

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,

Patent Owner

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

“Method of Increasing the Function of an AAV Vector”

IPR2024-00580

PETITIONER’S REPLY TO PATENT OWNER’S RESPONSE

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LIST OF EXHIBITS

Exhibit Number	Description
EX1058	Haberman <i>et al.</i> , “Therapeutic Liabilities of <i>in vivo</i> Viral Vector Tropism: Adeno-Associated Virus Vectors, NMDAR1 Antisense, and Focal Seizure Sensitivity,” <i>Molecular Therapy</i> (2002): 495-500 (“Haberman”)
EX1059	U.S. Provisional Patent Application 60/636,126 (“the ’126 provisional”)
EX1060	Wu <i>et al.</i> , “Single Amino Acid Changes Can Influence Titer, Heparin Binding, and Tissue Tropism in Different Adeno-Associated Virus Serotypes,” <i>Journal of Virology</i> (2006): 11393-97 (“Wu 2006”)
EX1061	U.S. Patent No. 7,892,809 (“the ’809 patent”)
EX1062	Bowles <i>et al.</i> “Phase 1 Gene Therapy for Duchenne Muscular Dystrophy Using a Translational Optimized AAV Vector,” <i>Molecular Therapy</i> (2012): 443-55 (“Bowles”)
EX1063	March 6, 2025 Samulski Deposition Transcript (“Samulski Dep. Tr.”)
EX1064	Nov. 1, 2024 Schaffer Deposition Transcript, with errata (“Schaffer Dep. Tr.”)
EX1065	U.S. Patent No. 9,012,224 (“the ’224 patent”)
EX1066	U.S. Patent Application Publication 2005/0053922 (“the ’922 publication”)
EX1067	PCT/US2005/045552 (“the ’552 PCT”)
EX1068	Kern <i>et al.</i> , “Identification of a Heparin-Binding Motif on Adeno-Associated Virus Type 2 Capsids,” <i>Journal of Virology</i> (2003): 11072-81 (“Kern”)
EX1069	U.S. Provisional Patent Application 60/484,111 (“the ’111 provisional”)
EX1070	Maersch <i>et al.</i> “Optimization of stealth adeno-associated virus vectors by randomization of immunogenic epitopes,” <i>Virology</i> (2010): 167-75 (“Maersch”)

Exhibit Number	Description
EX1071	Wang <i>et al.</i> , “Comparative Study of Liver Gene Transfer With AAV Vectors Based on Natural and Engineered AAV Capsids,” <i>Molecular Therapy</i> (2015): 1877-87 (“Wang”)
EX1072	Reply Declaration of David V. Schaffer, Ph.D.
EX1073	Lu <i>et al.</i> , “506. Transductional and Genome Biodistribution of Novel AAV Serotype Vectors after Systemic Delivery and Their Liver Specific Dose Response Profiles in Mice,” <i>Molecular Therapy</i> (2005): S196 (“Lu”)

I. PATENT OWNERS' ARGUMENTS ARE BASED ON UNRELIABLE OPINIONS OF DR. SAMULSKI

Dr. Samulski's opinions are unreliable. He failed to address the combinations asserted in the Petition or the analysis of those combinations in the declaration of Petitioner's expert, Dr. Schaffer. Thus, Patent Owners' arguments, which rely on Dr. Samulski's opinions, are not responsive or otherwise relevant to the issues of obviousness for the challenged claims.

A. Snowdy Is Highly Pertinent Prior Art, Despite Dr. Samulski's Attempts to Discredit It

Dr. Samulski's opinions are unreliable because he improperly dismissed the teachings of Snowdy. EX1072, ¶¶16-24. In his declaration, Dr. Samulski argues that "the particular study described in Chapter IV [of Snowdy] was never peer-reviewed or otherwise published, and in my view a skilled artisan would have accorded little, if any, weight to the results." EX2027, ¶72.

Notably, Dr. Samulski nowhere challenges the validity of the results in Snowdy. At his deposition, Dr. Samulski agreed with Dr. Schaffer's opinions about the import of Snowdy's results and how they would have been understood by a POSA at the relevant time.¹ EX1063, 98:23-99:15.

¹ Dr. Samulski commended Dr. Schaffer's stature in the field. EX1063, 82:13-19 (describing Dr. Schaffer as "very talented" and "a significant and

Moreover, Dr. Samulski testified that he was Snowdy's advisor on the thesis, the work was carried out in his lab, and he supervised, approved, and signed the dissertation, indicating that he believed the work to be sufficiently valuable to support the award of a Ph.D., as did the rest of the faculty members who reviewed and signed-off on the dissertation. EX1009, 1; EX1063, 16:3-17:6, 18:10-12, 19:10-13, 19:20-20:14.

Whether Snowdy was published in a peer-reviewed journal is not a basis for dismissing the thesis. References such as patent applications need not be peer-reviewed in order to be prior art. 35 U.S.C. §102(a). Moreover, Dr. Samulski's criticisms of Snowdy are particularly unreliable, given that the experiments and results were reviewed by Snowdy's thesis committee, which included Dr. Samulski as the advisor. Dr. Samulski further testified that as an older student and former Navy Seal, Snowdy was more mature and needed less supervision than younger graduate students, fresh out of college. EX1063, 16:3-8, 16:23-17:25.

At his deposition, Dr. Samulski attempted to discredit Snowdy's thesis as merely "acceptable," not "exceptional." EX1063, 18:23-19:7. Yet, in a 2004 patent

consistent contributor to our field," and calling out a gene therapy developed by Dr. Schaffer that is in Phase III clinical trials as "demonstrating the success" of Dr. Schaffer's work).

filing, Dr. Samulski appears to have used the teachings in Snowdy as the basis for many of the disclosures and claims. EX1059; EX1072, ¶¶127-99. Specifically, Dr. Samulski disclosed and claimed single amino acid substitutions in the capsid sequence of AAV2 based on the sequence of AAV1, with the objective of conferring the enhanced muscle transduction of AAV1 onto AAV2. EX1072, ¶¶127-65. The rational design approach employed by Dr. Samulski in this patent filing involved intentionally making single amino acid substitutions to replace a phosphorylatable threonine in AAV2 with the corresponding, non-phosphorylatable asparagine in AAV1 – just as Snowdy taught. *Id.*, ¶¶166-99.

Dr. Samulski’s testimony, and the remarkable similarities in Dr. Samulski’s subsequent patent filing that appear to build on Snowdy, demonstrate that he did not give proper weight in his analysis to the teachings in this reference as they would have been understood by a POSA at the relevant time. Patent Owners’ arguments that rely on these opinions are likewise unfounded.

B. Dr. Samulski’s Idiosyncratic Definition of Tropism Is Irrelevant to Obviousness

Patent Owners premise their arguments on two inconsistent and highly unusual definitions of the term “tropism” in Dr. Samulski’s declaration. *See, e.g.*, POR, 50-54; EX2027, ¶¶38, 73; EX1072, ¶¶4-6, 25-42.

First, Dr. Samulski defines “tropism” to mean “the steps that occur *before* the AAV reaches the cell.” EX2027, ¶38 (emphasis in original). Later, Dr. Samulski

defines “tropism” to include more than just reaching the cell, but also the steps of binding and endocytosis that allow an AAV vector to be “taken up” by the cell of interest. *Id.*, ¶73. Dr. Samulski distinguishes both of these definitions of “tropism” from “infectivity,” which, according to Dr. Samulski, relates to the intracellular steps “*after* the AAV vector reaches the cell,” such as “expression of the gene of interest.” *Id.*, ¶38 (emphasis in original); *see also id.*, ¶72.

Relying on Dr. Samulski’s unusual definitions of “tropism,” Patent Owners argue that a POSA would not have combined the teachings of Snowdy with those of the ’772 Publication. According to Dr. Samulski, Snowdy relates to “infectivity,” not “tropism,” so a POSA would not have combined Snowdy with the teachings in the ’772 Publication about the tropism of AAVrh.10. *See, e.g.*, EX2027, ¶73.

However, at his deposition, Dr. Samulski admitted that his idiosyncratic definitions of “tropism” are different from the way the term is used in the ’772 Publication – the primary reference in this proceeding – testifying that “they [the ’772 Publication] are using tropism in another manner.” EX1063, 47:22-48:3; *see also id.*, 43:5-12, 44:17-45:6; EX1072, ¶¶43-47.

Moreover, Dr. Samulski admitted that the experiments in Example 9 of the ’772 Publication – which are the basis for the comparison of AAVrh.10 to AAV1 and AAV8, and provide the starting point for motivation – use “gene expression” to evaluate tropism, which is expressly excluded from Dr. Samulski’s definitions of the

term. *Id.*, 45:17-47:1; EX1072, ¶¶48-58. Dr. Samulski admitted that he used a different definition of tropism in his analysis, and that he did not consider himself to be bound by the way the term is used in the '772 Publication when considering the teachings of this reference. *Id.*, 43:5-12.

Likewise, Dr. Samulski admitted that his definitions are also different from the way that he and his colleagues used the term in his own patent filings and research publications in 2005-2006. *Id.*, 159:11-21, 162:11-16; EX1072, ¶¶71-97.

Thus, by Dr. Samulski's own admissions, his opinions about the combination of the '772 Publication and Snowdy are premised on definitions of the term "tropism" that are inconsistent with the way the term is used in the '772 Publication and the way a POSA would have understood the term at the relevant time.

Additionally, the '772 Publication touts the superior *gene transfer* capability and *transduction* of AAVrh.10 across three tissues of AAVrh.10. EX1007, [0257]; EX1072, ¶¶26, 59-63. And Snowdy teaches that removing a putative phosphorylation site in the AAV capsid can greatly improve *transduction* of target tissues. EX1005, ¶¶95-96, 187-89, 272-76; EX1072, ¶¶26, 59-63. Therefore, a POSA would be motivated to combine these references to improve *transduction* of

AAVrh.10. Patent Owners’ arguments based on Dr. Samulski’s unusual definitions of tropism fail for this additional reason.²

C. Single Amino Acid Substitutions That Changed Tropism Were Well Known in the Art, Contrary to Dr. Samulski’s Opinions

Patent Owners argue that a POSA as of 2005, and even for a decade afterward, would not have made single amino acid substitutions in an AAV capsid to change tropism. *See, e.g.*, POR, 2-3, 17-22, 36; EX2027, ¶28. Dr. Samulski states in his declaration: “Notably, as I will discuss more below, while some techniques had been shown by 2005 to improve or change tropism, *none involved a single amino acid substitution. Nor am I aware today of any example* where tropism is significantly increased or changed to a materially different tissue type because of a single amino acid substitution.” EX2027, ¶32 (emphasis added).

Patent Owners’ arguments are undercut by the work of Dr. Samulski’s own graduate student in Snowdy, the disclosure of single amino acid substitutions to affect tropism in the ’772 Publication, and numerous patent filings and publications as of 2005-2006, including those from Dr. Samulski himself. EX1072, ¶¶ 7-15, 104-09, 371-82.

² Dr. Schaffer uses the term “tropism” consistently in his declaration and his prior publications. EX1072, ¶¶64-70. As such, Dr. Schaffer’s declaration does not support Dr. Samulski’s definitions of tropism. *Id.*, ¶¶98-103.

Contrary to Patent Owners' arguments, a POSA at the time seeking to alter the tropism of an AAV serotype such as AAVrh.10 would not have been limited to swapping large domains of AAV serotypes, or to creating vast numbers of random mutations, in an effort to alter tropism. EX1072, ¶¶371-82, 388-90, 403-09. The disclosures of the '772 Publication and Snowdy, and the published work of other researchers in the field, demonstrate that a rational design strategy, involving selected, single amino acid mutations in the AAV capsid, was readily available to a POSA at the time. *Id.*

1. Snowdy Discloses Single Amino Acid Substitutions That Improved Transduction Efficiency

The work of Dr. Samulski's own graduate student, Stephen Snowdy, as of 2003, demonstrates that a single amino acid change in the AAV2 capsid could substantially improve transduction efficiency, which a POSA would have understood could affect tropism. EX1072, ¶¶110-14, 371-74. As Dr. Snowdy's advisor, Dr. Samulski was plainly aware of these results. This work contradicts Patent Owners' arguments regarding single amino acid substitutions.

Dr. Samulski mischaracterizes Snowdy in multiple ways. EX1072, ¶¶280-318. First, the significance of Snowdy's results is not limited to the phenomenon of nuclear localization. On the contrary, Snowdy expressly teaches that the surprising improvement in transduction efficiency produced by a single amino acid change could not be readily explained as a nuclear localization effect, and therefore likely

was the result of a change in some other function of the AAV vector, broadening the significance of these results to a POSA. *Id.*, ¶¶282-94.

Dr. Samulski is also incorrect in characterizing Snowdy's mutagenesis approach as alanine scanning, particularly given that half the mutations Snowdy made in this set of experiments involved substituting in aspartic acid, rather than alanine. *Id.*, ¶¶295-309. In addition, Dr. Samulski incorrectly attempts to diminish the import of Snowdy's results on the grounds that some of the mutants he made had no effect. *Id.*, ¶¶310-18. But as Dr. Samulski testified, a researcher would be "lucky" to have one experiment out of three produce a positive result, let alone a result demonstrating the improvement of a function of AAV. EX1063, 86:24-87:5. Indeed, the unexpected nature of the results in Snowdy only highlights the significance of the teachings to a POSA. EX1072, ¶287-94.

2. The '772 Publication Teaches a Single Amino Acid Substitution to Affect Tropism

In his declaration, Dr. Samulski states that "the '772 Publication is *silent* as to using single amino acid substitutions to alter tissue tropism." EX2027, ¶53 (emphasis added).

However, at his deposition, Dr. Samulski admitted that the '772 Publication teaches that making a single amino acid change in the AAV capsid could alter tropism. EX1063, 50:9-16, 60:23-62:11, 67:4-69:1. Specifically, Dr. Samulski confirmed that the '772 Publication discloses a single amino acid mutation in the

AAV capsid, changing a methionine to a valine, that could affect the location of epitopes on the surface of the capsid, and thereby alter tropism, even under his definition. *Id.*; *see also* EX1007, [0072], [0091]; EX1005, ¶229; EX1072, ¶¶115-26, 371-74.

Despite this plain disclosure, Dr. Samulski testified that he did not consider these teachings of the '772 Publication because he viewed them as reflecting “a hypothesis I don’t believe in.” EX1063, 62:23-64:10. As with Snowdy, Dr. Samulski failed to consider the full teachings of the '772 Publication in his analysis.

3. Other Researchers at the Time Were Making Single Amino Acid Substitutions in AAV That Changed Tropism

At his deposition, Dr. Samulski walked back his opinions that ***no*** researchers as of 2005-2006 were investigating single amino acid substitutions in AAV that altered tropism. He testified that what he actually meant was that ***no one other than his group*** was carrying out such experiments. EX1063, 143:13-18.

Dr. Samulski is incorrect. For example, Kern is an AAV mutagenesis study, published in 2003, investigating the effects of single and double amino acid substitutions on various properties of AAV2, including cell binding *in vitro* and tissue tropism *in vivo*. EX1068; EX1072, ¶¶238-59. In that study, Kern found that a single mutation in the AAV2 capsid conferred increased cell binding *in vitro*. EX1068, 2-5 (Table 1, Fig. 2a). Moreover, Kern found that a double mutant containing a substitution at the same position as the mutant with increased cell

binding *in vitro* exhibited substantially increased tropism to heart tissue *in vivo*. EX1068, 6-7, Fig. 3.

Likewise, one of Dr. Schaffer's patent applications, published in 2005, discloses results from his lab that a single amino acid substitution in an AAV2 capsid (T716A) enhanced the ability of the rAAV to evade the immune system. EX1066, [0246], Table 1; EX1072, ¶¶260-64.

Therefore, in the time period from around 2003-2005, other researchers, including Dr. Schaffer, were exploring single amino acid substitutions to develop AAV capsids with altered properties, including altered tropism and ability to evade the immune system.³

4. Dr. Samulski Sought Patents and Published Articles on Single Amino Acid Substitutions to Change Tropism

In 2004, Dr. Samulski filed a provisional patent application (the '126 provisional), disclosing and claiming single amino acid substitutions in AAV2, based on the sequence of AAV1, to confer some of the favorable muscle tropism of AAV1 onto AAV2. EX1059; EX1072, ¶¶127-99.

³ Contrary to Patent Owners' arguments, Dr. Schaffer's publications do not suggest that single amino acid mutations in the AAV capsid will have no effect on tropism. EX1072, ¶¶265-79.

The '126 provisional also disclosed a single amino acid insertion in AAV2 of a threonine from the corresponding position of AAV1, which substantially improved muscle tropism of AAV2. EX1072, ¶¶128-65. Notably, the '126 provisional expressly discloses that, depending on the serotype at issue, this single amino acid “insertion” of threonine in AAV2 could be a single amino acid “substitution” in another serotype. EX1059, 15:24-27; 16:10-13; EX1072, ¶164.

And in 2006, Dr. Samulski published a paper titled, “Single Amino Acid Changes Can Influence Titer, Heparin Binding, and Tissue Tropism in Different Adeno-Associated Virus Serotypes.” EX1060. He testified that the work for this paper likely began in 2005, or perhaps even years earlier. EX1063, 202:7-9, 282:14-283:5. In this paper, he disclosed a single amino acid substitution in AAV1, substituting in a corresponding amino acid from AAV6, that conferred on AAV1 some of the liver tropism of AAV6, substantially improving the liver tropism of AAV1 both *in vitro* and *in vivo*. EX1072, ¶¶221-37.

Thus, Dr. Samulski’s own publications and patent filings directly contradict Patent Owners’ position regarding the state of the art in 2005 with respect to single amino acid substitutions to change tropism.

5. Dr. Samulski's Statements About Single Amino Acid Substitutions Are Not Responsive to Dr. Schaffer's Opinions

At his deposition, Dr. Samulski walked back his opinions regarding the state of the art in 2005. Dr. Samulski testified that what he *really* meant was that a POSA would not have been able to inspect the linear sequence of an AAV capsid and pick out just one amino acid to mutate, in the absence of any other information, and “assume it’s going to have an impact on viral function.” EX1063, 81:2-20.

But this argument is not responsive to the Petition or to Dr. Schaffer’s opinion on the state of the art as of 2005, which is that a POSA would have been able, given the teachings of the ’772 Publication and Snowdy, for example, to select a small number of positions to mutate in the AAVrh.10 capsid to create single amino acid mutations that could improve tropism. EX1005, ¶¶277-80; EX1072, ¶¶8-12, 404-09.

Importantly, Dr. Samulski admitted that “one approach” a POSA could have taken at the relevant time was to select several amino acids to test to see if any of them affected functions such as tropism or transduction. EX1063, 83:18-23. That is the basis of Dr. Schaffer’s obviousness opinions as set out in his original declaration. *See, e.g.*, EX1005, ¶¶277-80.

Therefore, Dr. Samulski's attempt to explain his statements about the state of the art in 2005 merely confirms that they are not on point, and do not address the arguments in the Petition or Dr. Schaffer's opinions in his declaration.

D. Dr. Samulski's Opinions Regarding the Crystal Structure in Xie Are Undercut by the Analysis in His Own Publication

Patent Owners argue that a POSA would not have been motivated to mutate S665 because it is "less accessible than at least twelve other residues" that differ between AAV8 and AAVrh.10 and lie on the surface of the AAV capsid. POR, 44-46. However, Dr. Samulski's publication (Wu 2006) contradicts the argument that a POSA seeking to alter tropism would not have been motivated to mutate less accessible residues on the surface of the AAV capsid. EX1060; EX1072, ¶¶147-52.

Wu 2006 found that a single amino acid residue was largely responsible for the superior liver tropism of AAV6 as compared to AAV1. EX1060, 4-5; EX1072, ¶¶149-50. Moreover, Wu 2006 found that this residue is located at the base of a peak on the surface of the AAV6 capsid. EX1060, 3, Figure 2; EX1072, ¶¶148-52. At his deposition, Dr. Samulski agreed that even residues at the base of a peak on the surface of an AAV capsid can affect binding to receptors on target cells and therefore influence tropism.⁴ EX1063, 231:21-233:9.

⁴ Similarly, Xie does not teach that single amino acids cannot affect tropism, contrary to Patent Owner's argument. EX1072, ¶¶153-57.

II. THE CHALLENGED CLAIMS ARE OBVIOUS

Patent Owners ignore the motivation discussed in the Petition that would have led a POSA to modify the AAVrh.10 vector, namely, its exceptional ability to transduce multiple different tissues – lung, liver, and muscle – giving rise to its “*intriguing biological significance.*” See EX1007, [0256]-[0257] (emphasis added). Despite the significance of these teachings, and the unusual emphasis placed on AAVrh.10 in the ’772 Publication, neither Patent Owners’ response nor Dr. Samulski’s declaration cites or otherwise refers to this “intriguing biological significance” reported in the ’772 Publication.

Moreover, Patent Owners selectively quote from the ’772 Publication to support their incorrect argument that a POSA at the relevant time would not have started with AAVrh.10 to target muscle tissue, but would have instead selected AAV1 or AAV7. They point to a disclosure touting the impressive tropism of AAV7 in muscle and of AAVrh.10 in lung, but fail to quote the next sentence, which states that uses of these vectors are *not* limited to these tissues, and that “one of skill in the art may utilize these vectors for delivery to other cell types, tissues or organs.” EX1007, [0142]; POR, 33-34; EX2027, ¶65.

As with Snowdy, Patent Owners avoid the most important teachings in the ’772 Publication demonstrating the obviousness of the challenged claims.

A. A POSA Would Have Modified AAVrh.10 to Improve Liver Tropism While Preserving Its Superior Tropism in Lung and Muscle

Patent Owners argue that a POSA as of 2005, interested in targeting muscle using an AAV vector for a gene therapy, would not have used AAVrh.10, or sought to modify AAVrh.10 to improve its liver tropism, but instead would have started with the natural serotypes AAV1 or AAV7 to target muscle, or AAV8 to target liver. *See, e.g.*, POR, 14-17, 23-26, 61-66. That argument is incorrect.

1. A POSA Would Have Chosen AAVrh.10 as the Basis for an AAV Vector

Importantly, a POSA as of 2005, in light of the teachings of the '772 Publication, would have understood that it was not necessary, or even desirable, to choose the best natural muscle transducer as the basis for a vector to target muscle, or the best natural liver transducer as the basis for a vector to transduce liver. *See, e.g.*, EX1007, [0142]; EX1072, ¶¶362-70, 399-409, 441-57.

Instead, the '772 Publication expressly teaches that a POSA would have understood that vectors based on a particular natural serotype such as AAVrh.10 could be used to target tissues other than lung, despite the fact that AAVrh.10 is an excellent transducer of lung tissue:

[0142] It will be readily apparent to one of skill in the art one embodiment, that certain serotypes of the invention will be particularly well suited for certain uses. For example, vectors based on AAV7 capsids of the invention are particularly well suited for use in muscle; whereas vectors based on rh.10 (44-2) capsids of the invention are

particularly well suited for use in lung. *Uses of such vectors are not so limited and one of skill in the art may utilize these vectors for delivery to other cell types, tissues or organs.* Further, vectors based upon other capsids of the invention may be used for delivery to these or other cells, tissues or organs.

Id. (emphasis added); *see also* Petition, 35. Notably, Patent Owners and Dr. Samulski quote selectively from this paragraph ([0142]) of the '772 Publication, omitting the sentence in bold and italics. POR, 33-34; EX2027, ¶65.

This paragraph supports Dr. Schaffer's opinions that a POSA would have been guided by the teachings of the '772 Publication to select AAVrh.10 as the basis for a vector because it showed excellent tropism across three important tissues. EX1072, ¶¶447-49. This paragraph expressly teaches that a POSA could use a vector based on AAVrh.10 for delivery to tissues in addition to lung, such as muscle and liver. *Id.* A POSA would have understood that considerations other than the capability of a particular serotype to transduce a particular tissue – such as usefulness for targeting multiple tissues, safety, and ease of purification – could determine which serotype to choose as the basis for an AAV vector. EX1072, ¶¶396-97, 447-49; EX1064, 50:13-15; 134:18-21; 138:1-10; EX1063, 106:23-107:23.

2. A POSA Would Have Modified AAVrh.10 to Improve Liver Transduction While Preserving Other Favorable Properties

A POSA, given the teachings of the '772 Publication about the interesting properties of AAVrh.10 – specifically, its superior transduction across three tissues – would also have been guided by the express teachings of the '772 Publication that

there was a particular need in the art for AAV vectors with improved liver transduction. EX1007, [0250]; EX1005, ¶¶137-38; EX1072, ¶¶351-61, 394-409.

Importantly, however, improving liver transduction while destroying the superior lung and muscle tropism would defeat the entire purpose of modifying AAVrh.10 in the first place, and would ignore the teachings of the '772 Publication about the importance of the superiority of AAVrh.10 across multiple tissues. EX1007, [0257]; EX1072, ¶358.

Nor did Dr. Schaffer change his testimony in this regard. EX1072, ¶¶410-33. As Dr. Schaffer explained in his original declaration: “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.” EX1005, ¶211 (emphasis added).

3. Petitioner and Dr. Schaffer Addressed Motivation to Target Muscle

Patent Owners also argue that Petitioner and Dr. Schaffer did not address motivation to target muscle with an AAVrh.10-based vector. POR, 1-2. This argument fails because Patent Owners improperly dismiss the portions of the

Petition and Dr. Schaffer's original declaration that expressly address motivation to target muscle for all asserted grounds. EX1072, ¶¶410-33, 457; Petition, 8, 26-27.

(a) Grounds 1-3

Both the Petition and Dr. Schaffer's original declaration expressly addressed motivation to use a modified AAVrh.10 in muscle. Petition, 8, 14, 26-27; EX1072, ¶410. Both Dr. Schaffer and the Petition relied on the key discussion in the '772 Publication comparing AAVrh.10 to AAV8 and AAV1, and describing AAVrh.10 as an excellent muscle transducer. EX1007, [0257]; EX1005, ¶¶123, 208; Petition, 14, 26-27.

The Institution Decision acknowledged the central importance of this disclosure in the '772 Publication: “We note that the '772 Publication states that *‘performance of clone 44.2 in liver and muscle directed gene transfer was also outstanding’ indicating that AAVrh.10 (at least before modification) performed well with muscle tissue . . .*” Paper 9, 28 (emphasis added).

Both the Petition and Dr. Schaffer explained that there was a need in the art to improve transduction of AAV vectors in various tissues, including muscle. EX1005, ¶¶85, 89-90; Petition, 8. Importantly, both the Petition and Dr. Schaffer also stated that “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.*”

EX1005, ¶211 (emphasis added); Petition, 27. The “desirable properties of AAVrh.10,” referred to all of the desirable properties of AAVrh.10, including its outstanding tropism in muscle and lung. EX1072, ¶¶416-17; Petition, 27.

Dr. Schaffer addressed targeting muscle in relation to Ground 1 of the Petition, and did not “admit” otherwise at his deposition. *See, e.g.*, EX1005, ¶¶121-23, 139-41, 208, 210, 211. As Dr. Schaffer explained at his deposition, whether or not the word “muscle” appears in every paragraph of his Declaration, his references to, for example, the overall superiority of AAVrh.10 and its desirable properties inherently address muscle tropism. *See, e.g.*, EX1064, 352:21-353:1.

Dr. Schaffer reiterated the importance of targeting delivery to muscle throughout his deposition. EX1072, ¶419.

(b) Grounds 4-6

Both the Petition and Dr. Schaffer, in addressing claim 8 (in Grounds 4-6), stated that Fabb teaches a “micro-dystrophin” that, when delivered in an AAV vector, restored dystrophin associated protein complexes and inhibited degenerative dystrophic muscle pathology in an animal model. Petition, 55; EX1005, ¶294.

Both the Petition and Dr. Schaffer’s Declaration cited portions of Fabb, including the Abstract, which states that the micro-dystrophin construct was “introduced into the skeletal muscle” of mice. *Id.*

They referred to the micro-dystrophin disclosed in Fabb as a “working example” of a micro-dystrophin that could fit in an AAV capsid. Petition, 55-56; EX1005, ¶296. Here, the phrase “working example” meant a micro-dystrophin gene that was packaged in an AAV capsid and delivered to muscle to restore function to muscle tissues. EX1072, ¶431.

Dr. Schaffer testified at his deposition that he could not agree that dystrophin was “primarily” or “predominantly” expressed in muscle without a clear understanding of what was meant by the term “predominantly.” EX1064, 359:12-360:10. Because dystrophin is expressed in many tissues including muscle, Dr. Schaffer does not believe that dystrophin would only ever be targeted to muscle. EX1072, ¶¶398, 434-40; EX1064, 343:17-18. In fact, a 2012 publication by Dr. Samulski discusses different tissues where dystrophin is expressed, does not say that dystrophin is expressed “primarily” in muscle, and lists non-muscle tissues (brain and retina) where various isoforms of dystrophin are expressed. EX1062, 1.

B. Dr. Samulski as of 2004 Chose to Modify AAV2 as a Vector for Delivery to Muscle Rather than Using AAV1 or AAV7

Patent Owners and Dr. Samulski argue that a POSA would not have tried to modify a vector to try to improve tropism to a particular tissue, but “would have merely selected the best available vector for the tissue she wanted to target.” EX2027, ¶43; *see also* POR, 14-16, 32-34.

But that is not the approach that Dr. Samulski took in his own 2004 patent filing – the '126 provisional. EX1059; EX1072, ¶¶127-99, 450. Instead, Dr. Samulski testified that in his '126 provisional, he chose to work with AAV2 as a vector to target muscle, despite the fact that AAV1 had superior muscle tropism as compared to AAV2. EX1063, 106:23-107:23; EX1072, ¶¶127-99, 450. He testified that his group chose to work with AAV2 for regulatory reasons and route of administration considerations. *Id.*

The express goal of the '126 provisional was to improve the muscle tropism of AAV2 by importing some of the favorable muscle tropism properties of AAV1 through mutagenesis, while preserving favorable properties of AAV2 such as ease of purification and safety. EX1059, 4:33-5:6; EX1072, ¶¶199, 397. In the '126 provisional, filed on December 15, 2004, Dr. Samulski carried out the exact approach that he argued in his declaration that no one in the field was carrying out as of 2005, or for many years thereafter. EX1072, ¶¶127-99.

C. A POSA Would Not Have Been Dissuaded by the Potential for Off-Target Expression

Patent Owners and Dr. Samulski argue that a POSA would have been concerned about “off-target expression” of a potential gene therapy vector. *See, e.g.*, POR, 23-24; EX2027 ¶¶33-36, 54. This argument fails for multiple reasons. EX1072, ¶¶319-36, 391-93.

First, a POSA would have understood that expression of a transgene can be limited to a particular tissue by using a promoter specific for that tissue, as the '772 Publication discloses and as Dr. Samulski testified at his deposition. EX1007 [0111]; EX1063, 215:1-25; EX1072, ¶321.

Second, a POSA as of 2005 would have understood that gene therapy vectors can be administered locally to the affected tissue, rather than intravenously, thereby reducing the chance that the vector will travel widely throughout the body and minimizing concerns about tropism to non-target tissues. EX1072, ¶¶322-24. The '772 Publication discloses local administration of AAV vectors to lung, liver, and muscle. EX1007, [0150], [0242], [0244], [0254]. At his deposition, Dr. Samulski acknowledged that local administration could obviate concerns about off-target expression, testifying that “if you had multiple tropisms attached to a capsid, the root [*sic*] of administration may restrict access to those tropisms. . . . If it's intramuscular, it's restricted. . . . You're not using the virus based on its promiscuity. You're restricting it based on the root [*sic*] of administration.” EX1063, 248:19-249:3.

Finally, a POSA would have understood that there is a difference between localization and transgene expression. EX1072, ¶¶325-36. A gene therapy vector may localize to certain tissues but not be very efficient in expressing the transgene in these cells. *Id.* As a result, improving liver tropism for AAVrh.10 can involve improving the efficiency with which AAVrh.10 expresses a transgene in liver tissue,

without changing the amount of AAVrh.10 that localizes to liver, or to any other tissue. *Id.* In such a case, improving liver tropism by increasing the efficiency of transgene expression in liver cells could actually improve safety by reducing the required dosage of the gene therapy vector. *Id.*

Moreover, one of Dr. Samulski's patents (the '809 patent) discloses and claims single amino acid substitutions from one serotype (AAV1) into another (AAV2) that can create tropism in a wholly new tissue (astrocytes), which both parent serotypes (AAV1 and AAV2) are unable to transduce. EX1072, ¶¶200-20. Therefore, Dr. Samulski's own patent contradicts Patent Owners' argument that a POSA would have always sought to restrict the tropism of an AAV vector to a narrower set of "target" tissues. *See, e.g.*, POR, 23-24; EX2027, ¶¶34-36, 54. The '809 patent demonstrates that people in the art at the time were actively modifying natural serotypes to alter their characteristics, and believed that properties such as expanded tropism could likely be beneficial in the search for new and better therapies.⁵

⁵ Patent Owners and Dr. Samulski also incorrectly characterize Dr. Schaffer's publications, which do not support their arguments regarding off-target localization. EX1072, ¶¶337-350.

D. A POSA Would Have Made the S665N Substitution

Patent Owners and Dr. Samulski argue that a POSA as of 2005 would not have sought to substitute in a non-phosphorylatable asparagine in place of a phosphorylatable serine in the AAVrh.10 capsid. They offer multiple, conflicting justifications for these arguments, including that such a substitution would “abrogate function” and that such a substitution would be a “conservative substitution” that would be expected to have little or no effect on tropism. *See, e.g.*, POR, 56-57; EX2027, ¶50. Dr. Samulski defines a “conservative substitution” as one that “does not alter the electrical charge or polarity of the side chain of the amino acid.” EX2027, ¶50. These arguments fail because they misread both the prior art and Snowdy’s teachings. EX1072, ¶¶383-87.

Notably, at his deposition, Dr. Samulski walked back the opinion in his declaration that he would not have made a substitution of asparagine in place of a serine because the two amino acids are too similar to one another. Instead, he testified that he considered amino acids such as serine and threonine to be “different” from asparagine because serine and threonine are phosphorylatable while asparagine is not.⁶ EX1063, 277:6-15.

⁶ Dr. Samulski mischaracterizes Dr. Schaffer’s discussion of Jans & Jans, which does not teach away from an S665N substitution in AAVrh.10 for multiple

Moreover, Dr. Samulski's '126 provisional disclosed and claimed two AAV2 variants, each having a single amino acid substitution in the capsid where an asparagine is substituted for a threonine (T450N and T716N). *See, e.g.*, EX1059, 21:20-22:5, 59:6-26 (claims 57-60); EX1061, 17:6-32, 75:13-24 (claims 22, 23).

Dr. Samulski admitted that the purpose of each of the threonine to asparagine substitutions disclosed in the '126 provisional was to remove a phosphorylation site in AAV2 to enhance transduction. *See, e.g.*, EX1059, 21:20-22:5, 59:6-29 (claims 57-61); EX1063, 172:11-21, 175:4-176:12, 184:22-24, 186:7-19, 197:22-198:2.

As Dr. Samulski testified, each of the threonine to asparagine substitutions in the AAV2 capsid was chosen because AAV1 has an asparagine at the corresponding position. EX1063, 184:16-21. Therefore, given the expressly stated goal of the '126 provisional to confer some of the superior muscle tropism of AAV1 onto AAV2, the purpose of creating the T450N and T716N single amino acid mutants was to try to improve the muscle tropism of AAV2 by replacing a phosphorylatable amino acid in AAV2 with a nonphorylatable amino from the corresponding position in AAV1.

reasons, including that there is an asparagine at the corresponding position in the naturally-occurring AAV8 capsid. EX1072, ¶¶458-505.

This approach is precisely the strategy, set forth in the Petition, that a POSA as of 2005 would have followed to improve the liver tropism of AAVrh.10, in light of the teachings of the '772 Publication and Snowdy.

III. SECONDARY CONSIDERATIONS

Patent Owners are completely silent regarding secondary considerations. *See* POR, 35-66; EX1072, ¶506. Without secondary considerations, there is nothing that counterbalances the compelling evidence of obviousness, and claims 1, 3-6, and 8 of the '274 patent are unpatentable.

March 20, 2025

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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 5588. 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.

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.6(e)(4), the undersigned certifies that on March 20, 2025, a complete and entire copy of this Petitioner's Reply to Patent Owner's Response and Exhibits 1058-1073 were provided via email to the Patent Owner and Exclusive Licensee by serving the email correspondence addresses of record as follows:

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