a Preliminary Response in which it raises challenges to the merits of the grounds in the Petition. Paper 8 ("Prelim. Resp.").

After considering the arguments and evidence presented at this stage of the proceeding, we are persuaded that Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. *See* 35 U.S.C. § 314(a). Accordingly, we institute *inter partes* review of all challenged claims on all asserted grounds. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1354, 1359–60 (2018); 37 C.F.R. § 42.108(a).

II. BACKGROUND

A. Real Parties in Interest

Petitioner identifies Sarepta Therapeutics, Inc., Sarepta Therapeutics Three, LLC, and Catalent, Inc. as real parties in interest. *See* Pet. 5. Patent Owner identifies The Trustees of the University of Pennsylvania, GlaxoSmithKline LLC, and REGENXBIO as the real parties in interest. *See* Paper 4, 1; Paper 7, 1.

B. Related Matters

Petitioner and Patent Owner identify the following litigation as a related matter in which Petitioner is a defendant: *REGENXBIO Inc. F/K/A*

ReGenX v. Sarepta Therapeutics, Inc., C.A. No. 23-667-RGA (D. Del.) ("Penn-II"). Pet. 5; Paper 4, 2; Paper 7, 3.

C. The '274 Patent

The '462 patent issued on June 20, 2023, and is a divisional of an application filed February 18, 2015, now U.S. Patent No. 10,301,648, which itself is a divisional of an application filed on April 7, 2006, now U.S. Patent No. 8,999,678. Ex. 1001, codes (45), (62); 1:6–12. The '462 patent also claims priority to two provisional applications, the earliest of which was filed on April 7, 2005. *See id.* at code (60); 1:12–14.

The '462 patent relates to "a method of correcting singletons in a selected [Adeno-associated virus] AAV sequence in order to increase[e] the packaging yield, transduction efficiency, and/or gene transfer efficiency of the selected AAV," which involves "altering one or more singletons in the parental AAV capsid to conform the singleton to the amino acid in the corresponding position(s) of the aligned functional AAV capsid sequences." Ex. 1001, Abst.; 2:1–11; 2:63–3:3. The '462 patent notes that "AAV vectors have been described for use as delivery vehicles for both therapeutic and immunogenic molecules. To date, there have been several different well-characterized AAVs isolated from human or non-human primates (NHP)." *Id.* at 1:47–50. It is also noted that the literature reported that "different AAVs exhibit different transfection efficiencies, and also exhibit tropism for different cells or tissues." *Id.* at 1:57–59.

The method described in the '462 patent improves the function of an AAV vector by improving the packaging yield, transduction efficiency, and/or gene transfer efficiency of an AAV vector having a capsid of an AAV

which contains one or more singletons. Ex. 1001, 2:1–4, 2:63–3:1, 3:32–35. The singleton is described as "a variable amino acid in a given position in a selected (*i.e.*, parental) AAV capsid sequence." *Id.* at 3:10–12.

> The "singleton" or variable amino acid may be found by
>
> aligning the sequence of the parental AAV capsid with a library of functional AAV capsid sequences. The sequences are then analyzed to determine the presence of any variable amino acid sequences in the parental AAV capsid where the sequences of the AAV in the library of functional AAVs have complete conservation. The parental AAV sequence is then altered to change the singleton to the conserved amino acid identified in that position in the functional AAV capsid sequences.

Ex. 1001, 3:13–21, 6:44–47; *see also id.* at 6:14–19 ("A singleton is identified where, for a selected amino acid position when the AAV sequences are aligned, all of the AAVs in the library have the same amino acid residue (i.e., are completely conserved), but the parental AAV has a different amino acid residue."). The replacement of the singleton with the conserved amino acid can be done by conventional site-directed mutagensis techniques. *Id.* at 6:44–50.

Although a parental AAV sequence may have more than six singletons, the '462 patent states that "according to the present invention, a parental AAV sequence may have 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 2 singletons." Ex. 1001, 3:21–23, 6:62–63. The '462 patent notes that improvement in function may be observed by correction of only one singleton. *Id.* at 6:63–64. The '462 patent states:

> In the embodiment where a parental AAV carries multiple singletons, each singleton may be altered at a time, followed by assessment of the modified AAV for enhancement of the desired function. Alternatively, multiple singletons may be

> altered prior to assessment for enhancement of the desired function.
>
> Even where a parental AAV contains multiple singletons and functional improvement is observed altered of a first singleton, it may be desirable to optimize function by altering the remaining singleton(s).
>
> . . . .
>
> These altered AAVs have novel capsids produced according to the method of the invention and are assessed for function. Suitable methods for assessing AAV function have been described herein and include, e.g., the ability to produce DNAse protected particles, in vitro cell transduction efficiency, and/or in vivo gene transfer. Suitably, the altered AAVs of the invention have a sufficient number of singletons altered to increase function in one or all of these characteristics, as compared to the function of the parent AAV.

Ex. 1001, 6:65–7:7, 7:14–24.

The library of functional AAV capsid sequences used for comparison to a parental AAV to identify singletons "is characterized by a desired level of packaging ability, a desired level of in vitro transduction efficiency, [and]/or a desired level of in vivo gene transfer efficiency (i.e., the ability to deliver to a target selected target tissue or cell in a subject)." Ex. 1001, 3:48–55. AAVs identified as suitable for use in the functional libraries include AAV1, AAV2, AAV6, AAV7, AAV8, AAV9, and other sequences described in two listed publications. *Id*. at 5:18–23.

The '462 patent also describes how the novel AAV capsid sequences generated by mutation of the parental AAV at one or more of the singletons may be used to deliver a transgene, which encodes a polypeptide, protein, or other product of interest, to a host. *See* Ex. 1001, 12:7–9, 19:35–21:26. The '462 patent states:

> In another aspect, the present invention provides a method for delivery of a transgene to a host which involves transfecting or infecting a selected host cell with a recombinant viral vector generated with the singleton-corrected AAV (or functional fragments thereof) of the invention. Methods for delivery are well known to those of skill in the art and are not a limitation to the present invention.

Ex. 1001, 19:35–41.

D. Challenged Claims

The Petition challenges claims 1, 3–6, and 8. *See* Pet. 1, 7–8. Challenged claim 1 is the sole independent claim. *See* Ex. 1001, 193:1–194:30. Claim 1 is illustrative of the challenged claims. Claim 1 is reproduced below.

> 1. A recombinant adeno-associated virus (AAV) comprising an AAV capsid and a minigene having AAV inverted terminal repeats and a heterologous gene operably linked to regulatory sequences which direct expression of the heterologous gene in a host cell, wherein the AAV capsid comprises AAV vp1 proteins, AAV vp2 proteins, and AAV vp3 proteins, wherein the AAV vp1 proteins have i) the sequence of amino acids 1 to 738 of SEQ ID NO: 4 (AAVrh46), or ii) an amino acid sequence at least 95% identical to the full length of amino acids 1 to 738 of SEQ ID NO:4, wherein the amino acid residue corresponding to position 665 in SEQ ID NO: 4 is N when aligned along the full length of amino acids 1 to 738 of SEQ ID NO: 4.

Ex. 1001, 35:42–44.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claim(s) Challenged	35 U.S.C. §[1]	Reference(s)/Basis
1, 3–6	103(a)	’772 Publication[2]
1, 3–6	103(a)	’772 Publication and Xie[3]
1, 3–6	103(a)	’772 Publication and Snowdy[4]
8	103(a)	’772 Publication and Fabb,[5]
8	103(a)	’772 Publication, Xie, and Fabb
8	103(a)	’772 Publication, Snowdy, and Fabb

Pet. 7–8.

Petitioner further relies on the declaration of David V. Schaffer, Ph.D. (Ex. 1005) submitted with the Petition.

[1] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), included revisions to 35 U.S.C. § 103 that became effective on March 16, 2013, after the filing of the applications to which the ’274 patent claims priority. Therefore, we apply the pre-AIA versions of Section 103.

[2] Guangping Gao et al., US 2003/0138772 A1, published July 24, 2003 (Ex. 1007, “’772 Publication”).

[3] Qing Xie et al., *The atomic structure of adeno-associated virus (AAV-2), a vector for human gene therapy*, 99 Proc. Nat’l Acad. Sci., 10405–10410 (2002) (Ex. 1008, “Xie”).

[4] Stephen Snowdy, *Nuclear targeting by adeno-associated virus capsid proteins and virions* (2003) (Ph.D. dissertation, University of North Carolina, Chapel Hill) (Ex. 1009, “Snowdy”).

[5] Stewart A. Fabb et al., *Adeno-associated virus vector gene transfer and sarcolemmal expression of a 144 kDa micro-dystrophin effectively restores the dystrophin-associated protein complex and inhibits myofiber degeneration in nude/mdx mice*, 11 Human Molecular Genetics 733–741 (2002) (Ex. 1010, “Fabb”).

III. ANALYSIS OF THE ASSERTED GROUNDS

A. Legal Standards

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

A claim is unpatentable under 35 U.S.C. § 103(a) 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 before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. *See 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) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the

patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420.

Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotation marks omitted). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

An obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see In re Translogic Tech, Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person of ordinary skill in the art:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that

> instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles. In making such an analysis, we find that Petitioner has shown a reasonable likelihood of prevailing in establishing that at least claim 1 of the '274 patent is unpatentable.

B. Level of Ordinary Skill in the Art

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

In addressing the level of ordinary skill in the art, Petitioner contends that a person of ordinary skill in the art ("POSA") would have had

> at least a Ph.D. in biochemistry, molecular biology, or a related field and between one and four years of post-doctoral experience in the field of gene therapy. Alternatively, a POSA would have had at least a Master's or Bachelor's Degree in biochemistry, molecular biology, or a related field, with a

> corresponding number of additional years of experience in the field of gene therapy.

Pet. 12 (citing Ex. 1005 ¶¶ 111–115). Patent Owner states that it does not dispute this definition for purposes of the Preliminary Response. Prelim. Resp. 16.

On the current record, and for the purposes of this decision, we accept Petitioner's proposed definition, as it appears consistent with the level of skill in the art reflected in the prior art of record and the disclosure of the '462 Patent. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[] an appropriate level" as evidence of the ordinary level of skill in the art (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Claim Construction

We interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b) (2020). Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.* Moreover, "the specification 'is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term.'" *In re Abbott Diabetes Care Inc.*, 696 F.3d 1142, 1149 (Fed. Cir. 2012) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc)).

Petitioner asserts that the '274 patent "does not specify a particular program or set of program parameters that should be used to align sequences

and calculate percent identity for purposes of determining whether a particular test sequence falls within the scope of the claims." Pet. 21. Petitioner asserts, however, that it analyzed the percent identity claim elements, as Patent Owner's did in the parallel District Court litigation, "using the Clustal program at default settings to generate amino acid sequence alignments and calculate percent identity values." *Id.* at 21–22. Petitioner does not ask for any particular construction of any claim term. *See id.*

Patent Owner states that it "does not challenge Petitioner's articulation of the lack of a need for claim construction" for purposes of the Preliminary Response. Prelim. Resp. 16.

Having considered the record, we determine that no express claim construction of any claim term is necessary to reach our decision. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) ("The Board is required to construe 'only those 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)); *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd. v. Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs.*, 200 F.3d at 803)).

D. Obviousness Grounds Involving Snowdy

Petitioner asserts six obviousness grounds challenging claims 1, 3–6, and 8 of the '274 patent. The first three grounds challenge claims 1 and 3–6 based on the '772 Publication alone, as well as in combination with Xie or

Snowdy. *See* Pet. 7–8. We have reviewed the grounds on the record before us and have determined that the ’772 Publication in combination with the teachings of Snowdy presents the strongest ground for these claims.

The last three grounds challenge claim 8 based on the ’772 Publication and Fabb, as well as in combination with Xie or Snowdy. *See* Pet. 7–8. After review of these grounds on the record before us, we have determined that the combination of the ’772 Publication, Fabb, and Snowdy present the strongest ground for claim 8.

Based on these determinations, we will focus our analysis on these grounds (which includes the discussion of the teachings of the ’772 Publication set forth in Ground 1) that we have determined are the strongest. We begin with our review of the pertinent teachings of the asserted art.

i. ’772 Publication (Ex. 1007)

The ’772 Publication describes

> a method which takes advantage of the ability of adeno-associated virus (AAV) to penetrate the nucleus, and, in the absence of a helper virus co-infection, to integrate into cellular DNA and establish a latent infection. This method utilizes a polymerase chain reaction (PCR)-based strategy for detection, identification and/or isolation of sequences of AAVs from DNAs from tissues of human and non-human primate origin as well as from other sources.

Ex. 1007 ¶ 15. The ’772 Publication also provides nucleic acid sequences identified by this method, such as serotype 7 or AAV7, AAV10, AAV11, and AAV12. *Id.* ¶ 16.

The ’772 Publication further discloses:

> FIG. 1 provides the non-human primate (NHP) AAV nucleic acid sequences of the invention in an alignment with the

> previously published AAV serotypes, AAV1 [SEQ ID NO:6], AAV2 [SEQ ID NO:7], and AAV3 [SEQ ID NO:8]. These novel NHP sequences include those provided in the following Table 1, which are identified by clone number:
>
> TABLE 1
>
> | AAV Cap Sequence | Clone Number | Source Species | Tissue | SEQ ID NO (DNA) |
> |---|---|---|---|---|
> | Rh.1 | Clone 9 (AAV9) | Rhesus | Heart | 5 |
> | Rh.2 | Clone 43.1 | Rhesus | MLN | 39 |
> | Rh.3 | Clone 43.5 | Rhesus | MLN | 40 |
> | Rh.4 | Clone 43.12 | Rhesus | MLN | 41 |
> | Rh.5 | Clone 43.20 | Rhesus | MLN | 42 |
> | Rh.6 | Clone 43.21 | Rhesus | MLN | 43 |
> | Rh.7 | Clone 43.23 | Rhesus | MLN | 44 |
> | Rh.8 | Clone 43.25 | Rhesus | MLN | 45 |
> | Rh.9 | Clone 44.1 | Rhesus | Liver | 46 |
> | Rh.10 | Clone 44.2 | Rhesus | Liver | 59 |
> | Rh.11 | Clone 44.5 | Rhesus | Liver | 47 |
> | Rh.12 | Clone 42.1B | Rhesus | MLN | 30 |
> | Rh.13 | 42.2 | Rhesus | MLN | 9 |
> | Rh.14 | Clone 42.3A | Rhesus | MLN | 32 |
> | Rh.15 | Clone 42.3B | Rhesus | MLN | 36 |
> | Rh.16 | Clone 42.4 | Rhesus | MLN | 33 |
> | Rh.17 | Clone 42.5A | Rhesus | MLN | 34 |
> | Rh.18 | Clone 42.5B | Rhesus | MLN | 29 |

Ex. 1007 ¶ 66 (reproducing a partial table showing clones Rh.1 to Rh.18). Of particular interest for this proceeding is Rh.10 or Clone 44.2. *See* Pet. 13–14.

In describing recombinant viruses and uses of them, the ’772 Publication states:

> Using the techniques described herein, one of skill in the art may generate a rAAV having a capsid of a novel serotype of the invention, or a novel capsid containing one or more novel fragments of an AAV serotype identified by the method of the invention. In one embodiment, a full-length capsid from a

> single serotype, e.g., AAV7 [SEQ ID NO: 2] can be utilized. In another embodiment, a full-length capsid may be generated which contains one or more fragments of a novel serotype of the invention fused in frame with sequences from another selected AAV serotype. For example, a rAAV may contain one or more of the novel hypervariable region sequences of an AAV serotype of the invention. Alternatively, the unique AAV serotypes of the invention may be used in constructs containing other viral or non-viral sequences.
>
> It will be readily apparent to one of skill in the art one embodiment, that certain serotypes of the invention will be particularly well suited for certain uses. For example, vectors based on AAV7 capsids of the invention are particularly well suited for use in muscle; whereas vectors based on rh.10 (44-2) capsids of the invention are particularly well suited for use in lung. Uses of such vectors are not so limited and one of skill in the art may utilize these vectors for delivery to other cell types, tissues or organs. Further, vectors based upon other capsids of the invention may be used for delivery to these or other cells, tissues or organs.

Ex. 1007 ¶¶ 141–142.

In Example 9, rh.10 or clone 44.2 was studied for tissue tropism in lung, liver, and muscle. Ex. 1007 ¶¶ 252–262. It was concluded that the "novel AAV capsid clone, 44.2, was found to be a very potent gene transfer vehicle in all 3 tissues with a big lead in the lung tissue particularly." *Id.* ¶ 253. The data from two additional experiment confirmed the "superb tropism" of clone 44.2 in lung-directed gene transfer. *Id.* ¶ 256. The '772 Publication concluded that "[i]nterestingly, performance of clone 44.2 in liver and muscle directed gene transfer was also outstanding, close to that of the best liver transducer, AAV8 and the best muscle transducer AAV1, suggesting that this novel AAV has some intriguing biological significance." *Id.* ¶ 257.

ii. Snowdy (Ex. 1009)

Snowdy discusses nuclear targeting by AAV capsid proteins in the latent phase of the AAV life cycle. *See* Ex. 1009, 31. Snowdy states: "Upon initial infection, the viral genome site-specifically integrates into the host genome, where it remains latent until rescued by one of several helper viruses." *Id.* at 31 (citations omitted). Snowdy notes that this site-specific integration is unique among other latent eukaryotic viruses. *Id.*

Snowdy teaches that it is accepted that AAV capsid proteins target the nucleus, but the mechanism by which it does so is not clear. Ex. 1009, 4, 41. Snowdy looked at a basic region in the AAV capsid including the amino acid sequence ^{307}RPKRLN^{311}, and determined that it plays a role in concentrating AAV capsid proteins in the nucleus during assembly of progeny virions. *Id.* at 5. With respect to a second, similar sequence in the AAV capsid, Snowdy states:

> We mutated several kinase consensus sequences near the AAV ^{166}PARKRLN^{172} region to determine whether the possible phosphorylation sites are important in the infectivity of the virus. We mutated each of three possible kinase phosphorylation targets to either alanine or aspartic acid. We found one site, serine 181, for which transduction efficiency was enhanced by the S181A substitution and for which transduction efficiency was abrogated by converse S181D substitution [that simulates phosphorylation].

Ex. 1009, 5; *see id.* at 128.

In analyzing these results, Snowdy concludes:

> Based on Jans' data for T-ag discussed above, we expected the serine to alanine mutations to result in lowered transduction efficiency if the residue is important for regulating the putative NLS. Likewise, we expected the serine to aspartic

> acid mutation to suffer, at most, a slight decrease in transduction efficiency versus the total loss of transduction ability that is shown in figure 23. It may be premature in the field's development to assume that a given phosphorylation status will have the same effect on all NLSs, as there is insufficient evidence in the literature to support this assumption. This issue will be better understood with future studies on other nuclear localization signals.

Ex. 1009, 128–129.

Finally, Snowdy notes that "[u]ntil we establish unequivocally that basic region 3 of AAV2 is an NLS [nuclear localization signal], it is premature to assign the cause of the changes in transduction efficiency resulting from mutations to S181 as interfering with the function of an NLS." Ex. 1009, 129. Snowdy, however, assumes that S181 regulates the function of an NLS to speculate on the mechanisms of NLS regulation by S181 to include "the phosphorylation status of S181 controls the folding of the capsid protein in such a way that results in masking and unmasking of the NLS," or the phosphorylation status "is important in the binding of some cytoplasmic factor that when bound to the capsid protein, causes cytoplasmic retention of the capsid, or interference with the capsid's binding to a nuclear transport factor or the nuclear pore complex." *Id*. at 129.

iii. Fabb (Ex. 1010)

Fabb reports using AAV vectors, which are known to only accommodate less than 5 kb of foreign DNA, with a micro-dystrophin cDNA gene construct that is less than 3.8 kb to restore the dystrophin-associated protein (DAP) complex components and significantly inhibit degenerative dystrophic muscle pathology to treat Duchenne muscular

dystrophy. Ex. 1010, 1 (Abstract). Fabb concludes that "[w]e have therefore shown that the current micro-dystrophin gene delivered *in vivo* using an AAV vector is not only capable of restoring sarcolemmal DAP complexes, but can also ameliorate dystrophic pathology at the cellular level." *Id.*

iv. Ground 3 – Obviousness Over the '772 Publication and Snowdy

Petitioner contends claims 1 and 3 through 6 would have been obvious in light of the '772 Publication and Snowdy. *See* Pet. 22–42, 47–53. Petitioner presents evidence and argument to show that each of the limitations of these claims is taught by these references. *Id.*

Beginning with independent claim 1, we determine that Petitioner has met its burden for institution. Based on the current record, Petitioner has shown a reasonable likelihood of succeeding in establishing that the combination of the '772 Publication and Snowdy renders at least claim 1 obvious.

For instance, Petitioner explains how the '772 Publication teaches "A recombinant adeno-associated virus (AAV) comprising an AAV capsid and a minigene having AAV inverted terminal repeats and a heterologous gene operably linked to regulatory sequences which direct expression of the heterologous gene in a host cell, wherein the AAV capsid comprises AAV vp1 proteins, AAV vp2 proteins, and AAV vp3 proteins." *See* Pet. 22–25, 47 (citing Ex. 1007 ¶¶ 23, 24, 80, 86, 90, 92, 93, 97, 99, 139, 141; Ex. 1005 ¶¶ 198–200); Ex. 1005 ¶¶ 195–202.

Petitioner also provides sufficient evidence that at this point in the proceeding is unrebutted that the '772 Publication also teaches the limitation, "wherein the AAV vp1 proteins have i) the sequence of amino

acids 1 to 738 of SEQ ID NO: 4 (AAVrh46), or ii) an amino acid sequence at least 95% identical to the full length of amino acids 1 to 738 of SEQ ID NO: 4." Pet. 25–26. According to Petitioner,

> the '772 Publication discloses the amino acid sequence of the vp1 capsid protein for the preferred embodiment, AAVrh.10, at SEQ ID NO: 81. Alignment of SEQ ID NO:81 (AAVrh.10) from the '772 Publication with SEQ ID NO: 4 (AAVrh.46) from the '274 patent using Clustal at default settings shows that the percent identity for these two sequences is 97.29%--which is greater than the "at least 95% identical" threshold in claim 1.

Pet. 25–26 (citing Ex. 1007 ¶¶ 98–103, 264–266, Table 1 (SEQ ID NO: 81, also referred to as "rh.10" and "clone 44.2"), 112–113, Fig. 2; Ex. 1018, 1–2; Ex. 1005 ¶¶ 204–205). Dr. Schaffer testifies that

> I have aligned SEQ ID NO: 81 (AAVrh.10) from the '772 Publication with SEQ ID NO: 4 (AAVrh.46) from the '274 patent using Clustal Omega at default settings. Sequence Alignment of AAVrh.46 (SEQ ID NO: 4) from the '274 Patent and AAVrh.10 (SEQ ID NO: 81) from the '772 Publication (EX1018), pp. 1-2. As shown in the alignment, Clustal reports that the percent identity for these two sequences is 97.29% – which is greater than the "at least 95% identical" threshold recited in claim 1. EX1018 (AAVrh.10/AAVrh.46 Alignment), pp. 1-2.

Ex. 1005 ¶ 205.

For the final limitation of claim 1—the amino acid residue corresponding to position 665 in SEQ ID NO: 4 is N when aligned along the full length of amino acids 1 to 738 of SEQ ID NO: 4—Petitioner points to statements in the '772 Publication that AAVrh.10 has "superb tropism" in lung-directed gene transfer, *see* Ex. 1007 ¶ 256; Ex. 1005 ¶ 207, and AAV8, which has asparagine (N) at position 665, provides "a substantial advantage over the other serotypes in terms of efficiency of gene transfer to liver, *see*

Ex. 1007 ¶ 250; Ex. 1005 ¶ 207." Pet. 26. Petitioner also points to statements in the '772 Publication that compares the performance of AAVrh.10 and AAV8 finding AAVrh.10 had outstanding performance in both liver and muscle directed gene transfer, which was close to the best liver transducer, AAV8. Pet. 26–27.

Petitioner reasons:

> The '772 Publication thus teaches the superiority of AAVrh.10 overall and in lung in particular, the superiority of AAV8 in liver, and the importance of efficient gene transfer to the liver for a variety of gene therapy applications. Given these teachings and the express comparison between AAVrh.10 and AAV8 in the '772 Publication, a POSA would have considered substitutions between AAVrh.10 (best overall and best in lung) and AAV8 (best in liver) as a promising strategy for obtaining an artificial variant of AAVrh.10 with even more efficient gene transfer in liver. EX. 1005 ¶ 210.
>
> Moreover, given the already superior performance of AAVrh.10 in lung, a POSA would not have sought to make sweeping substitutions throughout the AAVrh.10 sequence, such as changing multiple amino acids at once, for fear of damaging or destroying the desirable properties of AAVrh.10. Instead, a POSA would have taken a finer, more directed approach, modifying a single amino acid residue at a time. Ex. 1032, 5–6, Table 1; EX. 1005 ¶ 211.
>
> A POSA would have understood from the alignment in Figure 2 of the '772 publication that AAVrh.10 and AAV8 differ at only 48 positions. EX1007, 98-103, Fig. 2, [0071]. EX1019 reproduces the alignment of AAVrh.10 and AAV8 using Clustal O at default settings, similar to the Clustal W program used to create the alignment in Figure 2. EX1019, 1; EX1007, [0071]; EX1005, ¶212.
>
> One of the differences between AAV8 and AAVrh.10 is at position 665, where AAV8 has an asparagine (N), and AAVrh.10 has a serine (S). EX1019, 1. Thus, based on the

> teaching in Figure 2 and the experimental data regarding AAVrh.10 and AAV8 disclosed in the Examples, a POSA would have been motivated to make this single amino acid change in AAVrh.10 – namely, substituting an N for the S at position 665. EX1005, ¶213; EX1007, [0074], [0075] ("An artificial AAV serotype may be, without limitation, a chimeric AAV capsid, a recombinant AAV capsid, or a "humanized" AAV capsid.").

Pet. 27–28.

Petitioner offers testimony from one of Patent Owner's declarants, Dr. Paola Leone, in another litigation to confirm this reasoning. *See* Pet. 28–34 (citing Ex. 2012). Petitioner further asserts that analyzing the differences between AAVrh.10 and AAV8 and then making and testing the 48 variants of AAVrh.10, with each containing a single substitution, "was well within the skill of a POSA at the time, and required no more than routine experimentation." Pet. 35 (citing Ex. 1007 ¶¶ 18, 72; Ex. 1005 ¶¶ 227–229).

Petitioner concludes:

> Moreover, a POSA would have had a reasonable expectation of success that a variant of AAVrh.10 with an S to N substitution at position 665 would form a stable AAV capsid capable of packaging a minigene. EX1005, ¶232. According to Patent Owners' expert, Dr. Leone, a POSA would have known with a "reasonable degree of probability" that modified AAVrh.10 capsid sequences having only a small number of mutations – such as a single substitution according to the alignment in Figure 2 – would result in proteins that "may be used to form an AAV capsid." EX1012, ¶¶323, 334, 406.

Pet. 36.

Patent Owner counters that Petitioner's reasoning is fatally flawed because it employs impermissible hindsight by looking for a AAV with at

least 95% identity with the claims AAVrh46 capsid that was not yet known. Prelim. Resp. 16–18. Patent Owner asserts:

> To arrive at the sequence of the novel AAVrh46 capsid, the Petitioner starts by choosing just one of the more than fifty sequences disclosed in the ’772 Publication, AAVrh10—a choice it makes based on the sequence covered by the challenged claims. Petitioner then aligns that sequence with just one of the more than fifty other sequences in that publication, AAV8, to determine that there are more than forty differences between those sequences. Petitioner then replaces only a single amino acid, AAVrh10’s serine at position 665, with the asparagine that AAV8 has at that position.

Prelim. Resp. 17.

Patent Owner points to three perceived flaws in this reasoning with Petitioner’s alleged lack of showing concerning:

> 1. Why a POSA would have selected AAVrh.10 from among the dozens of AAV capsids (forty-eight novel capsids, thirteen of which are at least 95% identical to AAVrh46) disclosed in the ’772 Publication;
>
> 2. Why a POSA would have modified AAVrh.10 at all given its superior performance in lung and muscle tissue to the extent that liver targeting was desired and AAV8 already performed substantially better than AAVrh.10 in liver tissue; and
>
> 3. Why a POSA would have modified AAVrh.10 at position 665 as described as opposed to other modifications.

Prelim. Resp. 17–18.

Patent Owner reviews the disclosure of the ’772 Publication to point out the “numerous other preferred embodiments,” including the forty-eight

other novel AAVs useful for various tissues that were deemed "particularly desirable," and thirteen of which are at least 95% identical to AAVrh46. Prelim. Resp. 18–19 (citing Ex. 1007 ¶¶ 3, 66, 80, Table 1), 21–22. Patent Owner points out that "[t]he '772 Publication shows that other capsids have equal or superior targeting than AAVrh.10 depending on the tissue type," including the claimed AAV7 capsids that are "particularly well suited for use in muscle; where vectors based on rh.10 (44-2) capsids . . . are particularly well suited for use in lung." *Id*. at 19–20 (citing Ex. 1007 ¶ 142).

Patent Owner also points to Table 8 in which "[n]otably, AAV8 shows the highest gene transfer in liver tissue, surpassing AAVrh.10 by over fifty percent," *see* Prelim. Resp. 20 (citing Ex. 1007 ¶¶ 246, 253, Table 8), while "[i]n muscle tissue, on the other hand, AAV1 and AAVrh.10 show roughly equivalent gene transfer," *see id*. at 21 (citing Ex. 1007 ¶ 253, Table 8).

We find on the record before us that Petitioner has the better position. As we noted in our discussion of the '772 Publication, AAVrh.10 was singled out in Example 9 as an outstanding performer in liver and muscle directed gene transfer, and was close to the best liver transducer AAV8, "suggesting that this novel AAV has some intriguing biological significance." *See supra* Section III.D.i.; Ex. 1007 ¶ 257. Dr. Schaffer testifies:

> The data and discussion in the Examples highlight the unique properties of the newly identified AAVrh.10 variant as a potential rAAV vector, particularly in the transduction of lung cells. Specifically, Example 9 discloses two transduction experiments, in each of three different tissues: lung, liver and muscle. Example 9 states: "The data from both these

> experiments confirmed the superb tropism of clone 44.2 [AAVrh.10] in lung-directed gene transfer."

Ex. 1005 ¶ 122 (citing Ex. 1007 ¶¶ 133, 256).

Based on the disclosure of the '772 Publication and the unrebutted testimony of Dr. Shaffer, Petitioner has sufficiently shown on the record before us that a POSA would have been motivated to select the promising AAVrh.10 as a starting point. The fact that other novel AAVs may also have promise for targeting particular types of tissues does not diminish or deflect from the teachings of the '772 Publication regarding AAVrh.10.

Addressing Patent Owner's second concern as to why AAVrh.10 would have been modified at all because it already exhibited high performance, Dr. Shaffer points to the '772 Publication's express comparison of AAVrh.10 and AAV8 as strong performers, *see* Ex. 1005 ¶ 208, and notes that "the '772 Publication teaches that it was particularly important to identify serotypes with good 'efficiency of gene transfer to liver that until now has been relatively disappointing,'" *see id*. ¶ 209. Dr. Shaffer concludes:

> The '772 Publication thus teaches the superiority of AAVrh.10 overall and in lung in particular, the superiority of AAV8 in liver, and the importance of efficient gene transfer to the liver for a variety of gene therapy applications. Given these teachings and the express comparison between AAVrh.10 and AAV8 in the '772 Publication, a POSA would have considered substitutions between AAVrh.10 (best overall and best in lung) and AAV8 (best in liver) as a promising strategy for obtaining an artificial variant of AAVrh.10 with even more efficient gene transfer in liver.

Id. ¶ 210.

Based on the record before us, we credit Dr. Shaffer's testimony here and determine that Petitioner has sufficiently shown that a POSA would be motivated to modify AAVrh.10 based on a comparison with AAV8.

Turning to Patent Owner's last perceived flaw in Petitioner's reasoning concerning the teachings of the '772 Publication, we have some sympathy with Patent Owner's assertion that Petitioner has not shown why a POSA would have modified AAVrh.10 at position 665 based on the '772 Publication. Dr. Shaffer testifies that

> A POSA would have understood from the alignment in Figure 2 of the '772 publication that AAVrh.10 and AAV8 differ at only 48 positions. EX1007 ('772 Publication), pp. 98-103, Fig. 2, [0071]. I have reproduced the alignment of AAVrh.10 and AAV8 using Clustal O at default settings, similar to the Clustal W program used to create the alignment in Figure 2. Sequence Alignment of AAVrh.10 (SEQ ID NO: 81) and AAV8 (SEQ ID NO: 95) capsid protein sequences from the '772 Publication (EX1019); EX1007 ('772 Publication), [0071].
>
> One of the differences between AAV8 and AAVrh.10 is at position 665, where AAV8 has an asparagine (N), and AAVrh.10 has a serine (S). EX1019 (AAVrh.10/AAV8 Alignment). Thus, based on the teaching in Figure 2 and the experimental data regarding AAVrh.10 and AAV8 disclosed in the Examples, a POSA would have been motivated to make this single amino acid change in AAVrh.10 – namely, substituting an N for the S at position 665. EX1007 ('772 Publication), [0074], [0075] ("An artificial AAV serotype may be, without limitation, a chimeric AAV capsid, a recombinant AAV capsid, or a 'humanized' AAV capsid.").

Ex. 1005 ¶¶ 212–213. Dr. Shaffer bolsters his conclusions here based on the testimony of Dr. Leone involving "how a POSA would understand the teachings of a patent that has "the same specification and claims priority to

the same applications as the ’772 Publication.” Ex. 1005 ¶ 214 (citing Ex. 1011; Ex. 1012), *see id.* ¶¶ 214–226.

We agree with Patent Owner on the record before us that Petitioner does not appear to offer sufficient evidence and reasoning as to why a POSA would have modified AAVrh.10 at position 665 as described as opposed to other modifications based solely on the disclosure of the ’772 Publication. We do agree with Petitioner, however, that on the record before us, Snowdy provides such sufficient evidence and reasoning. *See* Pet. 47–52.

Dr. Shaffer testifies with supporting evidence that “a POSA would have understood that mutation of phosphorylatable residues such as serine to non-phosphorylatable residues improved the stability and decreased the rate of degradation of various proteins.” Ex. 1005 ¶ 273 (citations omitted); *see* Ex. 1005 ¶ 272. Dr. Shaffer also testifies that “a POSA at the time seeking to improve the transduction of AAVrh.10, would have been motivated to combine the ’772 publication with Snowdy, given that Snowdy disclosed a method of improving the transduction of AAV vectors by removing phosphorylatable sites in the capsid proteins.” *Id.* ¶ 276.

Dr. Shaffer testifies that he used the same program, NetPhos, that Snowdy used to determine potential phosphorylation sites in AAVrh.10. Ex. 1005 ¶¶ 278–279. Dr. Shaffer found only four such sites that correspond to non-phosphorylatable amino acids in AAV8, which includes S665N. *Id.* ¶ 279. Dr. Shaffer concludes that “a POSA at the relevant time would have been motivated to construct all four of these mutant versions of AAVrh.10, and could have done so using only routine experimentation, per Dr. Leone’s

opinion in the earlier litigation, as I discussed in Ground 1." *Id.* ¶ 280.

Dr. Shaffer further testifies:

> Making four variants of AAVrh.10, each containing a single substitution of a non-phosphorylatable amino acid for a phosphorylatable amino acid, and using those sequences to make rAAV vectors was well within the skill of a POSA at the time, and required no more than routine experimentation – as I discussed above for Ground 1.

Ex. 1005 ¶ 285.

At this point in the proceeding, Dr. Shaffer's testimony is unrebutted. *See* Prelim. Resp. 51–57. We credit Dr. Shaffer's unrebutted testimony here and determine that Petitioner has shown sufficiently for purposes of institution that a POSA would have been motivated to make the substitution at the 665 position with a reasonable expectation of success. Therefore, we determine that Petitioner has shown a reasonable expectation of success in showing that claim 1 would have been obvious over the combination of the '772 Publication and Snowdy.

v. Ground 6 - Obviousness Over the '772 Publication, Snowdy, and Fabb

Petitioner asserts that a POSA seeking to use the variant of AAVrh.10 with the claimed substitution at position 665 "as a delivery vehicle for a dystrophin gene would have been motivated to combine the '772 Publication and Snowdy with Fabb, which teaches the construction of a smaller version of dystrophin gene known as a 'micro-dystrophin' for use with an AAV vector" with a reasonable expectation of success. Pet. 58–59 (citing Ex. 1010, 2–3; Ex. 1005 ¶¶ 305–307).

Patent Owner does not question Fabb's teachings as set forth by Petitioner at this point, but responds that this ground fails because claim 8 requires tropism to *muscle* tissue, not to lung or liver, a fact Petitioner does not address. Prelim. Resp. 57. Patent Owner states "the Petition is silent as to why an AAV that was modified to have alleged improved liver tropism would have been used to carry a mini or micro-dystrophin and target muscle." *Id*. at 59.

We note that the '772 Publication states that "performance of clone 44.2 in liver and muscle directed gene transfer was also outstanding" indicating that AAVrh.10 (at least before modification) performed well with muscle tissue, but invite the parties to address this issue further at trial. *See* Ex. 1007 ¶ 257; *see id*. ¶ 253.

IV. CONCLUSION

Based on the current record, we determine that Petitioner has shown a reasonable likelihood that it will prevail in establishing that at least one claim of the '274 patent is unpatentable. Accordingly, we institute review of all claims challenged on all of the grounds in the Petition. *See* Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019), 64, *available at* https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim. Our view with regard to any conclusion reached in the foregoing analysis could change upon completion of the record.

V. ORDER

Accordingly, it is:

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1, 3–6, and 8 of the ’274 patent based on the unpatentability challenges presented in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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