UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAREPTA THERAPEUTICS, INC.,

Petitioner

v.

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA AND REGENXBIO INC.,

Patent Owners

U.S. Patent No. 11,680,274

"Method of Increasing the Function of an AAV Vector"

IPR2024-00580

PETITION FOR *INTER PARTES* REVIEW

TABLE OF CONTENTS

Page

LIST OF EXHIBITS

Number	Description
EX1001	U.S. Patent No. 11,680,274 ("the '274 patent")
EX1002	Prosecution history of U.S. Patent No. 11,680,274 ("the '274 Prosecution History")
EX1003	U.S. Provisional Patent Application No. 60/669,083, filed on April 7, 2005 ("the '083 Provisional")
EX1004	U.S. Provisional Patent Application No. 60/733,497, filed on November 4, 2005 ("the '497 Provisional")
EX1005	Declaration of Dr. David V. Schaffer under 37 C.F.R. § 1.68 ("Schaffer Decl.")
EX1006	*Curriculum vitae* of Dr. David V. Schaffer ("Schaffer CV")
EX1007	U.S. Patent Application Publication 2003/0138772 ("the '772 Publication")
EX1008	Xie *et al*., "The atomic structure of adeno-associated virus (AAV-2), a vector for human gene therapy," *Proc. Nat'l Acad. Sci*., 2002, pp. 10405-10410 ("Xie")
EX1009	Snowdy, "Nuclear targeting by adeno-associated virus capsid proteins and virions," A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the curriculum of Neurobiology (2003) ("Snowdy")
EX1010	Fabb *et al*., "Adeno-associated virus vector gene transfer and sarcolemmal expression of a 144 kDa micro-dystrophin effectively the dystrophin-associated protein complex and inhibits myofibre degeneration in nude/*mdx* mice," *Human Molecular Genetics*, 2002, Vol. 11, No. 7, pp. 733-741 ("Fabb")
EX1011	Opening Expert Report of Paola Leone (Public Excerpts) ("Leone Opening Report")

Number	Description
EX1012	Rebuttal Expert Report of Paola Leone (Public Excerpts) ("Leone Rebuttal Report")
EX1013	Rebuttal Expert Report of Michael Metzker (Excerpts) ("Metzker Rebuttal Report")
EX1014	U.S. Patent No. 10,526,617 ("the '617 patent")
EX1015	Declaration of Thomas Hyatt under 37 C.F.R. § 1.68 ("Hyatt Decl.")
EX1016	Declaration of Christopher DuBose under 37 C.F.R. § 1.68 ("DuBose Decl.")
EX1017	Jans and Jans, "Negative charge at the casein kinase II site flanking the nuclear localization signal of the SV40 large T-antigen is mechanistically important for enhanced nuclear import," *Oncogene*, 1994, Vol. 9, No. 10, pp. 2961-2968 ("Jans & Jans")
EX1018	Sequence Alignment of AAVrh.46 (SEQ ID NO: 4) from the '274 Patent and AAVrh.10 (SEQ ID NO: 81) from the '772 Publication ("AAVrh.10/AAVrh.46 Alignment")
EX1019	Sequence Alignment of AAVrh.10 (SEQ ID NO: 81) and AAV8 (SEQ ID NO: 95) Capsid Protein Sequences from the '772 Publication ("AAVrh.10/AAV8 Alignment")
EX1020	Sequence Alignment of AAV2, AAVrh.10, and AAV8 Capsid Protein Sequences ("AAV2/AAVrh.10/AAV8 Alignment")
EX1021	NetPhos/AAVrh.10 Phosphorylation Sites ("NetPhos-AAVrh.10")
EX1022	Sequence Alignment of AAVrh.10 (SEQ ID NO: 81) and AAV8 (SEQ ID NO: 95) Capsid Protein Sequences from the '772 Publication Showing Differences In Phosphorylation Sites ("AAVrh.10/AAV8 Phosphorylation Sites")
EX1023	Table Showing Xie Surface Amino Acids ("Xie Surface Table")

Number	Description
EX1024	D.I. 1, Complaint, Regenxbio Inc., *et al*. v. Sarepta Therapeutics, Inc. *et al*., C.A. No. 20-1226-RGA (D. Del.) ("Penn-I Complaint")
EX1025	D.I. 1, Complaint, Regenxbio Inc., *et al*. v. Sarepta Therapeutics, Inc. *et al*., C.A. No. 23-667-RGA (D. Del.) ("Penn-II Complaint")
EX1026	12/20/23 Regenxbio's Initial Claim Chart Relating Accused Product to the Asserted Claims of U.S. Patent 11,680,274, Regenxbio Inc., *et al*. v. Sarepta Therapeutics, Inc. *et al*., C.A. No. 23-667-RGA (D. Del.) ("Initial Claim Chart")
EX1027	U.S. Patent 9,434,928 ("the '928 patent")
EX1028	D.I. 20, Scheduling Order, Regenxbio Inc., *et al*. v. Sarepta Therapeutics, Inc. *et al*., C.A. No. 23-667-RGA (D. Del.) ("Scheduling Order")
EX1029	Kwon and Schaffer, "Designer Gene Delivery Vectors: Molecular Engineering and Evolution of Adeno-Associated Viral Vectors for Enhanced Gene Transfer," *Pharm. Research*, 2008, Vol. 25, No. 3, pp. 489-499 ("Kwon")
EX1030	Kotterman and Schaffer, "Engineering adeno-associated viruses for clinical gene therapy," *Nature Reviews, Genetics*, 2014, Vol. 15, pp. 445-451 ("Kotterman")
EX1031	Grimm and Kay, "From Virus Evolution to Vector Revolution: Use of Naturally Occurring Serotypes of Adeno-associated Virus (AAV) as Novel Vectors for Human Gene Therapy," *Curr. Gene Therapy*, 2003, Vol. 3, pp. 281-304 ("Grimm")
EX1032	Wu *et al*., "Mutational Analysis of the Adeno-Associated Virus Type 2 (AAV2) Capsid Gene and Construction of AAV2 Vectors with Altered Tropism," *J. Virol*., 2000, Vol. 74, No. 18, pp. 8635-8647 ("Wu")
EX1033	Blom *et al*., "Sequence and Structure-based Prediction of Eukaryotic Protein Phosphorylation Sites," *J. Mol. Biol*., 1999, Vol. 294, pp. 1351-1362 ("Blom")

Number	Description
EX1034	Ivanov *et al*., "Phosphorylation of the Potyvirus Capsid Protein by Protein Kinase CK2 and Its Relevance for Virus Infection," *The Plant Cell*, 2003, Vol. 15, pp. 2124–2139 ("Ivanov")
EX1035	Chen *et al*., "Signal-induced site specific phosphorylation targets IκBα to the ubiquitin-proteasome pathway," *Genes & Dev.*, 1995, Vol. 9, pp. 1586-1597 ("Chen")
EX1036	Lange *et al*., "Phosphorylation of human progesterone receptors at serine-294 by mitogen-activated protein kinase signals their degradation by the 26S proteasome," *Proc. Nat'l Acad. Sci*., 2000, Vol. 97, pp. 1032-1037 ("Lange")
EX1037	Patrick *et al*., "p35, the Neuronal-specific Activator of Cyclin-dependent Kinase 5 (Cdk5) Is Degraded by the Ubiquitin-Proteasome Pathway," *J. Biol. Chem*., 1998, Vol. 273, pp. 24057-24064 ("Patrick")
EX1038	Penrose and McBride, "Proteasome-Mediated Degradation of the Papillomavirus E2-TA Protein Is Regulated by Phosphorylation and Can Modulate Viral Genome Copy Number," *J. Virol*., 2000, Vol. 74, No. 13, pp. 6031-6038 ("Penrose")
EX1039	Whiteside *et al*., "N- and C-Terminal Sequences Control Degradation of MAD3/IκBα in Response to Inducers of NF-κB Activity," *Mol. and Cell. Biol*., 1995, Vol. 15, pp. 5339-5345 ("Whiteside")
EX1040	Alberts, MOLECULAR BIOLOGY OF THE CELL, 3rd Ed., Chapters 2 (excerpt), 3, and 6 ("Alberts I")
EX1041	https://www.genome.gov/about-genomics/fact-sheets/Deoxyribonucleic-Acid-Fact-Sheet ("DNA Fact Sheet")
EX1042	https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genomic-variation ("Genomic Variation")

Number	Description
EX1043	https://www.genome.gov/genetics-glossary/Central-Dogma ("Central Dogma")
EX1044	https://www.genome.gov/genetics-glossary/Genetic-Code ("Genetic Code")
EX1045	https://www.genome.gov/about-genomics/fact-sheets/Polymerase-Chain-Reaction-Fact-Sheet ("PCR Fact Sheet")
EX1046	https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy ("Gene Therapy")
EX1047	https://patienteducation.asgct.org/gene-therapy-101/vectors-101 ("Vectors 101")
EX1048	Mandal *et al*., "Optical Backbone-Sidechain Charge Transfer Transitions in Proteins Sensitive to Secondary Structure and Modifications," *Faraday Discussions*, 2018, Vol. 207, pp. 115-135 ("Mandal")
EX1049	Ponnazhagan *et al*., "Adeno-associated Virus for Cancer Gene Therapy," *Cancer Research*, 2001, Vol. 61, pp. 6313-6321 ("Ponnazhagan")
EX1050	Chiorini *et al*., "Cloning and Characterization of Adeno-Associated Virus Type 5," *J. Virol*., 1999, Vol. 73, No. 2, pp. 1309-1319 ("Chiorini")
EX1051	Mori *et al*., "Two novel adeno-associated viruses form cynomolgus monkey: pseudotyping characterization of capsid protein," *Virology*, 2004, Vol. 330, pp. 375-383 ("Mori")
EX1052	Hauck and Xiao, "Characterization of Tissue Tropism Determinants of Adeno-Associated Virus Type 1," *J. Virol*., 2003, Vol. 77, pp. 2768-2774 ("Hauck")
EX1053	Matsushita *et al*., "Adeno-associated virus vectors can be efficiently produced without helper virus," *Gene Therapy*, 1998, Vol. 5, pp. 938-945 ("Matsushita")

Number	Description
EX1054	Kim *et al*., "Substrate Specificities and Identification of Putative Substrates of ATM Kinase Family Members," *J. Biol. Chem*., 1999, Vol. 274, pp. 37538–37543 ("Kim")
EX1055	U.S. Patent 8,999,678 File History (Excerpts)
EX1056	Alberts, MOLECULAR BIOLOGY OF THE CELL, 3rd Ed., Chapters 7 and 8 ("Alberts II")

LIST OF CHALLENGED CLAIMS

Claim	Element
1 [pre]	A recombinant adeno-associated virus (AAV) comprising
1[a]	an AAV capsid and
1[b]	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,
1[c]	wherein the AAV capsid comprises AAV vp1 proteins, AAV vp2 proteins, and AAV vp3 proteins,
1[d]	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
1[e]	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.
3	The recombinant AAV according to claim 1, wherein the AAV vp1 capsid proteins have an amino acid sequence which is at least 97% 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 is N when aligned along the full length of amino acids 1 to 738 of SEQ ID NO: 4.
4	The recombinant AAV according to claim 1, wherein the AAV inverted terminal repeats are from a different AAV than the AAV supplying the capsid proteins.
5	A composition comprising the recombinant AAV according to claim 1 and a physiologically compatible carrier.

Claim	Element
6	The recombinant AAV according to claim 1, wherein the heterologous gene encodes an ornithine transcarbamylase, arginosuccinate synthetase, arginosuccinate lyase, arginase, fumarylacetacetate hydrolase, carbamoyl phosphate synthetase I, phenylalanine hydroxylase, alpha-1 antitrypsin, glucose-6-phosphatase, porphobilinogen deaminase, cystathione beta-synthase, branched chain ketoacid decarboxylase, isovaleryl-coA dehydrogenase, propionyl-CoA carboxylase, methylmalonyl-CoA mutase, glutaryl-CoA dehydrogenase (GCDH), betaglucosidase, pyruvate carboxylate, hepatic phosphorylase, phosphorylase kinase, β-glucuronidase (GUSB), glycine decarboxylase, a low density lipoprotein (LDL) receptor, high density lipoprotein (HDL) receptor, very low density lipoprotein (VLDL) receptor, scavenger receptor, glucocorticoid receptor, estrogen receptor, Vitamin D receptor, nuclear receptor, cystic fibrosis transmembrane regulator (CFTR) sequence, Factor IX or variants thereof, Factor VIII or variants thereof, a dystrophin gene product, or an immunoglobulin.
8	The recombinant AAV according to claim 6, wherein the dystrophin gene product is a mini-dystrophin or micro-dystrophin.

Sarepta Therapeutics, Inc. ("Sarepta" or "Petitioner") respectfully requests *inter partes* review of claims 1, 3-6, and 8 (the "challenged claims") of U.S. Patent No. 11,680,274 ("the '274 patent") (EX1001). The '274 patent is assigned to The Trustees of the University of Pennsylvania (EX1025, ¶23) and exclusively licensed to REGENXBIO Inc. (EX1025, ¶¶25-27) (collectively, "Patent Owners").

I. INTRODUCTION

Long before the earliest priority date of the '274 patent, adeno-associated viruses ("AAVs") were understood to be useful vectors for gene therapy. More than 50 naturally occurring AAV variants had been isolated and characterized. AAV vectors had been widely tested in animal studies and in human clinical trials to evaluate their use in gene therapy applications.

AAV capsid proteins in particular were the focus of a great deal of research and experimentation because they were widely understood to be important determinants of the ability of AAV vectors to deliver therapeutic genes to the appropriate cell types in the patient. Researchers had created many different mutant variants of AAV capsid proteins to determine the effects on AAV function of changing one or more amino acids in the capsid protein sequence. In particular, researchers mixed and matched amino acids and regions of capsid proteins from different AAV variants, seeking to confer the beneficial properties of one variant on another through these substitutions.

The challenged claims are directed to a recombinant AAV ("rAAV") with an AAV capsid comprising vp1, vp2, and vp3 capsid proteins. The vp1 capsid proteins in the claimed rAAVs have an amino acid sequence from a naturally occurring AAV variant designated AAVrh.46, or a sequence at least 95% identical to the AAVrh.46 sequence, and where the amino acid sequence has an asparagine (N) at position 665.

Here, the claimed rAAVs are obvious over the '772 Publication – alone and in combination with other references, Xie, Snowdy, and Fabb. Indeed, in an earlier case involving a patent having the same specification as the '772 Publication, Patent Owners' technical expert, Dr. Paola Leone, confirmed that the '772 Publication teaches the creation of at least one modified AAV capsid sequence that meets the limitations of the challenged claims in the '274 patent.[1]

[1] In the earlier case (the "Penn-I" litigation), Patent Owners asserted the '617 patent, which shares the same specification and claims priority to the same applications as the '772 Publication. EX1024, ¶1; EX1014; EX1007. In connection with that case, Patent Owners served technical expert reports discussing the teachings of the specification of the '617 patent (and thereby the teachings of the '772 publication) to a person of ordinary skill in the art.

The '772 Publication. The '772 Publication discloses rAAVs comprising an AAV capsid with vp1 capsid proteins having an amino acid sequence from a naturally occurring variant, designated AAVrh.10, which is a preferred embodiment. The vp1 capsid protein sequence for AAVrh.10 is "at least 95% identical" to AAVrh.46. Although AAVrh.10 has a serine (S) at position 665, the '772 Publication discloses another preferred embodiment, a naturally occurring variant, AAV8, with an asparagine (N) at position 665.

These two preferred embodiments differ somewhat in their favorable properties for use as gene therapy vectors, and in particular, their ability to target certain types of cells in the patient that are of interest for gene therapy. Consistent with the disclosures in the '772 Publication, it would have been obvious to the person of ordinary skill in the art ("POSA") to make substitutions from AAV8 into AAVrh.10, in an attempt to confer the uniquely favorable properties of AAV8 onto AAVrh.10. One such substitution from AAV8 to improve the properties of AAVrh.10 would have been the substitution of asparagine (N) for serine (S) at position 665 of AAVrh.10. Dr. Leone confirms that the '772 Publication teaches the creation of modified capsid sequences having single amino acid substitutions, such as AAVrh.10 with a serine (S) to asparagine (N) substitution at position 665.

The '772 Publication and Xie. Likewise, it would have been obvious to a POSA to make an rAAV having the vp1 sequence recited in the challenged claims

based on the '772 Publication in combination with the crystal structure data for the AAV capsid in Xie. Patent Owners' second technical expert in the Penn-I litigation, Dr. Michael Metzker, confirms that a POSA would have consulted available crystallography data in determining potential substitution sites for the AAVrh.10 capsid protein sequence in the '772 Publication. Xie discloses that position 665 is located on the surface of the AAV capsid. Thus, a POSA, having identified position 665 as a potential substitution site based on a comparison of the AAVrh.10 and AAV8 sequences, would have further identified position 665 as particularly promising, in light of its location on the surface of the capsid.

The '772 Publication and Snowdy. Further, it would have been obvious to a POSA to make an rAAV having the vp1 sequence recited in the challenged claims based on the combination of the '772 Publication and Snowdy – which teaches that the substitution of a phosphorylatable amino acid, such as serine (S), with a non-phosphorylatable amino acid, such as alanine (A) or asparagine (N), may improve the transduction efficiency of an rAAV vector. Thus, a POSA, having identified position 665 as one that could be substituted based on the comparison of AAVrh.10 with AAV8, would have further identified position 665 as a promising substitution site, in light of the fact that the amino acid in AAVrh.10, serine (S), is phosphorylatable, while the corresponding amino acid in AAV8, asparagine (N), is not. Moreover, a POSA would have reasonably expected an AAV capsid protein

with this single S665N mutation to form an rAAV, given the disclosure in Snowdy that all of the mutant capsids made with this type of substitution – a single amino acid change removing a phosphorylation site – formed virus at normal titers.

As explained in more detail below, there are multiple paths that lead a POSA to an rAAV having the vp1 capsid sequence recited in the challenged claims – the '772 Publication itself, the '772 Publication in combination with the crystallography data in Xie, and the '772 Publication in combination with the phosphorylation data in Snowdy. Thus, the evidence shows that there is a reasonable likelihood that Petitioner will prevail with respect to each of the challenged claims and establish the unpatentability of those claims by a preponderance of the evidence.

II. MANDATORY NOTICES

A. Real Parties-in-Interest (37 C.F.R. §42.8(b)(1))

Petitioner identifies Sarepta Therapeutics, Inc., Sarepta Therapeutics Three, LLC, and Catalent, Inc. as real parties-in-interest.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Petitioner identifies the following related matters. The '274 patent is being asserted in currently-pending litigation: Regenxbio Inc., *et al*. v. Sarepta Therapeutics, Inc. *et al*., C.A. No. 23-667-RGA (D. Del.) ("Penn-II"). EX1025.

Petitioner is currently unaware of any other lawsuits involving the '274 patent.

C. Related Patent Office Proceedings

This is the first petition challenging a claim of the '274 patent.

D. Lead and Back-up Counsel and Service Information

Petitioner provides the following counsel and service information. Pursuant to 37 C.F.R. §42.10(b), a Power of Attorney accompanies this Petition.

Lead Counsel	Back-Up Counsel
Robert Wilson (Reg. No. 45,227) Quinn Emanuel Urquhart & Sullivan, LLP 51 Madison Avenue, 22nd Floor New York, New York 10010 robertwilson@quinnemanuel.com (212) 849-7000	Anne Toker (Reg. No. 53,692) Quinn Emanuel Urquhart & Sullivan, LLP 51 Madison Avenue, 22nd Floor New York, New York 10010 annetoker@quinnemanuel.com (212) 849-7000
	James Glass (Reg. No. 46,729) Quinn Emanuel Urquhart & Sullivan, LLP 51 Madison Avenue, 22nd Floor New York, New York 10010 jimglass@quinnemanuel.com (212) 849-7000

III. REQUIREMENTS FOR IPR

A. Payment of Fees

The undersigned authorizes the Office to charge the fee required for this Petition for *inter partes* review to Deposit Account No. 50-5708.

B. Grounds for Standing

Petitioner certifies that the ’274 patent is available for IPR and Petitioner is not barred or estopped from requesting IPR on the grounds identified herein. Petitioner further certifies that the prohibitions of 35 U.S.C. §§315 (a)-(b) are inapplicable.

C. Statement of Relief Requested

Petitioner respectfully requests review and cancellation of claims 1, 3-6, and 8 of the ’274 patent. The challenged claims should be found unpatentable on the following grounds:

Prior Art References
’772 Publication (EX1007); published July 24, 2003; prior art under pre-AIA §102(b).
Xie (EX1008), published August 6, 2002; prior art under pre-AIA §102(b).
Snowdy (EX1009); published December 15, 2003; prior art under pre-AIA §102(b).
Fabb (EX1010); published 2002; prior art under pre-AIA §102(b).

Ground	Claims	Description
1	1, 3-6	Obvious in view of the ’772 Publication
2	1, 3-6	Obvious in view of the ’772 Publication and Xie
3	1, 3-6	Obvious in view of the ’772 Publication and Snowdy
4	8	Obvious in view of the ’772 Publication and Fabb

Ground	Claims	Description
5	8	Obvious in view of the ’772 Publication, Xie, and Fabb
6	8	Obvious in view of the ’772 Publication, Snowdy, and Fabb

Xie, Snowdy, and Fabb were not considered by the Patent Office during prosecution. EX1001 (“References Cited”); EX1002. Although the ’772 Publication appears in the “References Cited” section of the ’274 patent, the Patent Office did not discuss the ’772 Publication during prosecution.

IV. BACKGROUND

A. Overview of the Technology

Before the priority date, researchers were working to improve the tropism (ability to target particular cell types) and transduction efficiency (efficiency of delivering a therapeutic gene and expressing it in targeted cells) of known AAV variants. EX1029, 1-5; EX1005, ¶85. In particular, people of skill in the art understood that there was a need to improve transduction of liver cells (for the treatment of hemophilia, glycogen storage diseases, and various metabolic disorders), lung cells (for the treatment of diseases such as cystic fibrosis), and muscle cells (for the treatment of muscular dystrophies), and to circumvent the problem of neutralizing antibodies in the patient for clinical applications. EX1031, 12-17; EX1005, ¶85.

B. The ’274 Patent

The ’274 patent is titled “Method of Increasing the Function of an AAV Vector.” EX1001, 1. The patent lists as named inventors Luk Vandenberghe, Guangping Gao, and James Wilson. *Id*. The ’274 patent issued on June 20, 2023. *Id*.

1. The Claims

The challenged claims of the ’274 patent are directed to recombinant AAVs having vp1 capsid proteins with a particular amino acid sequence – specifically, the naturally occurring vp1 capsid protein sequence for AAVrh.46 or a sequence at least 95% identical to AAVrh.46, and where the amino acid corresponding to position 665 is asparagine (N). EX1001, 193:1-15. The challenged claims are reproduced in the list above. Challenged claim 1 is an independent claim. Challenged claims 3-6 and 8 are dependent claims, which recite additional elements that were well-known, routine, and conventional in the art as of the earliest priority date for the ’274 patent. *Id.*, 193:19-194:19, 194:24-26; EX1005, ¶104.

2. The Specification

The specification of the ’274 patent discusses the prior identification of naturally occurring AAV variants:

> Recently, investigators have described a large number of AAVs of different sequences [G. Gao, et al., Proc Natl Acad Sci USA, 100(10):6081-6086 (May 13, 2003); US-2003-0138772-A1 (Jul. 24, 2003)] and characterized these AAVs into different

> serotypes and clades [G. Gao, et al., J. Virol., 78(12):6381-6388 (June 2004); International Patent Publication No. WO 2005/033321]. It has been reported that different AAVs exhibit different transfection efficiencies, and also exhibit tropism for different cells or tissues.

Id., 1:51-59.

The specification discloses the capsid protein sequences for certain naturally occurring AAV variants isolated from Rhesus macaques – designated rh.20, rh.32/33, rh.39, rh.46, rh.73, and rh.74. *Id.*, 2:37-58, Figs. 4, 5, 6; 42-53. The specification also discloses alignments of the amino acid sequences for the vp1 capsid proteins of these naturally occurring AAV variants. *Id.*, 2:37-58, Figs. 5, 6.

The ’274 patent contains no examples, experimental data, or other disclosure indicating that the asparagine (N) at position 665 of AAVrh.46 has any unexpected biological significance or confers any favorable properties on AAVrh.46 for use as a gene therapy vector or otherwise. In fact, the ’274 patent contains no discussion of position 665 in AAVrh.46 at all, or any discussion of why it may be important to preserve asparagine (N) at that position in the capsid protein of an rAAV vector. The first identification of asparagine (N) at position 665 is in a set of amended claims filed during prosecution. EX1002, 122-26.[2]

[2] Notably, the claims of the ’274 patent were amended in 2019 to include the element that position 665 is asparagine (N) after Sarepta’s AAVrh.74 sequence – the

3. The Prosecution History

During prosecution, the Examiner issued two 35 U.S.C. §103 rejections based on prior art references that describe AAV capsid sequences. *Id.*, 265-82. Patent Owners traversed the first rejection on the ground that the cited reference was disqualified under pre-AIA 35 U.S.C. §103(c). *Id.*, 341. In response to the second rejection, Patent Owners cancelled two pending claims. *Id.*, 342. The Examiner allowed the remaining claims, but Patent Owners filed two subsequent Requests for Continued Examination. *Id.*, 425-29, 503-507. The '274 patent issued on June 20, 2023.

The Examiner did not evaluate the challenged claims in light of the primary prior art at issue here – the '772 Publication, Xie, Snowdy, and Fabb.

4. Priority Date

The '274 patent claims priority to two provisional applications the '083 application, filed April 7, 2005, and the '497 application, filed November 4, 2005. EX1001; EX1003; EX1004. The earliest non-provisional application listed on the face of the '274 patent is PCT/US2006/013375, filed on April 7, 2006. EX1001.

---

accused sequence in the related litigation – was published in U.S. Patent 9,434,928, which issued in 2016. EX1027, Figure 1, 37-39.

V. LEVEL OF ORDINARY SKILL IN THE ART

A POSA in the technical field of the '274 patent 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. EX1005, ¶¶111-15. 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. *Id*.

VI. OVERVIEW OF THE PRIOR ART

A. The '772 Publication

The '772 Publication is titled "Method of detecting and/or identifying adeno-associated virus (AAV) sequences and isolating novel sequences identified thereby." EX1007. The '772 Publication lists Guangping Gao, James Wilson, and Mauricio Alvira as named inventors. *Id.*

The '772 Publication was published on July 24, 2003 – more than a year before the filing date of the earliest provisional application for the '274 patent, on April 7, 2005. *Id.* The '772 Publication discloses nucleic acid sequences encoding the capsid proteins for naturally occurring AAV variants that were identified in tissue samples taken from non-human primates. *Id*., [0046]. The disclosed AAV variants are listed in Table 1. *Id*., 112-13. Figure 1 is an alignment of the nucleic

acid sequences encoding the capsid proteins of the disclosed AAV variants. *Id*., 2-97.

The ’772 Publication also discloses the amino acid sequences of the capsid proteins for these AAV variants. *Id*., 140-43, 225-330. Figure 2 is an alignment of the amino acid sequences for the disclosed AAV capsid proteins. *Id*., 98-103.

The ’772 Publication teaches that the disclosed sequences may be used to make rAAV vectors for gene therapy applications. *Id*., [0075], [0086]-[0095]; EX1005, ¶120.

1. The ’772 Publication Identifies AAVrh.10 as a Particularly Preferred Embodiment

The ’772 Publication discloses the results of various experiments in the Examples. EX1007, 125-37; EX1005, ¶¶121-58. 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.[3] EX1005, ¶¶121-22. Specifically, Example 9 discloses two transduction experiments, in each of three different tissues: lung, liver, and muscle. EX1007, [0252]-[0257]; EX1005, ¶122. Example 9 states: “The data from both these experiments confirmed the

[3] AAVrh.10 is sometimes referred to as the “44-2” or “44.2” variant. EX1007, Table 1, 112-13, [0089], [0142].

superb tropism of clone 44.2 [AAVrh.10] in lung-directed gene transfer." EX1007, [0256].

The '772 Publication compares AAVrh.10 to another variant, AAV8, which showed superior performance liver, and which has an asparagine (N) at position 665. EX1005, ¶123. Example 9 states: "Interestingly, 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." EX1007, [0257]; *see also* [0253].

2. The '772 Publication Teaches the Modification of Naturally Occurring Sequences to Create Artificial AAV Vectors

The '772 Publication teaches the creation of "artificial" AAV vectors by modifying the AAV capsid proteins encoded by the naturally occurring sequences disclosed in Figures 1 and 2. EX1005, ¶159. Specifically, the '772 Publication teaches that artificial AAV vectors may be made by combining AAV capsid sequences from one or more different AAV variants. EX1007, [0074], [0075]. The '772 Publication explains:

> In addition to including the nucleic acid sequences provided in the figures and Sequence Listing, the present invention includes . . . artificial AAV serotypes generated using these sequences and/or unique fragments thereof.

> As used herein, artificial AAV serotypes include, without limitation, AAV with a non-naturally occurring capsid protein. Such an artificial capsid may be generated by any suitable technique, using a novel AAV sequence of the invention (e.g., a fragment of a vp1 capsid protein) in combination with heterologous sequences which may be obtained from another AAV serotype (known or novel), non-contiguous portions of the same AAV serotype, from a non-AAV viral source, or from a non-viral source. An artificial AAV serotype may be, without limitation, a chimeric AAV capsid, a recombinant AAV capsid, or a "humanized" AAV capsid.

Id.

As an example, the '772 Publication discloses that a "novel NHP [non-human primate] clone was made by splicing capsids fragments of two chimp adenoviruses [*sic*] into an AAV2 rep construct. This new clone, A3.1, is also termed Ch.5 [SEQ ID NO: 20] [*sic*]." *Id.*, [0067]; EX1005, ¶160.

The '772 Publication also discusses sequences with varying degrees of homology to the naturally occurring sequences: "Further included in this invention are nucleic acid sequences which are greater than 85%, preferably at least about 90%, more preferably at least about 95%, and most preferably at least about 98 to 99% identical or homologous to the sequences of the invention, including FIG. 1 and the Sequence Listing [SEQ ID NOS: 1, 9-59, and 117-120]." EX1007, [0069].

B. Xie

Xie discloses the three-dimensional crystal structure of the vp3 protein of AAV2. EX1008, Abstract, 2; EX1005, ¶162. Xie was published in 2002, more than

one year before the earliest priority date for the '274 patent on April 7, 2005. EX1008.

Xie discusses the importance of amino acids on the surface of the AAV capsid for determining characteristics of the virus such as tropism, transduction efficiency, and immunogenicity. EX1008, 3 (discussing "the surface features of the virus that govern interactions with antibodies and cellular receptors"); EX1005, ¶163.

Xie discloses that the surface of the AAV2 viral capsid is composed of 60 triangular facets made up of vp1, vp2, and vp3 capsid proteins. EX1008, 4, Fig. 4, Fig. 4 legend; EX1005, ¶164. Figure 2 of Xie shows a sequence alignment in which the triangles indicate the AAV2 vp3 amino acids that are on the capsid surface, according to the crystal structure. EX1008, 3, Fig. 2, Fig. 2 legend; EX 1005, ¶165.

C. Snowdy

Snowdy is a doctoral thesis published in 2003. EX1009, 1. The advisor for the Snowdy thesis was Dr. R. Jude Samulski, a recognized figure in the field of gene therapy and the use of AAV vectors for gene therapy applications. EX1009, 1; EX1005, ¶166.

1. Snowdy Was Publicly Accessible by at Least February 2004

Snowdy is a printed publication that was publicly accessible by at least February 2004 – more than one year before the earliest priority date for the '274 patent on April 7, 2005. EX1015, ¶8; EX1016, ¶8.

A "Record" of the Snowdy thesis was first published to the ProQuest Dissertations and Theses database on December 15, 2003. EX1015, ¶¶3, 4, 7, 8. This Record included information about the dissertation – including a complete copy of the abstract, index record, and citation information (title, author name, degree granting institution, and degree date). EX1015, ¶3. The full text of Snowdy was also available before the priority date of the '274 patent for purchase from ProQuest as of December 15, 2003. EX1015, ¶¶8, 9. A POSA in 2003 was familiar with the ProQuest database and would have been able to find the thesis readily in a number of ways, including keyword search and author search. EX1005, ¶174; EX1015, ¶¶10-12, 14.

As an alternative to purchasing the full copy from ProQuest, the full Snowdy thesis was on the shelf of the Wilson Library at the University of North Carolina (UNC) no later than February 2004. EX1016, ¶¶8-10, 12. Thus, a POSA, a researcher or other member of the public who had located the entry for the Snowdy thesis in the ProQuest index in December of 2003 would have been able to locate the full copy of the thesis in the Wilson Library by no later than February 2004. EX1005, ¶175.

EX1009 is a true and correct copy of Snowdy. EX1016, ¶¶5-7. EX1009 is also identical to the copy of Snowdy attached to the Hyatt Declaration, which is a

true and correct copy of the full Dissertation as originally published and kept by ProQuest. EX1015, ¶15; EX1005, ¶176.

2. Snowdy Teaches the Removal of Phosphorylation Sites in AAV Capsid Proteins to Improve Transduction Efficiency

Snowdy discloses methods of improving AAVs as a gene therapy tool. EX1009, 4-5. Snowdy examined the effect of modifying possible phosphorylation targets (serines and threonines) in the AAV2 capsid on transduction efficiency. Snowdy found that substituting one of these phosphorylation targets with the non-phosphorylatable amino acid alanine increased transduction efficiency, while substituting aspartic acid, which mimics a constitutively phosphorylated state, at this position decreased transduction efficiency. EX1009, 4-5; EX1005, ¶¶177-82.

Snowdy focused on the effect of phosphorylation on putative nuclear localization signals in the AAV2 capsid protein. EX1009, 4-5. Using a software program known as NetPhos, Snowdy identified three phosphorylation sites in the vicinity of a putative nuclear localization signal: serine 148, threonine 159, and serine 181. EX1009, 125; EX1005, ¶184. Snowdy mutated each of these amino acids to either a non-phosphorylatable alanine (A), to simulate an unphosphorylated serine, or to an aspartic acid (D) to simulate a constitutively (*i.e.*, always)

phosphorylated serine – resulting in six mutants altogether, S148A, S148D, T159A, T159D, S181A, and S181D.[4] EX1009, 4-5, 125; EX1005, ¶185.

Snowdy found that all of the mutants were capable of forming virus at normal titers. EX1009, 126. The S148A, S148D, T159A, and T159D mutations had no effect, or little effect, on the virus' ability to infect HeLa cells and to deliver the eGFP gene carried as their cargo. *Id*. However, the S181A and S181D substitutions had large effects on virus infectivity. EX1009, 5, 126-9; EX1005, ¶¶186-87. The same number of particles containing the S181A mutation infected far more cells than did the wild-type, and the same number of particles containing the S181D mutation infected almost no cells at all. EX1009, 5, 126-9; ¶¶186-87.

Based on studies involving phosphorylation sites near nuclear localization signals of other viruses, Snowdy expected the serine to alanine mutations to lower

[4] Snowdy also teaches the substitution of asparagine (N), in addition to alanine (A), as a nonphosphorylatable amino acid to remove a phosphorylation site. EX1009, 28 (citing Jans & Jans (EX1017)); EX1005, ¶¶180-81. A POSA would have understood that substituting asparagine (N) for serine (S) would be a more conservative substitution, because both serine (S) and asparagine (N) are polar, uncharged amino acids, while alanine (A) is nonpolar. EX1040, 5; EX1005, ¶182.

transduction efficiency, if the phosphorylation site was important for regulating the putative nuclear localization signals. EX1009, 128; EX1005, ¶188. However, Snowdy's results for the S181A substitution, where the non-phosphorylatable alanine was substituted in for the phosphorylatable serine, showed the opposite – *i.e*., an increased level of infection compared to wild type. *Id*.

These results suggested that mutating a phosphorylation site to a non-phosphorylatable amino acid in the AAV2 capsid had an effect on some characteristic of the virus other than nuclear localization, resulting in greater transduction efficiency. EX1009, 129 ("Until 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."); EX1005, ¶189.

D. Fabb

Fabb discloses a "micro-dystrophin" gene used as part of an AAV vector for gene therapy. EX1010, Abstract. Fabb was published in 2002, more than one year before the earliest priority date for the '274 patent of April 7, 2005. *Id*., 1.

Fabb discloses that the full-length dystrophin gene is too large to be packaged in an AAV vector. *Id.*, Abstract. Fabb also discloses the construction of a smaller version of the dystrophin cDNA known as a "micro-dystrophin" gene. *Id*., Abstract, 2-3. Fabb discloses that this micro-dystrophin gene restored dystrophin associated

protein complexes and ameliorated dystrophic pathology at the cellular level in an animal model. *Id*., Abstract.

VII. CLAIM CONSTRUCTION

Challenged claims 1, 3-6, and 8 of the '274 patent recite an AAV capsid protein having an amino acid sequence "at least 95% identical" or "at least 97% identical" to the full length of amino acids 1 to 738 of SEQ ID NO: 4. The '274 patent provides that for purposes of determining percent identity, "[a]lignments are performed using any of a variety of publicly or commercially available Multiple Sequence Alignment Programs." EX1001, 5:31-45. The '274 patent identifies examples of available programs. EX1001, 5:45-6:8. However, 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.

In a currently-pending litigation in the District of Delaware, Patent Owners have asserted the '274 patent against Sarepta. In their Initial Claim Chart, Patent Owners used the Clustal Omega program (available at https://www.ebi.ac.uk/jdispatcher/msa/clustalo) at default settings to perform sequence alignments and calculate percent identity. EX1026, 3. For purposes of this Petition, Sarepta has analyzed the percent identity elements as Patent Owners did in their preliminary infringement contentions, using the Clustal program at

default settings to generate amino acid sequence alignments and calculate percent identity values.

VIII. DETAILED EXPLANATION OF GROUNDS

As discussed in detail below, each of the challenged claims is unpatentable.

A. Ground 1: Claims 1 and 3-6 Are Obvious Over the '772 Publication, as Confirmed by the Opinions of Patent Owners' Expert in Earlier Litigation

1. Claim 1

(a) "A recombinant adeno-associated virus (AAV)"

The '772 Publication discloses "[a] recombinant adeno-associated virus (AAV)." EX1007, [0093]; [0023] ("The AAV sequences and fragments thereof are useful in production of rAAV . . ."); [0024] ("The rAAV vectors of the invention are particularly advantageous in rAAV re-administration and repeat gene therapy."); [0086] ("IV. Production of rAAV with Novel AAV Capsids"); [0139] ("Thus, the invention further provides vectors generated using the nucleic acid and amino acid sequences of the novel AAV of the invention . . . . Particularly desirable for delivery of therapeutic molecules are recombinant AAV containing capsids of the novel AAV of the invention.").

(b) "An AAV capsid"

The '772 Publication discloses recombinant AAVs comprising an AAV capsid. EX1007, [0086] ("IV. Production of rAAV with Novel AAV Capsids");

[0092] ("The vectors described herein, e.g., a plasmid, are useful for a variety of purposes, but are particularly well suited for use in production of a rAAV containing a capsid comprising AAV sequences or a fragment thereof."); [0139] ("Particularly desirable for delivery of therapeutic molecules are recombinant AAV containing capsids of the novel AAV of the invention."); [0141] ("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.").

(c) "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"

The '772 Publication discloses minigenes, which are DNA constructs that include, for example, therapeutic genes that can be delivered by AAV vectors. EX1007, [0090] ("Optionally, the vectors of the invention further contain a minigene comprising a selected transgene which is flanked by AAV 5' ITR and AAV 3' ITR.").

The version of the therapeutic gene included in the minigene is referred to as a "transgene" or a "heterologous gene," because it is not endogenous to AAV. EX1007, [0099] ("The transgene is a nucleic acid sequence, heterologous to the vector sequences flanking the transgene, which encodes a polypeptide, protein, or other product, of interest."); EX1005, ¶198.

In addition to the transgene, the minigene includes regulatory sequences that determine how the transgene will be expressed in a cell. EX1007, [0099] ("The nucleic acid coding sequence is operatively linked to regulatory components in a manner which permits transgene transcription, translation, and/or expression in a host cell"); EX1005, ¶199.

The minigene also includes sequences of DNA from the AAV genome known as "inverted terminal repeats" ("ITRs") that are required for viral functions such as replication and packaging. EX1007, [0097] ("The minigene is composed of, at a minimum, a transgene and its regulatory sequences, and 5' and 3' AAV inverted terminal repeats (ITRs)"); EX1005, ¶200.

(d) "The AAV capsid comprises AAV vp1 proteins, AAV vp2 proteins, and AAV vp3 proteins"

The '772 Publication discloses AAV capsids comprising AAV vp1 proteins, AAV vp2 proteins, and AAV vp3 proteins. EX1007, [0080] ("The sequences of many of the capsid proteins of the invention are provided in an alignment in FIG. 2 and/or in the Sequence Listing, SEQ ID NO: 2 and 60 to 115, which is incorporated by reference herein. The AAV capsid is composed of three proteins, vp1, vp2 and vp3, which are alternative splice variants").

Based on the vp1 protein sequences in the '772 Publication, a POSA could determine the sequences of the corresponding vp2 and vp3 proteins for other AAV

variants. EX1007, [0080] ("The full-length sequence provided in these figures is that of vp1. Based on the numbering of the AAV7 capsid [SEQ ID NO:2], the sequences of vp2 span amino acid 138-737 of AAV7 and the sequences of vp3 span amino acids 203-737 of AAV7. With this information, one of skill in the art can readily determine the location of the vp2 and vp3 proteins for the other novel serotypes of the invention."); EX1005, ¶202.

(e) "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"

The '772 Publication discloses 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."

The '772 Publication discloses sequences that are at least 95% identical to the full length of amino acids 1 to 738 of SEQ ID NO: 4. Specifically, the '772 Publication discloses the amino acid sequence of the vp1 capsid protein for the preferred embodiment, AAVrh.10, at SEQ ID NO: 81. EX1007, 264-66, Table 1 (SEQ ID NO: 81, also referred to as "rh.10" and "clone 44.2"), 112-113, Fig. 2, 98-103.

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. EX1018, 1-2; EX1005, ¶¶204-205.

(f) "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"

The '772 Publication also teaches the limitation "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."

(i) The '772 Publication Teaches the Substitution of Asparagine (N) for Serine (S) at Position 665 of AAVrh.10

The '772 Publication singles out AAVrh.10 as a particularly preferred embodiment, and touts "the superb tropism of clone 44.2 [AAVrh.10] in lung-directed gene transfer." EX1007, [0256]; EX1005, ¶207. The '772 Publication also identifies AAV8, which has an asparagine (N) at position 665, as providing "a substantial advantage over the other serotypes in terms of efficiency of gene transfer to liver," EX1007, [0250]; EX1005, ¶207.

The '772 Publication compares the performance of AAVrh.10 to AAV8: "Interestingly, performance of clone 44.2 [AAVrh.10] 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." EX1007, [0257], [0252]-[0256], Tables 8-10. The '772 Publication also teaches that it was particularly important to identify serotypes with good "efficiency of gene transfer to liver that until now has been relatively disappointing . . . ." *Id.*, [0250].

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. EX1005, ¶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. EX1032, 5-6, Table 1; EX1005, ¶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.").

(ii) Patent Owners' Expert in Earlier Litigation Agrees that the '772 Publication Teaches the Substitution of Asparagine (N) for Serine (S) at Position 665 of AAVrh.10

In the Penn-I litigation, Patent Owners served expert reports that include opinions about how a POSA would understand the teachings of the '617 patent, which has the same specification and claims priority to the same applications as the '772 Publication. EX1011, 4, ¶10; EX1012 ¶1; EX1013. In their submissions in the

earlier case, Patent Owners contend that a POSA would understand Figure 2 to teach the creation of artificial sequences where an amino acid in the naturally occurring sequence (*e.g.*, AAVrh.10) has been substituted for an amino acid appearing in the corresponding position in the capsid sequence of a different variant in the alignment. EX1012, ¶¶313, 316-19.

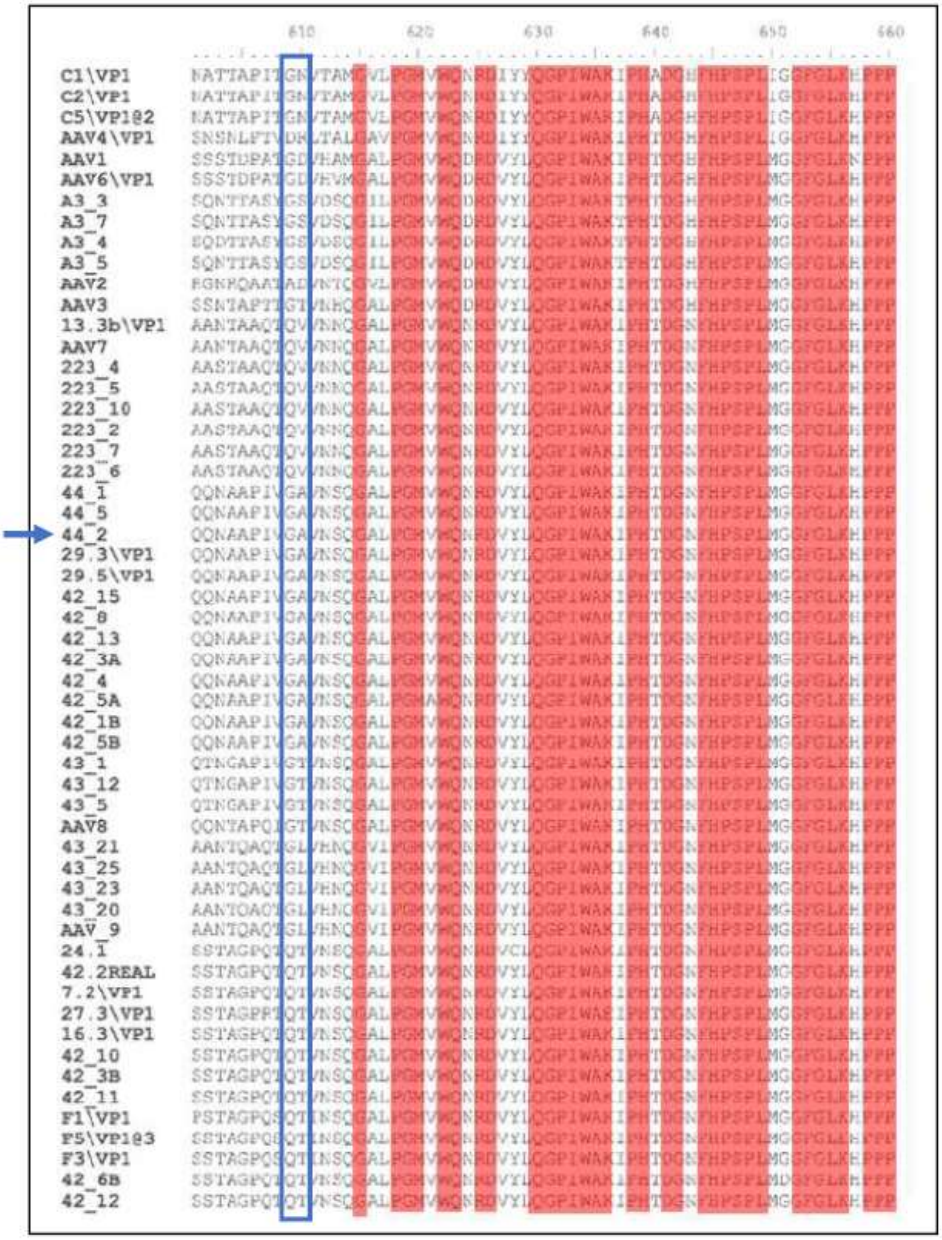
Plaintiffs' expert, Dr. Paola Leone, sets out certain guidelines for the creation of these artificial sequences. First, she explains that, from the alignment in Figure 2, a POSA could readily identify "conserved" and "non-conserved" regions of the aligned capsid protein sequences. EX1012, ¶315. In her expert report, Dr. Leone includes an annotated version of a portion of Figure 2 where she colored the "conserved" regions in red. *Id*., ¶316. Dr. Leone explains that, "[p]ersons of ordinary skill in the art would have understood that changes should be avoided in the red regions, and that changes should be concentrated in the regions that are not highlighted in red." *Id*., ¶ 318.

Next, Dr. Leone explains that for those positions where substitutions may be made, Figure 2 guides a POSA as to which alternative amino acids to choose. According to Dr. Leone, a POSA would have understood to substitute an "alternate amino acid" recruited from the corresponding position of one of the other AAV capsid protein sequences in the alignment at one of the non-conserved positions. *Id*., ¶398.

Dr. Leone concludes that the alignment in Figure 2 teaches a POSA what amino acid positions "can be changed," and for those positions that can be changed, Figure 2 teaches a POSA "what those changes should be." *Id*., ¶¶310, 311.

Dr. Leone provides an example in her report of how a POSA would have been guided by Figure 2. *Id*., ¶319. She examines positions 609 and 610, which are not highlighted in red, and therefore, are positions where a POSA would understand that substitutions may be made. *Id*., ¶319.

This page from Dr. Leone's annotated version of Figure 2 is reproduced below. Positions 609 and 610 are boxed in blue, and the AAVrh.10 (clone 44_2) capsid protein sequence is indicated with a blue arrow:



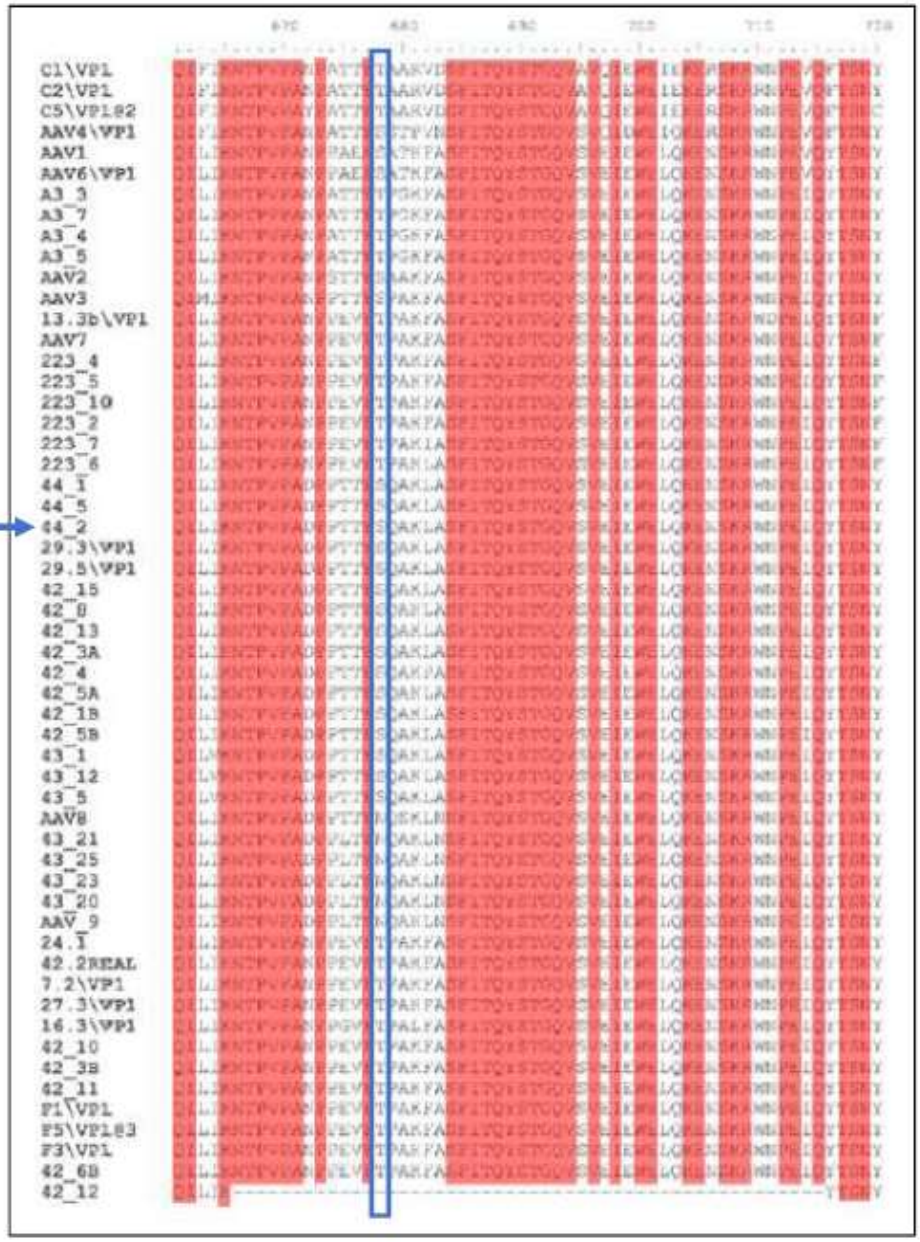
Id., 33 (blue arrow and blue box added).

As Dr. Leone explains, the AAVrh.10 sequence (identified as variant "44_2") has a "G" (glycine) at position 609 and "A" (alanine) at position 610. *Id*., ¶319. Other sequences in Figure 2 have D (aspartic acid), A (alanine) or Q (glutamine) at

position 609; and N (asparagine), R (arginine), D (aspartic acid), S (serine), T (threonine), V (valine) or L (leucine) at position 610. *Id*., ¶319.

Dr. Leone contends that a POSA would have reasonably expected that changing the G or A in positions 609 and 610 in sequence 44_2 (AAVrh.10) to one of the amino acids present at the corresponding position in other sequences in Figure 2 would result in a capsid protein that may be used to form an AAV capsid. *Id*., ¶319.

According to Dr. Leone's opinions in the earlier case, one of the substitutions that Figure 2 teaches would be the substitution of asparagine (N) for the serine (S) at position 665 of AAVrh.10. Position 665 in AAVrh.10 corresponds to position 678 in the alignment in Figure 2. EX1005, ¶223. The page from Dr. Leone's annotated Figure 2 that includes position 678 is reproduced below:



EX1012, 34 (blue arrow and blue box added).

The amino acids at position 678 – corresponding to position 665 in the ’274 patent – are boxed in blue. As shown in the annotated figure, position 678 is in a non-red, non-conserved region, and therefore is a position at which, according to Dr. Leone, a POSA would understand that substitutions could be made. At this position,

AAVrh.10 (variant "44_2") has an S (serine) amino acid, while other sequences in the figure have T (threonine) or N (asparagine) amino acids. Thus, according to Dr. Leone, a POSA would have understood Figure 2 to teach the creation of artificial variants of AAVrh.10, in which T or N has been substituted for the S at position 665 in AAVrh.10.

In her report, Dr. Leone explains that "persons of ordinary skill in the art would have understood from the patent's specification that the fewer amino or nucleic acids that were changed, the more likely the sequences would encode proteins that, if expressed, may be used to form an AAV capsid . . . ." *Id.*, ¶334.

Applying Dr. Leone's analysis, the '772 Publication teaches the creation of artificial variants of AAVrh.10, containing single amino acid substitutions of amino acids at the corresponding positions of other sequences disclosed in Figure 2, including at position 665, and including the substitution of N for S at that position, resulting in the sequence recited in claim 1.

(iii) A POSA Would Have Had a Reasonable Expectation of Success in Making the Claimed Combination

A POSA would have had a reasonable expectation of success in creating artificial variants of AAVrh.10 with single amino acid substitutions based on amino acids at corresponding positions of the other sequences disclosed in Figure 2. EX1005, ¶227. The creation of these artificial sequences would have required no

more than routine experimentation, along with the use of various analytical techniques that were well within the skill of a POSA at the time. EX1005, ¶227.

A POSA would have analyzed the alignment of preferred embodiments AAVrh.10 and AAV8 disclosed in Figure 2 of the '772 Publication. EX1005, ¶228. Analyzing such an alignment to determine that the two sequences differed at 48 positions would have been routine for a POSA. EX1005, ¶228. The '772 Publication states that it was known in the art how to create and analyze such sequence alignments. EX1007, [0018]; EX1005, ¶228.

Making 48 variants of AAVrh.10, each containing a single substitution, 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. EX1005, ¶229. The '772 Publication states that making mutants of this type was routine experimentation. EX1007, [0072] (describing site directed mutagenesis as a "conventional" technique).

Testing 48 variants of AAVrh.10, each containing a single amino acid substitution, was also well within the skill of a POSA at the time, and required no more than routine experimentation. EX1007, [0251]; EX1005, ¶230. The '772 Publication states that methods for determining the suitability of various AAV vector constructs in different tissues would have been well known to a POSA. EX1007, [0142].

The opinions of Patent Owners' expert, Dr. Leone, in the Penn-I litigation confirm that a POSA would have had a reasonable expectation of success in constructing and testing 48 variants of AAVrh.10. As Dr. Leone explained, a 2000 study which "tested 93 different sequences" is "an excellent example of conducting routine experimentation . . . ." EX1012, ¶415 (citing Wu (EX1032)).

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.

Therefore, because a POSA would have been motivated to create a variant of AAVrh.10 containing an N instead of an S at position 665, and because that person would have had a reasonable expectation of success in making that variant, claim 1 is obvious over the '772 Publication. EX1005, ¶233.

3. Claim 3: "The recombinant AAV according to claim 1, wherein the AAV vp1 capsid proteins have an amino acid sequence which is at least 97% 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 is N when aligned along the full length of amino acids 1 to 738 of SEQ ID NO: 4"

As discussed above with respect to claim 1, the alignment of SEQ ID NO: 81 (AAVrh.10) from the '772 Publication with SEQ ID NO: 4 (AAVrh.46) from the '274 patent yields a percent identity of 97.29% – which meets the "at least 97% identical" threshold in claim 3. EX1018, 1-2; EX1005, ¶234. Therefore, dependent claim 3 of the '274 patent is obvious over the '772 Publication, as confirmed by the opinions of Patent Owners' expert in the Penn-I litigation. EX1005, ¶235.

4. Claim 4: "The recombinant AAV according to claim 1, wherein the AAV inverted terminal repeats are from a different AAV than the AAV supplying the capsid proteins"

The '772 Publication teaches the recombinant AAV of claim 1 with inverted terminal repeats from a different AAV than the AAV supplying the capsid proteins: "Chimeric packaging constructs are generated by fusing AAV2 rep with cap sequences of novel AAV serotypes. These chimeric packaging constructs are used, initially, for pseudo typing recombinant AAV genomes carrying AAV2 ITRs by triple transfection in 293 cell using AdS helper plasmid." EX1007, [0214]; EX1005, ¶236.

A POSA would have been motivated to create, and would have had a reasonable expectation of success in creating, an rAAV where the AAV ITRs are from a different AAV than the AAV supplying the capsid protein to evaluate the transduction and gene transfer efficiency of different AAV variants: "These pseudotyped vectors are used to evaluate performance in transduction-based serological studies and evaluate gene transfer efficiency of novel AAV serotypes in different animal models including NHP and rodents, before intact and infectious viruses of these novel serotypes are isolated." EX1007, [0214]; EX1005, ¶237.

Here, the '772 Publication discloses creating recombinant AAVs through triple transfection. EX1005, ¶¶97-99, 238. Using this method, a plasmid carrying the cap gene (coding for the AAV capsid proteins) of one of the variants, such as AAVrh.10, is co-transfected with another plasmid containing the ITRs from a different AAV variant – here AAV2. *Id*. Therefore, dependent claim 4 of the '274 patent is obvious over the '772 Publication, as confirmed by the opinions of Patent Owners' expert in the Penn-I litigation. *Id*. ¶239.

5. Claim 5: "A composition comprising the recombinant AAV according to claim 1 and a physiologically compatible carrier"

The '772 Publication teaches a composition comprising the recombinant AAV according to claim 1 and a physiologically compatible carrier. EX1007, [0148].

Therefore, dependent claim 5 is obvious over the '772 Publication, as confirmed by the opinions of Patent Owners' expert in the Penn-I litigation. EX1005, ¶¶240-42.

6. Claim 6: "The recombinant AAV according to claim 1, wherein the heterologous gene encodes an ornithine transcarbamylase, arginosuccinate synthetase, arginosuccinate lyase, arginase, fumarylacetacetate hydrolase, carbamoyl phosphate synthetase I, phenylalanine hydroxylase, alpha-1 antitrypsin, glucose-6-phosphatase, porphobilinogen deaminase, cystathione beta-synthase, branched chain ketoacid decarboxylase, isovaleryl-coA dehydrogenase, propionyl-CoA carboxylase, methylmalonyl-CoA mutase, glutaryl-CoA dehydrogenase (GCDH), betaglucosidase, pyruvate carboxylate, hepatic phosphorylase, phosphorylase kinase, β-glucuronidase (GUSB), glycine decarboxylase, a low density lipoprotein (LDL) receptor, high density lipoprotein (HDL) receptor, very low density lipoprotein (VLDL) receptor, scavenger receptor, glucocorticoid receptor, estrogen receptor, Vitamin D receptor, nuclear receptor, cystic fibrosis transmembrane regulator (CFTR) sequence, Factor IX or variants thereof, Factor VIII or variants thereof, a dystrophin gene product, or an immunoglobulin"

The '772 Publication teaches the limitation of the recombinant AAV according to claim 1 wherein the heterologous gene encodes any of the proteins in the list recited in dependent claim 6. Specifically, the '772 Publication identifies the following proteins listed in claim 6 as possible heterologous genes in the recombinant AAVs disclosed in the '772 Publication:

> Other useful gene products include, carbamoyl synthetase 1, ornithine transcarbamylase, arginosuccinate synthetase, arginosuccinate lyase, arginase, fumarylacetacetate hydrolase, phenylalanine hydroxylase, alpha-1 antitrypsin, glucose-6-

> phosphatase, porphobilinogen deaminase, factor VIII, factor IX, cystathione beta-synthase, branched chain ketoacid decarboxylase, . . . isovaleryl-coA dehydrogenase, propionyl CoA carboxylase, methyl malonyl CoAmutase, glutaryl CoA dehydrogenase, . . . betaglucosidase, pyruvate carboxylate, hepatic phosphorylase, phosphorylase kinase, glycine decarboxylase, H-protein, T-protein, a cystic fibrosis transmembrane regulator (CFTR) sequence, and a dystrophin cDNA sequence.

EX1007, [0155], [0157].

Therefore, dependent claim 6 is obvious over the '772 Publication, as confirmed by the opinions of Patent Owners' expert in the Penn-I litigation. EX1005, ¶¶243-47.

7. Secondary Considerations Do Not Change the Conclusion of Obviousness

For evidence of "secondary considerations" to be informative of obviousness, there must be a "nexus" or link between the alleged secondary consideration and the subject matter recited in the Asserted Claims. Petitioner is not aware of any secondary considerations of non-obviousness with the required nexus to the claims of the '274 patent. For example, Petitioner is not aware of any commercial success attributable to a recombinant AAV vector having an AAVrh.46 capsid protein

sequence with an N at position 665.[5] Likewise, Petitioner is not aware of any licenses directed specifically to the '274 patent or the subject matter recited in challenged claims 1, and 3-6.

Finally, Petitioner is not aware of any unexpected results having a nexus to the claimed subject matter. The '274 patent does not disclose unexpected properties of an rAAV vector with capsid proteins having the amino acid sequence of AAVrh.46. To the extent the N at position 665 in the AAVrh.46 sequence eliminates a phosphorylation site found in other naturally occurring AAV capsid sequences, the potential benefits were not unexpected to a POSA. EX1005, ¶249. Instead, as discussed above, the effects of phosphorylation on the biological properties of rAAV vectors, such as transduction efficiency, had been studied before the '274 patent and disclosed in prior art references, such as Snowdy. *Id*.

[5] If Patent Owner attempts to rely on the commercial success of Sarepta's gene therapy treatment for Duchenne muscular dystrophy – Elevidys™ – there is no nexus to the challenged claims of the '274 patent. Elevidys™ uses the vp1 capsid protein from a different, naturally occurring AAV variant – AAVrh.74. Patent Owner cannot show a nexus between the commercial success of Elevidys™ and the AAVrh.46 sequence recited in the challenged claims.

To the extent that an N at position 665 of AAVrh.46 confers any favorable properties on AAVrh.46 for use as a gene therapy vector or otherwise, the '274 patent contains no such discussion. *Id.*, ¶250. In fact, the '274 patent contains no discussion of position 665 in AAVrh.46 at all, other than the recitation in the claims. *Id*.

To the extent Patent Owners attempt to raise secondary considerations that have only a marginal nexus, if any, to claims 1 and 3-6 of the '274 patent, such evidence of secondary considerations should not outweigh the compelling evidence of obviousness discussed above. Thus, secondary considerations do not alter the conclusion that claims 1 and 3-6 of the '274 patent are obvious over the '772 Publication, as confirmed by Patent Owners' expert in the Penn-I litigation.

B. Ground 2: The '772 Publication, in view of Xie, Renders Claims 1 and 3-6 Obvious

As discussed above, a POSA would have been motivated, based on the disclosures of the '772 Publication, to combine the preferred embodiment, AAVrh.10, with elements of another preferred embodiment, AAV8, to improve the beneficial properties of AAVrh.10 as a gene therapy vector. EX1005, ¶252. Such a combination would have led a POSA to create 48 artificial variants of AAVrh.10, each containing a single amino acid substitution with the amino acid at the corresponding position of AAV8. *Id*. Combining the '772 Publication with Xie

would have further directed a POSA to 18 of these 48 artificial variants. *Id*. Xie discloses that 18 of the 48 amino acids that differ between AAVrh.10 and AAV8 lie on the surface of the capsid, and teaches that amino acids on the surface of the capsid govern characteristics of AAV such as tropism, transduction efficiency, and immunogenicity. *Id.*, ¶253.

1. A POSA Would Have Been Motivated to Combine the '772 Publication with Xie to Obtain an AAVrh.10 Sequence with an N Substitution at Position 665

As discussed above, the '772 Publication discloses elements 1[pre], 1[a], 1[b], 1[c], and 1[d] in independent claim 1 of the '274 patent.

(a) Applying the Teachings of Xie, a POSA Would Have Identified 18 Amino Acids on the Surface of the AAV Capsid as the Most Promising Substitution Sites in AAVrh.10

In considering which mutations to make in the AAVrh.10 capsid to confer some of the favorable properties of AAV8 on AAVrh.10, a POSA would have routinely consulted available AAV crystal structures to identify those amino acids in the AAV capsid likely to be most important to the properties of AAV based upon their location in the three dimensional structure of the capsid shell. *Id*., ¶255. In fact, another of Patent Owners' experts in the Penn-I litigation, Dr. Michael Metzker, stated that, in addition to looking at the one-dimensional sequences aligned in Figure 2 of the '772 Publication to determine where to make substitutions in AAVrh.10,

"one of ordinary skill in the art would have consulted known crystal structures of related sequences to guide where to introduce mutations to a sequence." EX1013, ¶306.

A POSA would, therefore, have consulted the 2002 crystal structure of the AAV2 vp3 capsid protein published by Xie. EX1008; EX1005, ¶256. As discussed above, Xie teaches that the amino acids that lie on the surface of the capsid "govern interactions with antibodies and cellular receptors." EX1008, 3; EX1005, ¶256. A POSA at the time would have understood this disclosure to mean that the amino acids on the surface of the capsid govern characteristics of AAV such as tropism, transduction efficiency, and immunogenicity. EX1005, ¶256.

Therefore, a POSA, motivated by the '772 Publication to create 48 variants of AAVrh.10, each containing a single substitution with the amino acid at the corresponding position of AAV8, would have further focused on those variants of the 48 that involve amino acids that lie on the surface of the capsid according to Xie. EX1008, 3-4, Fig. 2, Fig. 2 legend, Fig. 4, Fig. 4 legend; EX1005, ¶257.

Xie discloses that 18 of the 48 amino acids that differ between AAVrh.10 and AAV8 lie on the surface of the capsid. EX1008, 3-4, Fig. 2, Fig. 4, Fig. 4 legend; EX1005, ¶258; EX1023, 1-2. Therefore, a POSA would have been motivated by the '772 publication in view of Xie to focus on mutating these 18 amino acids out of the 48 total differences between AAVrh.10 and AAV8. EX1005, ¶259.

(b) One of the 18 Most Promising Substitution Sites Is the Serine at Position 665

Xie further discloses that the amino acid in AAV2 corresponding to the serine at position 665 of AAVrh.10 is also a serine that lies on the surface of the capsid. EX1008, 3-4, Fig. 2, Fig. 2 legend, Fig. 4, Fig. 4 legend; EX1005, ¶¶260-61. Given that serine 665 is one of the 18 amino acids out of the 48 total differences between AAVrh.10 and AAV8 that lie on the surface of the capsid, a POSA would have been motivated by the '772 publication in view of Xie to substitute the serine at position 665 of AAVrh.10 for the asparagine at the corresponding position of AAV8. EX1005, ¶262.

2. A POSA Would Have Had a Reasonable Expectation of Success in Combining the '772 Publication with Xie

For the same reasons discussed in Section VIII.A.1.(f)(iii) above, the combination of the '772 Publication with Xie to create 18 substituted versions of AAVrh.10 would have required nothing more than routine experimentation, along with the use of various analytical techniques that were well within the skill of a POSA at the time. EX1005, ¶263.

Moreover, it would have been well within the level of ordinary skill in the art at the time to have consulted the published crystal structure of the AAV2 capsid to determine which amino acids are positioned on the surface and to have correlated these with the corresponding amino acids in AAVrh.10 and AAV8. EX1013, ¶306;

EX1005, ¶264. Additionally, Xie teaches that the surface amino acids in the AAV capsid tend to be in loop structures of the vp3 capsid protein, which are more flexible than, for example, the core, interior beta barrel of the vp3 protein, and therefore, likely more tolerant of single amino acid substitutions. EX1008, 3; EX1005, ¶265.

For these reasons, a POSA would have had a reasonable expectation of success in combining the '772 Publication with Xie to obtain an rAAV vector having the combination of elements recited in claim 1. EX1005, ¶266.

Thus, claim 1 of the '274 patent is obvious over the combination of the '772 Publication and Xie. EX1005, ¶267.

3. Claims 3-6 Are Obvious Over the Combination of the '772 Publication with Xie

As discussed above with respect to claim 1, a POSA would have been motivated to combine the '772 Publication with Xie. EX1005, ¶268. As discussed above for Ground 1, claims 3-6, the '772 Publication teaches each of the additional elements of these claims. *Id*. As further discussed above, a POSA would have had a reasonable expectation of success in combining the '772 Publication with Xie to obtain an rAAV vector having the combination of elements recited in claims 3-6. *Id*. Thus, claims 3-6 of the '274 patent are obvious over the combination of the '772 Publication and Xie. *Id*. ¶269.

4. Secondary Considerations Do Not Change the Conclusion of Obviousness

For the reasons discussed above for Ground 1, secondary considerations do not alter the conclusion that claims 1 and 3-6 of the '274 patent are obvious over the combination of the '772 Publication and Xie. *Id*. ¶270.

C. Ground 3: The '772 Publication, in View of Snowdy, Renders Claims 1 and 3-6 Obvious

1. A POSA Would Have Been Motivated to Combine the '772 Publication with Snowdy to Obtain an AAVrh.10 Sequence with an N Substitution at Position 665

As discussed above, the '772 Publication discloses elements 1[pre], 1[a], 1[b], 1[c], and 1[d] in independent claim 1 of the '274 patent. EX1005, ¶271.

(a) Snowdy Teaches That Mutating Phosphorylatable Amino Acids in the AAV Capsid to Non-Phosphorylatable Amino Acids Improved Transduction Efficiency

A POSA understood that certain amino acids were particularly interesting in viral capsids because they have the capability to be phosphorylated. *Id*., ¶272. Serine, threonine, and tyrosine are the amino acids most commonly phosphorylated. EX1033, Abstract; EX1005, ¶272. It would have been well known to a POSA that phosphorylation of proteins was an important mechanism for regulation of their stability and degradation in cells, and was the subject of a great deal of research. EX1035, Abstract; EX1036, Abstract; EX1037, Abstract; EX1038, Abstract; EX1039, Abstract; EX1005, ¶272. A POSA would also have understood that

phosphorylation plays an important role in the regulation and function of viral proteins, in particular, viral capsid proteins. EX1034, Abstract; EX1038, Abstract; EX1005, ¶272.

Specifically, 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. EX1035, 5-7; EX1036, Abstract; EX1037, 7; EX1038, Abstract; EX1039, 4; EX1005, ¶273.

Snowdy investigated the effects on the function of AAV of mutating phosphorylatable amino acids in AAV capsids to non-phosphorylatable amino acids, with the goal of improving AAV as a gene therapy vector. EX1009, 17, 125-30 (reporting that an S181A mutation in the AAV2 capsid improved the transduction efficiency of the virus); EX1005, ¶¶274-75. Snowdy found that mutating a serine in the AAV2 capsid to a non-phosphorylatable alanine improved the transduction efficiency of AAV2. EX1009, 125-30. Snowdy also teaches the substitution of asparagine (N) as a nonphosphorylatable amino acid to remove a phosphorylation site. EX1009, 28-29 (citing Jans & Jans (EX1017)); EX1005, ¶274.

Therefore, 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. EX1005, ¶276.

(b) Applying the Teachings of Snowdy, a POSA Would Have Identified Four Phosphorylatable Amino Acids as the Most Promising Substitution Sites in AAVrh.10, One of Which Is the Serine at Position 665

A POSA, seeking to improve the transduction of AAVrh.10 in liver to approach that of AAV8, in view of Snowdy, would have looked to see which positions in AAVrh.10 had phosphorylatable amino acids, where the corresponding position in AAV8 had a non-phosphorylatable amino acid. EX1005, ¶277.

Snowdy used a program, NetPhos, known to people of ordinary skill in the art at the time to determine which phosphorylatable amino acids in a protein are most likely to be the actual targets of kinases – enzymes that phosphorylate proteins. EX1009, 125; EX1005, ¶278. As Snowdy states, it was known in the art that the context – meaning the sequence surrounding a phosphorylatable amino acid such as serine – could determine the probability that a given serine was phosphorylated by one or more kinases. EX1009, 125; EX1005, ¶278.

When the AAVrh.10 sequence is run through NetPhos, the program identifies a number of different potential phosphorylation sites in AAVrh.10. EX1021; EX1005, ¶279. However, there are only four such predicted phosphorylated positions in AAVrh.10 that correspond to non-phosphorylatable amino acids in

AAV8 – S269A, S496G, S665N, and T722V – one of which is S665N.[6] EX1021, 7, 15, 20, 22-23; EX1022; EX1005, ¶279.

As such, 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 Penn-I litigation. EX1012, ¶415; EX1005, ¶280. One of these four mutations would be a substitution of asparagine (N) for serine (S) at position 665 of AAVrh.10. EX1005, ¶¶280-81. And, as discussed above, Snowdy teaches that the increased transduction efficiency

[6] Snowdy also raises the issue of whether any given phosphorylatable amino acid resides on the surface of the AAV capsid. EX1009, 135-36. As Xie discloses, three out of four of the positions where AAVrh.10 has a phosphorylatable amino acid and AAV8 has a nonphosphorylatable amino acid (S496G, S665N, and T722V) are on the surface of the AAV2 capsid, where they would be accessible to kinases. EX1008, 3-4, Fig. 2, Fig. 2 legend, Fig 4, Fig. 4 legend; EX1023; EX1005, ¶279 n.9. Therefore, a POSA would have understood these three phosphorylatable positions in AAVrh.10 to be particularly interesting targets for mutagenesis to substitute with the corresponding non-phosphorylatable amino acid from AAV8. EX1005, ¶279 n.9.

resulting from removing a capsid phosphorylation site could not be readily attributed to mechanisms relating to the NLS. EX1005, ¶280. Therefore, Snowdy implicates a different mechanism and phosphorylation sites throughout the capsid, not merely those in the vicinity of the NLS. EX1009 128-30; EX1005, ¶280.

2. A POSA Would Have Had a Reasonable Expectation of Success in Combining the '772 Publication with Snowdy

For the reasons discussed above regarding the combination of the '772 Publication and Xie, the combination of the '772 Publication with Snowdy to create substituted versions of AAVrh.10 would have required nothing more than routine experimentation, along with the use of various analytical techniques that were well within the skill of a POSA at the time. EX1005, ¶282. Therefore, a POSA would have had a reasonable expectation of success in making this combination. *Id*.

It would have been routine for a POSA in view of Snowdy to have determined which of the 48 positions that differ between AAVrh.10 and AAV8 involve phosphorylatable amino acids in AAVrh.10, and then to have identified the subset of these positions at which the corresponding position in AAV8 had a non-phosphorylatable amino acid. EX1009, 125; EX1033, Abstract; EX1021; EX1022; EX1005, ¶283.

Given that the Snowdy reference is a Ph.D. thesis, Snowdy was likely at or below the level of a POSA at the time. EX1005, ¶284. Therefore, Snowdy's use of

the NetPhos program to determine phosphorylation sites in an AAV capsid was also well within the level of ordinary skill in the art at the time. EX1009, 125; EX1033, Abstract; EX1005, ¶284.

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. EX1005, ¶285. Indeed, Snowdy itself discloses this type of mutagenesis. EX1009, 125-26; EX1005, ¶285. And Snowdy found that "[a]ll of the mutants were capable of forming virus at normal titers," confirming that a POSA would have had a reasonable expectation of success that the four AAVrh.10 capsid variants would similarly form rAAVs. EX1009, 126; EX1005, ¶285.

For these reasons, a POSA would have had a reasonable expectation of success in combining the '772 Publication with Snowdy to obtain an rAAV vector having the combination of elements recited in claim 1. EX1005, ¶286.

Thus, claim 1 of the '274 patent is obvious over the '772 Publication and Snowdy. *Id.*, ¶287.

3. Claims 3-6 Are Obvious Over the '772 Publication and Snowdy

As discussed above for claim 1, a POSA would have been motivated to combine the '772 Publication with Snowdy. As discussed above for Ground 1, claims 3-6, the '772 Publication teaches each of the additional elements of these claims. EX1005, ¶288. As further discussed above, a POSA would have had a reasonable expectation of success in combining the '772 Publication with Snowdy to obtain an rAAV vector having the combination of elements recited in each of claims 3-6. *Id*. Thus, claims 3-6 of the '274 patent are obvious over the '772 Publication and Snowdy.

4. Secondary Considerations Do Not Change the Conclusion of Obviousness

For the reasons discussed above for Ground 1, secondary considerations do not alter the conclusion that claims 1 and 3-6 of the '274 patent are obvious over the '772 Publication and Snowdy. *Id*. ¶289.

D. Ground 4: Claim 8 Is Obvious Over the '772 Publication, as Confirmed by the Opinions of Patent Owners' Expert in Earlier Litigation, and Fabb

1. A POSA Would Have Been Motivated to Combine the '772 Publication with Fabb

Claim 8 recites: "The recombinant AAV according to claim 6, wherein the dystrophin gene product is a mini-dystrophin or micro-dystrophin."

The ’772 Publication discloses “a dystrophin cDNA sequence.” EX1007, [0157]. The ’772 Publication also discloses the issue, well known to those of skill in the art at the time, that AAV vectors have a size limit on the transgenes that they can package and deliver. EX1007, [0103], [0104]; EX1031, 6; EX1010, Abstract (reporting the use of a < 3.8kb micro-dystrophin cDNA in mice); EX1005, ¶291. The ’772 Publication states:

> In certain situations, a different transgene may be used to encode each subunit of a protein, or to encode different peptides or proteins. ***This is desirable when the size of the DNA encoding the protein subunit is large, e.g., for an immunoglobulin, the platelet derived growth factor, or a dystrophin protein.***
>
> **********
>
> Suitable transgenes may be readily selected by one of skill in the art.

EX1007, [0103], [0104] (emphasis added).

A POSA reading these disclosures would have understood that the large dystrophin gene would need to be reduced in size to be packaged in an AAV vector. EX1005, ¶292. The reference in the ’772 Publication to a “dystrophin cDNA sequence” would also have indicated to a POSA that the ’772 Publication teaches the use of a reduced size dystrophin made from cDNA rather than the longer, native DNA encoding the entire dystrophin gene. *Id*.

A POSA at the time would have further understood that the full length cDNA of the dystrophin gene (14kb) is too large to be packaged into an AAV vector. EX1010, Abstract; EX1031, 6 ("Since the capsids of AAV types 1 to 6 are similar in diameter (this is likely also true for AAV-7 and -8), the size of the foreign DNA to be encapsidated, including the ITRs, must not exceed the approximate 5 kb packaging limit of AAV"); EX1005, ¶293. A POSA would therefore have been motivated to create DNA constructs smaller in length than the full length dystrophin cDNA for use as part of an AAV vector. EX1005, ¶293.

Fabb teaches the construction of a smaller version of the dystrophin gene known as a "micro-dystrophin" for use with an AAV vector. EX1010, Abstract, 2-3. Indeed, Fabb teaches that a < 3.8 kb micro-dystrophin delivered as part of an AAV gene therapy vector restored dystrophin associated protein complexes and inhibited degenerative dystrophic muscle pathology in an animal model. *Id*.

A POSA would therefore have been motivated to combine the '772 publication with Fabb to create such a micro-dystrophin construct. EX1005, ¶295.

2. A POSA Would Have Had a Reasonable Expectation of Success in Combining the '772 Publication with Fabb

A POSA would have needed only routine experimentation to create a micro-dystrophin that could fit within an AAV capsid. EX1005, ¶296. Given that working examples of such constructs were already known in the art, including the example

disclosed in Fabb, a POSA could have used Fabb as a guide to create a micro-dystrophin that would fit within the claimed AAV capsid. EX1010, 2-3; EX1005, ¶296. A POSA would have needed only routine techniques to create such a micro-dystrophin, as taught by the '772 publication, which states:

> The preparation of a host cell according to this invention involves techniques such as ***assembly of selected DNA sequences***. This assembly may be accomplished utilizing conventional techniques. ***Such techniques include cDNA*** and genomic ***cloning***, ***which are well known*** and are described in Sambrook et al., cited above, use of overlapping oligonucleotide sequences of the adenovirus and AAV genomes, combined with polymerase chain reaction, synthetic methods, and any other suitable methods which provide the desired nucleotide sequence.

EX1007, [0135] (emphases added); EX1005, ¶296. Given that a micro-dystrophin is constructed from a dystrophin cDNA, the cDNA techniques described in the '772 Publication as routine were the same techniques that would have been used by a POSA to create a micro-dystrophin. EX1010, 2-3; EX1005, ¶296.

Therefore, claim 8 of the '274 patent is obvious over the combination of the '772 Publication with Fabb. EX1005, ¶297.

3. Secondary Considerations Do Not Change the Conclusion of Obviousness

For the reasons discussed above regarding Ground 1, secondary considerations do not alter the conclusion that claim 8 of the '274 patent is obvious over the combination of the '772 Publication with Fabb. EX1005, ¶298.

E. Ground 5: Claim 8 Is Obvious Over the '772 Publication and Xie, in Combination with Fabb

1. A POSA Would Have Been Motivated to Combine the '772 Publication and Xie with Fabb

For the reasons discussed above regarding Ground 2, a POSA would have been motivated to combine the '772 Publication with Xie to improve the properties of AAVrh.10 as a gene therapy vector, by creating variants of AAVrh.10, each containing a substitution of a single amino acid in the capsid protein from the preferred embodiment AAV8, where the substituted amino acids lie on the surface of the AAV capsid. EX1005, ¶299.

A POSA seeking to use such a variant of AAVrh.10 as a delivery vehicle for a dystrophin gene would have been motivated to combine the '772 Publication and Xie with Fabb, which teaches the construction of a smaller version of the dystrophin gene known as a "micro-dystrophin" for use with an AAV vector. EX1010, 2-3; EX1005, ¶300.

A POSA would therefore have been motivated to combine the '772 publication and Xie with Fabb to create such a micro-dystrophin. EX1005, ¶300.

2. A POSA Would Have Had a Reasonable Expectation of Success in Combining the '772 Publication and Xie with Fabb

For the reasons discussed above with respect to Ground 4, a POSA would have needed only routine experimentation to create a micro-dystrophin that could fit within an AAV capsid. *Id*., ¶302.

Therefore, claim 8 of the '274 patent is obvious over the combination of Fabb with the '772 Publication and Xie. *Id*., ¶303.

3. Secondary Considerations Do Not Change the Conclusion of Obviousness

For the reasons discussed above with respect to Ground 1, secondary considerations do not alter the conclusion that claim 8 of the '274 patent is obvious over the combination of Fabb with the '772 Publication and Xie. *Id*., ¶304.

F. Ground 6: Claim 8 Is Obvious Over the '772 Publication and Snowdy, in Combination with Fabb

1. A POSA Would Have Been Motivated to Combine the '772 Publication and Snowdy with Fabb

For the reasons discussed above regarding Ground 3, a POSA would have been motivated to combine the '772 Publication with Snowdy to improve the properties of AAVrh.10 as a gene therapy vector, by creating variants of AAVrh.10, each containing a substitution of a single amino acid in the capsid protein from the preferred embodiment AAV8, where non-phosphorylatable amino acids are substituted for phosphorylatable amino acids. EX1005, ¶305.

A POSA seeking to use such a variant of AAVrh.10 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 the dystrophin gene known as a "micro-dystrophin" for use with an AAV vector. EX1010, 2-3; EX1005, ¶306.

A POSA would therefore have been motivated to combine the '772 Publication and Snowdy with Fabb to create the rAAV of claim 8. EX1005, ¶307.

2. A POSA Would Have Had a Reasonable Expectation of Success in Combining the '772 Publication and Snowdy with Fabb

For the reasons discussed above with respect to Ground 4, a POSA would have needed only routine experimentation to create a micro-dystrophin that could fit within an AAV capsid. EX1005, ¶308.

Therefore, claim 8 of the '274 patent is obvious over the combination of Fabb with the '772 Publication and Snowdy. *Id*., ¶309.

3. Secondary Considerations Do Not Change the Conclusion of Obviousness

For the reasons discussed above with respect to Ground 1, secondary considerations do not alter the conclusion that claim 8 of the '274 patent is obvious over the combination of Fabb with the '772 Publication and Snowdy. *Id*., ¶310.

IX. DISCRETIONARY DENIAL IS NOT APPROPRIATE HERE

A. Discretionary Denial Under *General Plastic* Is Not Appropriate

Petitioner has never before filed a Patent Office challenge to the '274 patent.

B. Discretionary Denial Under the *Fintiv* Factors Is Not Appropriate

The Board should institute this proceeding because the relevant factors weigh against discretionary denial and strongly favor institution. *See Apple Inc. v. Fintiv, Inc*., IPR2020-00019, Paper 11, at 5-6 (PTAB Mar. 20, 2020).

1. Factor 1: Whether the District Court Granted a Stay or a Stay May Be Granted if a Proceeding Is Instituted

The case is still in the early stages of litigation, with trial currently scheduled for November 17, 2025. Petitioner represents that it will seek a stay in district court upon institution. Given that the district court case between Petitioner and Patent Owners is in an early stage, with the complaint having been filed approximately eight months ago, and key dates very far in the future (*e.g*., the Markman hearing is scheduled for August 22, 2024, and trial is scheduled to begin November 17, 2025), there is a strong likelihood such a stay will be granted. EX1028, 8, 11.

2. Factor 2: Proximity of the Court's Trial Date to the Board's Projected Statutory Deadline for a Final Written Decision

The trial is not scheduled to begin until November 17, 2025 – approximately 21 months after the filing of this Petition. As such, a final written decision would precede trial.

3. Factor 3: Investment in the Parallel Proceeding by the Court and the Parties

There is still significant investment required for resolution of the district court litigation. Claim construction, discovery, pre-trial motions, preparing for trial, going through the trial process, and engaging in post-trial motions practice, all lie in the future. EX1028.

4. Factor 4: Overlap Between Issues Raised in the Petition and in the Parallel Proceeding

Petitioner has not yet served preliminary invalidity contentions, given the early stage of the litigation. Although the invalidity contentions that will be served in the district court are likely to include prior art cited in this Petition, they are also likely to include additional references and might not advance the same grounds set forth in this Petition. Instituting a proceeding will allow the Board to address the art, and the issues will be narrowed in the litigation due to the estoppel provisions of 35 U.S.C. §315(e).

Additionally, Patent Owners assert claims 1, 3-6, and 8 of the '274 patent in their preliminary infringement contentions. EX1026, 2. This Petition challenges all of those claims, further weighing against discretionary denial. *3Shape A/S v. Align Tech., Inc*., IPR2020-00223, Paper 12, at 34 (PTAB May 26, 2020); *see also Apple, Inc. v. Maxell, Ltd*., IPR2020-00204, Paper 11, at 15-17 (PTAB June 19, 2020).

5. Factor 5: Whether the Petitioner and the Defendant in the Parallel Proceeding Are the Same Party

Petitioner is one of the co-defendants in the parallel district court proceeding. EX1025. This is true of most petitioners in IPR proceedings. *Fintiv* indicates that a difference between the district court defendant and the IPR petitioner might weigh against discretionary denial. However, *Fintiv* does not suggest that this factor weighs in favor of discretionary denial if the district court defendant is the IPR petitioner. Thus, this factor is neutral.

6. Factor 6: Other Circumstances that Impact the Board's Exercise of Discretion Including the Merits

As shown above, the merits of this Petition are strong. Further, the prior art asserted in this Petition was not considered during prosecution of the '274 patent. This is also the first petition challenging the claims of the '274 patent. Each of these additional factors weigh against discretionary denial.

C. Discretionary Denial Under 35 U.S.C. § 325(d) Is Not Appropriate

The Board should not exercise its discretion under §325(d). *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 7 (PTAB Feb. 13, 2020). This analysis employs a two-prong framework: (1) whether the arguments presented in the petition are the same or substantially the same as those previously presented to the Office; and (2) if so, whether the petitioner has demonstrated a material error by the Office in its prior consideration of those

arguments. *Id*. In evaluating each of these prongs, the Board considers several non-exclusive factors from *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-015786, Paper 8 (PTAB Dec. 15, 2017).

1. Step One of *Advanced Bionics*

Petitioner's arguments and prior art are neither the same nor substantially the same art or arguments previously before the Office. During prosecution, Xie, Snowdy, and Fabb were not submitted to the PTO. EX1001, References Cited; EX1002. There is therefore no basis for denying this Petition because "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. §325(d).

Patent Owners might argue that the '772 Publication was cited in an IDS. EX1001, References Cited; EX1002, 142. But the '772 Publication was not applied against the claims in an Office Action or otherwise discussed during prosecution. EX1002. "The Board frequently holds that a reference that was neither applied against the claims nor discussed by the Examiner does not weigh in favor of exercising the Board's discretion under §325(d) to deny a petition." *Amazon.com, Inc. v. M2M Sols. LLC*, IPR2019-01205, Paper 14, at 16 (PTAB. Jan. 27, 2020); *Adv. Energy Indus. Inc. v. Reno Tech. Inc*., IPR2021-01397, Paper 7, at 7 (PTAB Feb. 16, 2022); *Fasteners for Retail, Inc. v. RTC Indus*., Inc., IPR2019-00994, Paper 9, at 7-11 (PTAB Nov. 5, 2019).

Patent Owners might also argue that the '772 Publication was the subject of a rejection during prosecution of a related application involving claims to methods of identifying "singletons" in aligned AAV vp1 amino acid sequences. EX1055, 11-18. However, the claims examined in the earlier application did not include limitations to vp1 capsid proteins having the recited AAVrh.46 sequence or a sequence at least 95% identical to the recited AAVrh.46 sequence, and having an asparagine (N) at position 665. *Id*., 4-10. Further, in response to the Examiner's rejection during prosecution of the earlier application, the applicant cancelled the rejected claims. *Id*., 19-24.

Moreover, during prosecution of the '274 patent, the Examiner did not have the benefit of the testimony of Patent Owners' experts in the Penn-I litigation setting out their understanding of the disclosures of the '772 Publication or the information that a POSA would consult – such as the crystallography data in Xie – when determining where to make modifications to the AAVrh.10 capsid protein sequence disclosed in the '772 Publication. Thus, the '772 Publication is not cumulative of the disclosures relied upon during prosecution and the Examiner's failure to apply the '772 Publication was material error, as described below.

Similarly, the Examiner did not address prior art similar to Xie, nor is Xie cumulative to art considered during prosecution. EX1002. During prosecution, no references disclosing the importance of mutating references on the surface of the

AAV capsid based on a crystal structure in efforts to improve the function of rAAVs (like Xie) were considered. *Id*.

Likewise, the Examiner did not address prior art similar to Snowdy, nor is Snowdy cumulative to art considered during prosecution. *Id*. During prosecution, no references disclosing the importance of phosphorylation in efforts to improve the function of rAAVs (like Snowdy) were considered. *Id*.

Finally, the Examiner did not address prior art similar to Fabb, nor is Fabb cumulative to art considered during prosecution. *Id*. During prosecution, no references disclosing micro-dystrophin genes and methods of creating micro-dystrophin genes that fit within an AAV capsid (like Fabb) were considered. *Id*.

Thus, during prosecution, the Examiner did not have the benefit of considering combinations of Xie, Snowdy, or Fabb with the ’772 Publication.

2. Step Two of *Advanced Bionics*

Because Petitioner presents new arguments and combinations in this Petition, it is unnecessary to analyze step two. However, even if the same or substantially the same art had been previously presented to the Office, the Examiner made material errors in evaluating the art.

As discussed in Section IX.C.1, during prosecution, the Examiner did not consider substitutions to AAVrh.10 that Patent Owners’ expert in the Penn-I litigation said are taught in the ’772 Publication. *Id*. Additionally, the Examiner did

not consider references such as Xie that provide clear teachings to focus on amino acids on the surface of the capsid to improve the biological properties of AAV, such as tropism and transduction efficiency. *Id*. The Examiner also did not consider references such as Snowdy that provide clear teachings to focus on substituting amino acids that can be phosphorylated with those that cannot to improve the properties of AAV, such as tropism and transduction efficiency. *Id*. Finally, the Examiner did not consider references such as Fabb that disclose micro-dystrophins and methods of creating micro-dystrophin genes that fit within AAV vectors. *Id*. Accordingly, discretionary denial is not warranted.

X. CONCLUSION

Sarepta respectfully requests institution of IPR for claims 1, 3-6, and 8 of the '274 patent based on the grounds specified in this Petition.

Respectfully submitted,

February 21, 2024

By: /Robert B. Wilson/

Robert B. Wilson (Reg. No. 45,227)
Anne S. Toker (Reg. No. 53,692)
James M. Glass (Reg. No. 46,729)
Quinn Emanuel Urquhart & Sullivan, LLP
51 Madison Avenue, 22nd Floor
New York, New York 10010
Tel.: 212-849-7000
Fax: 212-849-7100

Attorneys for Petitioner Sarepta Therapeutics, Inc.

WORD COUNT CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), Petitioner hereby certifies, in accordance with and reliance on the word count provided by the word-processing system used to prepare this Petition, that the number of words in this paper is 13,681. Pursuant to 37 C.F.R. §42.24(d), this word count excludes the table of contents, table of authorities, mandatory notices under §42.8, certificate of service, certificate of word count, appendix of exhibits, and any claim listing.

Respectfully submitted,

February 21, 2024

By: /Robert B. Wilson/

Robert B. Wilson (Reg. No. 45,227)
Anne S. Toker (Reg. No. 53,692)
James M. Glass (Reg. No. 46,729)
Quinn Emanuel Urquhart & Sullivan, LLP
51 Madison Avenue, 22nd Floor
New York, New York 10010
Tel.: 212-849-7000
Fax: 212-849-7100

Attorneys for Petitioner Sarepta Therapeutics, Inc.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §42.6 (e) and 37 C.F.R. §42.105, I hereby certify that on February 21, 2024, I caused the foregoing Petition for *Inter Partes* Review, Power of Attorney, and Exhibits 1001–1056 to be served on Patent Owners by depositing them for shipment with Federal Express to the correspondence address of record listed on the Patent Center:

270 - HOWSON & HOWSON LLP
325 Sentry Parkway East, Five Sentry East
Suite 160
Blue Bell, PA 19422
UNITED STATES

Respectfully submitted,

February 21, 2024

By: /Robert B. Wilson/

Robert B. Wilson (Reg. No. 45,227)
Anne S. Toker (Reg. No. 53,692)
James M. Glass (Reg. No. 46,729)
Quinn Emanuel Urquhart & Sullivan, LLP
51 Madison Avenue, 22nd Floor
New York, New York 10010
Tel.: 212-849-7000
Fax: 212-849-7100

Attorneys for Petitioner Sarepta Therapeutics, Inc.