

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
and REGENXBIO INC.,
Exclusive Licensee

Case IPR2024-00580
Patent 11,680,274

PATENT OWNERS' RESPONSE

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- EX2018 Makoto Uchino et al., *Dystrophin and Dystrophin-Related Protein in the Central Nervous System of Normal Controls and Duchenne Muscular Dystrophy*, 87 Acta Neuropathol. 129 (1994).
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- EX2020 Clustal Omega Sequence Alignment of rh46, rh2, rh4, rh14, rh24, rh12, rh18, bb2, bb1, rh25, rh20, rh9, rh10, and rh11
- EX2021 Declaration of Dr. Casey M. Kraning in support of Motion for *Pro Hac Vice* Admission
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- EX2030 Deposition Transcript of Dr. David Schaffer
- EX2031 Essential Amino Acids: Chart, Abbreviations and Structure
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- EX2042 Fengqi Jiang et al., *Bibliometric analysis of global research trends in adeno-associated virus vector for gene therapy (1991-2022)*, Front. Cell. Infect. Microbiol. (2023)
- EX2043 A Gene Therapy Pioneer: The Jude Samulski Story website printout, <https://www.askbio.com/the-jude-samulski-story/>, last accessed Dec. 5, 2024

LISTING OF CHALLENGED CLAIMS

Claim 1	
[1]	A recombinant adeno-associated virus (AAV) comprising an AAV capsid and a minigene having AAV inverted terminal repeats and a heterologous gene operably linked to regulatory sequences which direct expression of the heterologous gene in a host cell, wherein the AAV capsid comprises AAV vp1 proteins, AAV vp2 proteins, and AAV vp3 proteins, wherein the AAV vp1 proteins have i) the sequence of amino acids 1 to 738 of SEQ ID NO: 4 (AAVrh46), or ii) an amino acid sequence at least 95% identical to the full length of amino acids 1 to 738 of SEQ ID NO:4, wherein the amino acid residue corresponding to position 665 in SEQ ID NO: 4 is N when aligned along the full length of amino acids 1 to 738 of SEQ ID NO: 4.
Claim 3	
[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.
Claim 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.
Claim 5	
[5]	A composition comprising the recombinant AAV according to claim 1 and a physiologically compatible carrier.
Claim 6	
[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), betaglucoisidase, 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.
Claim 8	
[8]	The recombinant AAV according to claim 6, wherein the dystrophin gene product is a mini-dystrophin or micro-dystrophin.

I. INTRODUCTION

U.S. Patent No. 11,680,274 (“the ’274 Patent”) covers a novel gene therapy comprising recombinant adeno-associated viral (“AAV”) vectors composed of novel AAV capsids and minigenes. Specifically, the ’274 Patent claims a gene therapy product using the novel capsid AAVrh46, or a capsid with a sequence at least 95% identical to AAVrh46, with an asparagine at amino acid residue 665.

EX1001, cl. 1. All six of Petitioner’s obviousness grounds rely upon an argument that a POSITA would take known capsid proteins and modify them in a specific way in order to improve the ability of the AAV virus to target the liver. Each ground begins with an analysis of U.S. Patent Publication 2003/0138772 (“the ’772 Publication”), which discloses more than fifty different AAV sequences.

Petitioner argues that a POSITA would choose just one of those sequences, AAVrh10, as a starting point, and then would modify it with just one of the other more than fifty sequences, AAV8, at just one of the nearly fifty positions where those sequences differ to reach the invention. Petitioner offers no other motivation for the modifications in its Petition other than to increase targeting of the virus to the liver.

At deposition, however, Petitioner’s expert attempted to pivot, offering a new motivation – to improve the virus’s targeting of the liver, while also “preserving” its ability to target muscle and lung tissue. But the Petition did not

address this new motivation at all, and therefore Petitioner did not argue that a POSITA seeking to improve the virus's ability to target the liver would take a different path than a POSITA seeking to maintain targeting to the muscle and lung. Moreover, the Petition did not address that claim 8, which specifically requires that the gene to be delivered be a version of dystrophin, a protein found predominantly in muscle tissue, would require delivery to the muscle as opposed to the liver. A POSITA seeking to target muscle would take yet a third path, different from targeting liver and different from preserving targeting to lung and muscle. Petitioner never addresses these varying paths, or how they impact its theory of obviousness. Instead, the entire Petition focuses solely on the first path, improving targeting of the virus to the liver. For this reason alone, the claim 8 grounds 4-6 fail, as the Petition is devoid of any motivation that would allow targeting of muscle tissue. For this reason alone, the claim 8 grounds 4-6 fail.

Even following the path laid out in the Petition—improving targeting to the liver—Petitioner offers no support that their modifications would have been expected to increase liver targeting. Petitioner argues that a POSITA would change just a single amino acid at one specific position from a serine to an asparagine out of many possible options. But all of the evidence in this proceeding thus far, including art cited by Petitioner, articles written by Petitioner's expert, and credible testimony from Patent Owners' expert, Dr. Jude Samulski, one of the

founders of the modern field of gene therapy, shows that in 2005 a single amino acid change would not have been expected to change or affect the tissue to which a virus is targeted. Instead, all the evidence shows that to confer targeting to a specific tissue, a POSITA would change or add a section or fragment of the capsid protein. Petitioner never addresses this evidence, either.

For at least these reasons, Petitioner has failed to meet its burden, and Patent Owner respectfully requests that the Board find each of claims 1, 3-6, and 8 patentable.

II. SUMMARY OF THE '274 PATENT

A. Specification and Claims

The '274 Patent disclosed two inventions. The first invention was improving non-functional or weakly performing AAV vectors (referred to herein as “AAVs”) by correcting individual amino acids, referred to as “singletons.” EX1001, 2:1-4 (“a method for correcting singletons in a selected AAV sequence in order to increase the packaging yield, transduction efficiency, and/or gene transfer efficiency”). To do this, the '274 Patent describes taking the capsid sequence of a weakly performing AAV, aligning it with a library of sequences from functional AAV capsids, and looking for positions where the amino acid in the weakly performing AAV differs within an area that is unchanged among the functional AAVs. *Id.*, 1:65-2:10, 3:12-24. The '274 Patent refers to these positions as

“singletons,” and teaches that correction of these amino acids is desirable. *Id.*, 3:10-12, 3:29-45.

The '274 Patent's second invention was the use of an additional six different novel AAVs for gene therapy, including AAVrh46, and it disclosed both the nucleic acid (DNA) and amino acid (protein) sequences of these novel AAVs. *Id.*, 8:32-34. Embodiments of the second invention included AAVs with capsids having 95% to 99% amino acid sequence identity to the six novel AAVs. *Id.*, 8:41-44, 8:49-55.

The claims of the '274 Patent are directed to the second invention, and in particular, gene therapy using the novel AAVrh46. EX1001, cls. 1-8. The “rh” label indicates that AAVrh46 was identified for the first time in rhesus monkey tissue. EX2003, 4; *id.*, Fig. 3. The '274 Patent has one independent claim and eight dependent claims. The independent claim is directed to a specific recombinant adeno-associated viral vector composed of an AAV capsid comprising vp1, vp2, and vp3 proteins of AAVrh46 or proteins 95% identical to those sequences, containing heterologous (i.e. non-AAV) genetic material in the form of a minigene.

Specifically, the claimed vector must contain amino acid sequence number 4 (or a specified percentage), or be encoded by nucleic acid sequence number 22 (or a specified percentage). The claims also require that the amino acid residue

located at position 665 of the AAV be asparagine (N). The dependent claims specify further sequence modifications, minigene terminal repeats and specific transgenes, such as mini-dystrophin or micro-dystrophin in claim 8. Dystrophin is a protein found in muscle cells that plays a critical role in maintaining the structural integrity of muscle fibers. EX2011, 7-8. Because dystrophin is one of the largest genes in the human genome (2,500,000 base pairs), only a “mini” or “micro” abridged version of dystrophin can be delivered using AAV vectors, which, due to the small size of the AAV virus, can only contain up to 4,700 base pairs of DNA. *See id.*, 3, 5; EX2012, 1. Claims 1 and 8 are reproduced below:

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

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

EX1001, cls. 1, 8.

B. Prosecution History

The prosecution history of the '274 Patent reflects that AAV vectors of the

invention are designed to better understand and improve the properties of AAV vectors. The Examiner rejected the claims that became the claims of the '274 Patent over U.S. Patent Publication 2007/0036760 to Wilson et al. ("Wilson '760 App."). EX1002, 265-276. In doing so, the Examiner identified the focus of the '274 Patent as "making AAV vectors with their clade variants *to test for improved properties for using such vectors in gene therapy experiments.*"¹ EX1002, 276. Similarly, the Examiner rejected the additional claims over a June 2004 Journal of Virology article authored by Gao that disclosed "a known AAV capsid variant for the rationale of producing sufficient quantities ... of such variant *to test and analyze.*" EX1002, 276-278.

The applicant overcame the Wilson '760 App. by disqualifying it as prior art because of common assignment, and canceled the claims rejected over Gao. EX1002, 341-342. The '274 Patent issued on June 20, 2023.

III. OVERVIEW OF THE CITED REFERENCES

A. The '772 Publication

United States Patent Publication No. 2003/0138772 ("the '772 Publication") is a 2003 publication of a 2001 patent application which discloses a method for detecting novel AAV serotypes and host cells encoding them. As discussed above,

¹ All emphasis added herein unless otherwise noted.

in 2001 only six serotypes of AAVs had been identified: AAV1-6. EX1007, [0003]. While AAV was believed to be a potentially useful “vehicle for gene therapy,” a need existed for additional AAV-based constructs, including additional capsids that could be used to create viral vectors. *Id.*, [0003]-[0004].

The ’772 Publication discloses a method to identify additional capsids by utilizing bioinformatics, polymerase chain reaction (PCR), and cloning. These novel AAV serotypes can be used as novel AAV vectors. *Id.*, [0040]-[0046]. The ’772 Publication does not disclose AAVrh46.

The ’772 Publication also discloses that fragments of AAV sequences can be isolated and spliced (i.e. combined) with portions of other AAV sequences to form “chimeric AAV capsids.” *Id.*, [0075]. It identifies many examples of “suitable fragments” that can be used. *See, e.g., id.*, [0071]-[0073].

The disclosure of the ’772 Publication facilitated analysis and characterization of existing AAV sequences, but neither taught nor suggested *individual specific mutations* to sequences as they existed in any given sample for purposes of improving functionality. *Id.*, [0058]. Instead, it describes the production of capsids, including artificial capsids, using host cells and based on specific sequences of AAV proteins. *Id.*, [0091]-[0093], [0135]-[0138], [0141].

B. Xie

Xie is a 2002 article titled “The atomic structure of adeno-associated virus

(AAV-2), a vector for human gene therapy.” EX1008, 1. Xie describes the crystal structure of AAV2. EX1008, 1. In describing AAV2, Xie noted that AAV2 was “one of five distinct serotypes,” further noting that AAV serotypes “1, 2, and 3 share ~85% capsid sequence identity ... whereas serotypes 4 and 5 are more distantly related.” *Id.* Notably, Xie did not disclose or address any other AAV serotypes or comment on the specific structure of any AAV besides AAV2. *Id.*

Xie discloses that AAV2 contains a serine at position 665, not asparagine. *Id.*, 3; *Id.*, Fig. 2; EX2016, 1.

C. Snowdy

Snowdy is a 2003 dissertation titled “Nuclear targeting by adeno-associated virus capsid proteins and virions.” EX1009, 1. Snowdy addresses two “impediments to the development of [AAV] as research and gene therapy tools.” *Id.*, 4. The first, not relevant to the issues here, is “the difficulty of producing the virus in large amounts and high purity.” *Id.*

The second impediment Snowdy addresses is “the incomplete understanding of the biology of the virus, including its nuclear targeting by the capsid proteins during initial infection and during progeny viral assembly.” *Id.*, 4. Snowdy reported on past work identifying known nuclear localization signals (NLSs), and ultimately determined that the NLSs were necessary for infectivity. *Id.*, 68-70, 72, 107. Snowdy noted that NLS activity “often depends on the status of nearby

phosphorylation sites,” meaning amino acid residues that had the ability to be conjugated to a phosphate group. *Id.*, 123. Phosphorylation of proteins allows cells to respond dynamically to changes in their environment and coordinate complex biological processes. *See generally* EX2017. Snowdy determined that one particular putative phosphorylation site, serine 181, had the ability to mediate “AAV2’s ability to infect its target cell,” while another putative phosphorylation site, serine 148, “had no effect, or little effect, on the virus’ ability to infect” its target cell. EX1009, 126, 128. Notably, Snowdy reports that the results of its experiments were the *opposite* of what the researchers expected based on what was known in the art at the time. *Id.*, 128.

Additionally, Snowdy cautioned that the disclosed research was only “preliminary evidence,” and noted that it would be “premature” to “assume that a given phosphorylation status will have the same effect on all NLSs, as there is insufficient evidence in the literature.” *Id.*, 128-29. Instead, Snowdy suggested avenues for future research. *Id.*, 131-136.

D. Fabb

Fabb is a 2002 article entitled “Adeno-associated virus vector gene transfer and sarcolemmal expression of a 144 kDa micro-dystrophin effectively restores the dystrophin-associated protein complex and inhibits myofiber degeneration in nude/*mdx* mice.” EX1010, 1. It describes advantages of AAV-based vectors, but

notes that AAV vectors “can only accommodate <5 kb of foreign DNA.” *Id.*, 1.

Fabb also describes that dystrophin is a large protein, encoded by a long sequence of DNA (14 kb), which “precluded it from being used in early first and second generation adenovirus (Ad)- or retrovirus-based gene therapy vectors.” *Id.*, 2.

Fabb notes that the solution was to use “smaller recombinant dystrophin minigenes,” and created a “new micro-dystrophin cDNA of <3.8 kb ... for use in studies on AAV vector-mediated gene transfer and complementation of dystrophin deficiency.” *Id.*

Fabb tested expression of micro-dystrophin injected in mice, achieving promising results, and suggested that use of certain AAV serotypes—in particular, AAVs 1, 3, and 5—could produce more efficacious results because of their improved efficacy in *skeletal muscle* transduction. *Id.*, 6 (citing EX2013, 1 (“AAV vectors types 1, 3, 4, and 5 transduce *skeletal muscle* more efficiently ... than rAAV2.”)). Fabb does not teach AAVrh10, nor does it suggest implementing individual point mutations to improve tropism in any tissue.

IV. LEVEL OF ORDINARY SKILL IN THE ART

Patent Owner does not challenge Petitioner’s definition of the qualifications of a person of skill in the art. Here, Patent Owner relies on the declaration from Dr. Richard Jude Samulski (EX2027), a pioneer in the field of gene therapy, who has been actively working in this field for over 40 years. *See* EX2043. During his

graduate work in 1982, Dr. Samulski was the first scientist to clone an adeno-associated virus, enabling the entire field of AAV gene therapy that followed. He is the second highest contributing author in the field of AAV, with 151 articles that have been cited over 17,000 times, and is one of the most collaborative authors in the field. *See* EX2042, 5-8. Over the course of his career, he has received over \$82 million in research support, numerous accolades, and he has founded several companies that have gone on to complete hundreds of human clinical trials using AAV gene therapy. *See* EX2027, ¶¶1-18; *see also* EX2028; EX2043. Dr. Samulski presents background on the field of AAV gene therapy and an overview of AAV biology in his declaration. EX2027, ¶¶20-38.

V. CLAIM CONSTRUCTION

Patent Owner does not challenge Petitioner's articulation of the lack of a need for claim construction.

VI. PETITIONER PREDICATES EVERY GROUND ON A POSITA'S MOTIVATION TO IMPROVE TROPISM TO THE LIVER

Each of Petitioner's six grounds begins with an analysis of the '772 Publication, a prior art patent disclosing more than 50 different AAV sequences. Petitioner argues that a POSITA would choose just one of those sequences, AAVrh10, as a starting point, and then would choose only one of the other more than 50 sequences, AAV8, as a comparator, and then make a modification at only a

single position (out of 48 positions) where those two sequences differ to reach the invention. Pet., 26-28, 42-43, 49, 57-58.

The *sole motivation* Petitioner identifies for this set of decisions and modifications, which runs across all six grounds, is to improve targeting of AAVrh10 to the *liver*. Pet., 27 (“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*”), 43 (discussing how “to confer some of the favorable properties of AAV8 on AAVrh.10”), 49 (“A POSA, seeking to improve the transduction of AAVrh.10 *in liver* to approach that of AAV8...”); EX2030, 133:18-134:7, 211:20-214:20, 349:9-359:7. But the Petition fails to address two overarching and critical points. First, Petitioner fails to address whether and how a single amino acid change would be expected to change tissue tropism. All the literature cited by Petitioner, and articles by its own expert, teach that a single amino acid change would *not* alter tropism. Second, as even the Board acknowledged, (I.D., 28), Petitioner failed to address why improving tropism to the liver would be beneficial to the delivery of therapies that have *different* target tissues, such as delivering dystrophin to *muscle* tissue as required by challenged claim 8.

Recognizing this weakness in the arguments in the Petition, Petitioner's expert, Dr. Schaffer, attempted to pivot at his deposition, suggesting that a POSITA would be motivated to increase AAVrh10's tropism to the liver while *preserving* its tropism to muscle and lung. EX2030, 128:3-21, 133:18-134:21, 136:6-139:15, 140:16-147:18, 349:9-359:7. But, as explained further below and in the expert declaration of Dr. Samulski, improving tropism to the liver, modifying a vector to "preserve" its tropism in multiple tissues, and targeting a therapy to muscle are each different goals, and each would have led a POSITA to different solutions. EX2027, ¶70. Critically, none of these solutions would result in the AAV vector claimed in the '274 Patent as the Petition advocates.

The Petition fails to account for these differing goals or the differing paths down which they would lead, and it fails to explain why a POSITA would have been motivated to make the specific series of choices laid out in the Petition to arrive at the claimed invention. This failure infects all six grounds of the Petition, and thus Petitioner cannot meet its burden to show the challenged claims are unpatentable.

A. Petitioner Has Failed to Show Why a POSITA Would Modify AAVrh10 at Only a Single Amino Acid to Improve Liver Tropism

1. The Petition Failed to Establish Why a POSITA Would Have Started with AAVrh10 for Targeting Liver Instead of AAV8

Petitioner does not credibly explain why, if liver targeting was the goal, a POSITA would have started with AAVrh10. The Petition contends that a POSITA would have been motivated to modify AAVrh10 to obtain increased gene transfer in liver tissue. Pet., 27 (“a POSA would have considered substitutions between AAVrh.10 ... and AAV8 ... as a promising strategy for obtaining an artificial variant of AAVrh.10 with even more efficient gene transfer in liver”). For support, Petitioner points to the ’772 Publication’s purported “teaching” “that it was *particularly important to identify serotypes with good* ‘efficiency of gene transfer to liver that until now has been relatively disappointing[.]’” Pet., 27 (quoting EX1007, [0250]). But that is not what the ’772 Publication says. What it says is that gene transfer to liver had been disappointing *until* the discovery of *AAV8*:

Importantly, *AAV2/8 provides a substantial advantage* over the other serotypes in terms of *efficiency of gene transfer to liver that until now has been relatively disappointing* in terms of the numbers of hepatocytes stably transduced. AAV2/8 consistently achieved a *10 to 100-fold improvement in gene transfer efficiency* as compared to the other vectors.

EX1007, [0250] (Petitioner’s quote highlighted).

Thus, while the Petition points to language in the '772 Publication touting the potential advantages of AAVrh10, it ignores that the '772 publication explains that AAV8 “provides a substantial advantage over the other serotypes in terms of efficiency of gene transfer to liver[.]” EX1007, [250]. AAV8’s superiority is shown by the gene transfer data, showing that in 2003, AAV8 surpassed all other vectors in gene transfer to liver tissue, including both known AAVs (Table 6) and the novel AAVs disclosed in the '772 Publication (Table 8):

TABLE 6

Expression of β -unit of Rhesus Monkey Chorionic Gonadotropin (rhCG)		
Vector	Muscle	Liver
AAV2/1	4.5 $\pm$ 2.1	1.6 $\pm$ 1.0
AAV2	0.5 $\pm$ 0.1	0.7 $\pm$ 0.3
AAV2/5	ND*	4.8 $\pm$ 0.8
AAV2/7	14.2 $\pm$ 2.4	8.2 $\pm$ 4.3
AAV2/8	4.0 $\pm$ 0.7	76.0 $\pm$ 22.8

*Not determined in this experiment.

TABLE 8

Vector	Target Tissue		
	Lung	Liver	Muscle
AAV2/1	ND	ND	45 $\pm$ 11
AAV2/5	0.6 $\pm$ 0.2	ND	ND
AAV2/8	ND	84 $\pm$ 30	ND
AAV2/rh.2 (43.1)	14 $\pm$ 7	25 $\pm$ 7.4	35 $\pm$ 14
AAV2/rh.10 (44.2)	23 $\pm$ 6	53 $\pm$ 19	46 $\pm$ 11
AAV2/rh.13 (42.2)	3.5 $\pm$ 2	2 $\pm$ 0.8	3.5 $\pm$ 1.7
AAV2/rh.21 (42.10)	3.1 $\pm$ 2	2 $\pm$ 1.4	4.3 $\pm$ 2

Id., [0244], [0253]; EX2027, ¶¶40-43. Petitioner provides no explanation for why a POSITA wanting to maximize the efficiency of gene transfer in liver

(Petitioner’s stated motivation) would not simply have selected AAV8, the best performing vector in liver, rather than selecting AAVrh10. EX2027, ¶¶40-43.

Indeed, the effect on tissue tropism of modifying AAVrh10 was unknown, whereas AAV8 was already known in 2005 to provide superior gene transfer in liver. *See* EX1007, [0246] (“AAV8 is the ***most efficient vector for liver-directed gene transfer...***”). As Dr. Samulski explains, if a POSITA wanted to maximize gene transfer in the liver, then starting with AAV8, which performed ***over 50% better*** than AAVrh10 in liver, would have been the logical choice. EX2027, ¶42.

Even if a POSITA were motivated to modify AAVrh10—which Petitioner has not shown—by combining it with AAV8, the Petition fails to explain why a POSITA would have modified AAVrh10 in the way the Petition suggests to improve liver tropism, as opposed to one of the many other modification options she could have chosen, as discussed below in Section VII(A). In the small molecule context, the patent challenger bears the burden to identify a motivation to “modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound.” *Eisai Co. v. Dr. Reddy’s Laby’s., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008). The same logic applies here.

2. The Petition Did Not Establish Modifying a Single Amino Acid Could Confer Different Tissue Tropism

Even if the Petition established that modification of AAVrh10 by comparison with AAV8 was a path that a POSITA would have taken—which it has not—Petitioner has not established that modifying a single amino acid would have been expected to alter or improve targeting of AAV to a particular tissue. The Petition contends a POSITA would *not* have “chang[ed] multiple amino acids at once, for fear of damaging or destroying the desirable properties of AAVrh.10.” Pet., 27. Rather, the Petition asserts a POSITA would have “modif[ied] a single amino acid residue at a time.” *Id.* But Petitioner cites nothing *in the* ’772 **Publication** to support that point. *See id.* (citing EX1032, 5-6, Table 1; EX1005, ¶211). That is because the ’772 Publication does not teach or suggest modifying specific amino acid residues in this manner to improve function. EX2027, ¶53.

Instead, to support modifying one residue at a time, Petitioner cites only its expert’s declaration (EX1005) and an article published by Wu et al. in 2000 that describes a study that used individual mutations to “obtain a comprehensive genetic map of the [AAV2] capsid gene.” EX1032, abstract. But the expert declaration “offers only a *verbatim* restatement” of the Petition, is entirely conclusory, and is therefore of little value. *Xerox Corp. v. Bytemark, Inc.*, No. IPR2022-00624, Paper 9 at 15-16 (P.T.A.B. Aug. 24, 2022) (precedential,

emphasis in original) (when testimony “is conclusory and unsupported, [and] adds little to the conclusory assertion for which it is offered to support, [it] is entitled to little weight.”). Moreover, Petitioner has cited no evidence that a single amino acid change would be expected to affect tropism, and indeed, the evidence of record—including Petitioner’s own evidence—shows that a single amino acid change would **not** have been expected to alter tropism. *See* EX2027, ¶¶44-48.

The Wu article, cited by Petitioner, teaches that changing a single amino acid in the AAV2 capsid protein from the native residue to an alanine either has no impact at all, or that it has a negative impact on the ability of the capsid to infect and deliver genetic material. EX1032. Nowhere does it teach or suggest that such a mutation would impact the tissue AAV2 would target. *Id.* Wu and colleagues made a number of mutants to the AAV2 capsid protein, the first 48 of which (*mut1* through *mut48*) mutated one or more residues to alanine, with mutant numbers 29, 31, 45, and 48 changing just a single amino acid. *Id.*, 5. As Wu explained, two of those mutants, 29 and 45, had no impact on infectivity. *Id.* (showing mutants 29 and 45 are Class 1); *id.*, 4 (“Class 1 contained mutants that have an infectious titer similar to the wt titer.”). The other two mutants, 31 and 48, continued to form a capsid, but either were non-infectious or had reduced infectivity. *Id.* (showing *mut31* was class 4c, non-infectious with an “empty particle” and *mut48* was class 2a); *id.*, 4 (“Class 2 contained partially defective mutants with infectious titers 2 to

3 logs lower than the wt titer”); *id.* (“This meant *mut31* formed intact virus particles that were empty.”); *see also* EX2030, 157:10-161:11; EX2027, ¶49. There is no discussion in Wu suggesting that any of these 4 single amino acid mutations could change the ***tissue tropism*** of AAV2, or that a single amino acid mutation had the potential to impact the tissue AAV2 targets at all. EX2027, ¶¶50-51.

While it does not teach or even suggest that a ***single amino acid*** change could alter or confer new or different tropism, Petitioner’s Wu article does contain a section that discusses changing the tropism of AAV2 by inserting ***larger DNA fragments***. EX1032, 9; *see also* EX2030, 167:21-169:1. Wu states that, “[t]o determine whether we could change the tropism of rAAV by inserting a novel receptor ligand into the capsid, we constructed two mutant plasmids that contained a serpin receptor ligand.” EX1032, 9; *see also id.* (results from peptide fragment insertion “suggested...that the tropism of the mutant rAAVs had been changed”); EX2027, ¶52. So too does another article cited by Petitioner’s expert, which suggests placing large DNA fragments of AAV1 into AAV2 in order to confer increased muscle tropism to AAV2. EX1052, 3-5 (describing AAV2 vectors mutated to contain sections of AAV1 of between 40 and over 100 amino acids); EX2027, ¶27. Those articles are consistent with the teaching of the ’772 Publication, which does not discuss ***single*** amino acid changes for improving

functionality. Rather than modifying individual residues, they teach modifying AAV fragments instead, therefore teaching that fragments of AAV sequences can be used and combined with other portions of AAVs to form an “artificial capsid.” EX1007, [0075]; *see also id.*, [0071]-[0073], [0081], [0083]-[0085], [0118], [0141]. The ’772 Publication explains such modifications “may be to increase expression, yield, and/or to improve purification in the selected expression systems, or for another desired purpose (e.g., to change tropism or alter neutralizing antibody epitopes.)” *Id.*, [0091]; EX2027, ¶53. Additionally, it teaches that “fragments may be readily utilized in a variety of vector systems and host cells” and “may be used alone, in combination with other AAV sequences or elements, or in combination with elements from other AAV or non-AAV viral sequences.” EX1007, [0017]. The Petition acknowledges this in the “Overview of the Prior Art” section (Pet., 14-15 (citing EX1007, [0067])) but ignores this teaching in its obviousness analysis.

The publications of Petitioner’s own expert, Dr. Schaffer, confirm that single amino acid changes would not be expected to alter tropism. In October 2007, several years after the priority date of the ’274 Patent, Dr. Schaffer published a review paper discussing strategies for engineering AAV vectors. EX2024. In the section of the paper discussing “strategies to modify AAV tropism,” Dr. Schaffer recommends three strategies:

(i) association with “adaptor” bispecific antibodies, with one arm directed against AAV and the other against a target receptor, (ii) chemical or metabolic conjugation of biotin to the virus, followed by the addition of avidin and a biotinylated-targeting molecule, and (iii) genetic modification of the viral capsid structures through the insertion of defined peptide sequences[.]

EX2024, 520 (internal citations removed); *see also* EX2030, 180:14-22, 184:4-187:13. Nowhere in that 2007 article does Dr. Schaffer discuss, teach, or suggest the feasibility of single amino acid changes to alter or confer tropism. Dr. Schaffer also published a consistent review paper in October 2011, discussing various strategies for avoiding pre-existing immunity to AAV. EX2023. In one section of his review, Dr. Schaffer discusses a study where three amino acids in AAV2 were mutated, at positions 459, 493, and 551. EX1032, 8. While those mutants successfully improved immunity, Dr. Schaffer concluded that the “relatively minor sequence changes” in those mutants “likely *did not change the mutant’s tropism* relative to AAV2.” EX1032, 8; *see also* EX2030, 169:14-170:6, 171:9-179:12.

Thus, Petitioner’s contention that a POSITA would ignore the ’772 Publication’s teaching of creating artificial capsids using AAV fragments in favor of site-specific mutagenesis—a technique described nowhere in the ’772 Publication for affecting tropism—fails to meet Petitioner’s burden. That is particularly true where all the evidence cited in the Petition explains that changing a *fragment* is the method that should be used if changing tropism is the goal, and

that same evidence, along with articles from Petitioner's expert, shows that a single amino acid change would not be expected to alter tropism. Petitioner has cited nothing to support its contention that a POSITA would have expected that changing a single amino acid residue would have had an impact on the tissue an AAV would target.

Finally, Petitioner never addresses that modifying AAVrh10 based on AAV8 to attempt to improve tropism for liver, could *negatively* impact AAVrh10's tropism to other tissues, and could do so *without* improving performance in the liver. EX2027, ¶43.

B. “Maintaining” AAVrh10’s Tropism to Lung and Muscle Does Not Lead to the Invention

As discussed above, the only motivation Petitioner provides in its Petition for modifying AAVrh10 based on AAV8 is to improve the tropism of AAVrh10 to the liver. Pet., 26-28, 43, 49. Petitioner cites no other motivation in its Petition, and Dr. Schaffer could not identify any other motivation in his declaration when questioned at his deposition. EX2030, 142:4-147:3, 349:9-359:7. Petitioner should be held to the sole motivation it identified in its Petition. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1370 (Fed. Cir. 2016) (finding “the Board did not err in refusing the reply brief as improper under 37 C.F.R. §42.23(b) because [Petitioner] relied on an entirely new rationale to explain

why [a POSITA] would have been motivated to combine Tsien or Ju with a modification of Zavgorodny.”).

1. “Targeting Liver” and “Preserving Lung and Muscle Targeting” are Different Motivations That Would Have Led POSITA Down Different Paths

During his deposition, Dr. Schaffer appears to have altered his motivation from merely “targeting liver” to “improving tropism to the liver while preserving tropism to muscle and lung.” EX2030, 128:3-21, 133:18-134:21, 136:6-139:15, 140:16-147:18, 349:9-359:7. But this motivation is nowhere in the Petition or Dr. Schaffer’s declaration. Dr. Schaffer admitted as much by his attempts to back-fill this glaring omission at every turn. *Id.*; *see also id.*, 349:9-359:7. Therefore, Petitioner should be precluded from relying on this different motivation now. *Intelligent Bio-Sys.*, 821 F.3d at 1370.

But even if the Board considers this new motivation, improving liver tropism is a different goal, and would lead down a different path, from maintaining tropism to the muscle and lung. As Dr. Samulski explains, a POSITA seeking to improve tropism to one particular tissue would aim to reduce or minimize tropism to off-target tissues. EX2027, ¶¶31-33, 54. Off-target delivery results in a gene therapy that requires higher dosages to deliver an effective amount to the tissue of interest. EX2027, ¶¶35, 54; EX2037, 3-4. Delivering higher dosages is not trivial, and can result in both cost-prohibitive increases to manufacturing expenses as well

as significant increased risk of serious side effects, including death. EX2027, ¶¶34-36, 54; EX2036, 1-2; EX2037; EX2038; EX2039. Both of these drawbacks would have led a POSITA to carefully select a vector that maximized delivery to the target tissue of interest with minimal off-target delivery. EX2027, ¶¶34-36, 54.

To date, neither Petitioner nor Dr. Schaffer have identified any gene of interest that a POSITA would have desired to specifically target to the liver, muscle, and lung simultaneously (and to the exclusion of other tissues). EX2027, ¶¶55-56. To the extent they do so in Reply, that argument should have been made in the Petition and is therefore waived. *Colas Sols., Inc. v. Blacklidge Emulsions, Inc.*, 759 F. App'x 986, 989 (Fed. Cir. 2019) (“the Board did not abuse its discretion by finding Colas’s overlapping ranges theory waived. It is of ‘the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify ‘with particularity’ the ‘evidence that supports the grounds for the challenge to each claim.’”) (quoting *Intelligent Bio-Sys.*, 821 F.3d at 1369, and 35 U.S.C. §312(a)(3)) (non-precedential); Fed. R. App. P. 32.1(a). Additionally, such a gene of interest is unlikely because, as Dr. Samulski explains, the liver is the “default destination” for gene therapies. EX2027, ¶¶35-36, 55. And therefore a POSITA desiring to target *any* non-liver tissue would have been motivated in 2005 to *avoid* targeting the liver, because, as

Dr. Schaffer's previous work shows, the liver represents a "barrier" for targeting non-liver tissues. EX1030, 3.

In a comment paper, Dr. Schaffer explains that one challenge for gene delivery is that "upon systemic administration, natural serotypes typically exhibit tropism for liver, or alternatively for multiple organs, **which renders targeted delivery to other tissues difficult.**" EX2025, 1. Similarly, in a *Nature Reviews, Genetics* paper that Dr. Schaffer wrote and relied upon in his declaration (see EX1005, ¶¶61, 67-74), in a section titled "[c]hallenges of adeno-associated virus gene delivery and efficacy," he writes that "[f]or systemically administered viruses, the **liver is often the default destination**, which can represent a **barrier** when other organs are the intended targets." EX1030, 3. Dr. Schaffer's new position that a POSITA desiring to improve tropism to the liver would want to nevertheless "preserve" tropism to muscle and lung is litigation-inspired, contradicted by his previous work, and more importantly, is at odds with what a POSITA would actually have been motivated to do in 2005. A POSITA in 2005 would **either** have wanted to improve tropism to liver **or** preserve tropism to muscle and lung, not both. EX2027, ¶¶55-57.

2. Dr. Leone's Enablement Opinions Support the Vast Number of Modifications Available to a POSITA if Her Goal Was "Preserving" Tropism

If a POSITA's goal was to preserve AAVrh10's tropism to muscle and lung, a POSITA had two options. Either the POSITA would not have sought *any* modifications to AAVrh10, ensuring no change in tropism, or the POSITA would have had a huge potential number of changes available—i.e., all of the possible amino acid changes in non-conserved regions in known AAVs, as shown by Figure 2 in the '772 Publication. EX2027, ¶¶57-59.

Petitioner's obviousness arguments rely in part on a declaration from Dr. Paola Leone, an expert who submitted a report on behalf of Patent Owner in litigation on U.S. Patent No. 10,526,617 (EX1014), a patent that claims priority to the application published as the '772 Publication. *See* Pet., 34. The opinions Petitioner relies upon relate to Dr. Leone's written description and enablement analysis, and Petitioner misapplies those opinions to attempt to support its obviousness analysis. Properly read, Dr. Leone's opinions support the *non-obviousness* of the invention claimed in the '274 Patent.

Dr. Leone's litigation report related to enablement, addressing the *scope* of the disclosure of the '617 patent's specification. EX1012, ¶1. Obviousness and enablement are separate issues. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015). In an *enablement* analysis, the focus is on identifying whether a

patent's disclosure supports the scope of its claims. That is what Dr. Leone did: she determined that, from the disclosures of the specification of that patent, a POSITA could readily identify "conserved" and "non-conserved" regions of capsid protein sequences, and, using Figure 2, identify which amino acid positions could be changed and in what ways and still have a reasonable likelihood that a capsid would form. Pet., 29-30; EX1012, ¶¶310-11. Dr. Leone gave no testimony on how any modifications might impact *tissue tropism*, because the claims at issue in that matter did not require targeting a particular tissue.

A POSITA's understanding of the scope of the disclosure of a specification, however, does not mean that every sequence falling within that scope would be obvious. *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 705 (Fed. Cir. 2012) ("[T]he prior art's teaching of a broad genus does not necessarily disclose every species within that genus."); *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006); *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994). The obviousness analysis is about whether a POSITA *would* have made those changes. *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) ("[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention." (emphasis in original)). The math bears out that such a specific change was not likely.

A POSITA considering the disclosure of the '772 Publication and desiring to preserve AAVrh10's tropism to muscle and lung would have understood that there are an overwhelming number of possible combinations of modifications that could be made to AAVrh10 without diminishing muscle and lung tropism. Based on Dr. Leone's analysis of Figure 2, that Petitioner and Petitioner's expert adopt (*see* Pet., 28-34; EX2030, 192:4-197:18), of the 738 amino acids in the AAVrh10 vp1 sequence, 353 are conserved and 385 are variable. EX2027, ¶58. Based on the other sequences shown in Figure 2, each of the 385 variable amino acids could be changed to each of the other alternative amino acids (~1-6 possibilities) Figure 2 disclosed at that position. The total number of possible substitutions at those positions is **764**; in other words, according to Figure 2, each of those 385 variable positions can be changed to between 1 and 6 amino acids, for a total of 764 amino acids that can potentially be used in those 385 positions. That works out to an average of about two for each variable amino acid position. If a POSITA were to change just one amino acid from the variable regions of AAVrh10, they would be left with 384 other amino acids that could also be modified. A POSITA could also modify two amino acids, leaving 383 additional variable region amino acids, any one of which could also have been further modified.

The sum total potential modifications that could be derived from the '772 Publication's Figure 2 that would have been expected to not affect AAVrh10's

tissue tropism is enormous. EX2027, ¶58. It can, however, be calculated: there are 385 total variable amino acids. The number of possible combinations is thus a function of (1) whether a POSITA modifies a given site of the 385 modifiable sites; (2) how many sites of the 385 sites that the POSITA chooses to modify; and (3) how many substitutions are available at each site based on the teachings of Figure 2 (here, represented by the number 1.984 as it is the average of substitutions at each site).² The number of combinations increases exponentially, even for a small handful of combinations, as shown below:

Number of Modified Sites	Possible Combinations (Rounded to nearest whole number)
1	764
2	291,732
3	7.399*10 ⁷
4	1.4038*10 ¹⁰
5	2.125*10 ¹²

The total number of possible combinations of the 385 modifiable sites disclosed within the '772 Publication is **6.274*10¹⁸²**. While a POSITA would have

² This is represented by the generic formula, where n is the number of modified sites out of a possible x (up to 385) sites to modify:

$$\sum_{n=1}^x \left\{ \frac{x!}{(n! * (x - n)!)} * 1.984^n \right\}$$

understood the scope of the '772 Publication's disclosure, it would have been mathematically improbable for a POSITA seeking to "preserve" AAVrh10's tropism to muscle and lung, to the extent she would have modified AAVrh10 at all, to have selected the single S665N modification that yields the claimed invention.

Even if a POSITA applied Petitioner's expert's unsupported opinion that a POSITA would have been motivated to further select AAV8 in an attempt to improve tropism to liver while preserving tropism to lung and muscle, as an attempt to cabin the scope of amino acids that she would consider changing, a POSITA would recognize that there are 48 amino acid differences between AAVrh10 and AAV8. Applying the mathematical analysis from above yields a total of 3.86×10^{14} *combinations* informed by the combination of AAVrh10 and AAV8. A POSITA would not have arrived at the claimed asparagine at position 665 as required by the claims of the '274 Patent.

C. Petitioner Fails to Discuss Targeting Therapies to Muscle

Petitioner's Grounds 4-6 are directed to dependent claim 8. Claim 8 narrows independent claim 1 by requiring that the gene delivered by the AAV vector is a dystrophin gene product, specifically a mini-dystrophin or micro-dystrophin. EX1001, cl. 8. Dystrophin is a protein predominantly found in muscle tissue, including skeletal muscle, cardiac muscle, and smooth muscle. EX2027, ¶¶60-61; EX1010, 1-6; EX2040, 4-5; EX2041, 1. Petitioner's prior art clearly identifies

dystrophin as a therapy that should be targeted to the muscle.³ Fabb, Petitioner's secondary ground reference, makes abundantly clear that dystrophin (and by association micro-dystrophin) are targeted to **muscle** tissue. *See* EX1010, 3 ("Expression of micro-dystrophin Δ 3788 in the skeletal muscle of nude/mdx mice transduced with rAAV"); *id.*, 4 (discussing analysis of muscle sections); *id.*, 5 ("In order to utilize an AAV vector system to provide gene transfer based on complementation of dystrophin deficiency in muscle tissues in vivo, we have reduced the cDNA sequence of this gene down from 14 to ~3.8 kb to produce a microdystrophin cDNA."); *see also* EX2027, ¶¶60-61. Indeed, it is well understood in gene therapy that **dystrophin** is a desirable protein to deliver to muscles of patients suffering from muscular **dystrophy**, including Duchenne muscular dystrophy, the disease that Petitioner's infringing product treats.

Yet the Petition is wholly silent on delivery to muscle. Dr. Schaffer admitted at deposition that his declaration does not discuss targeting to muscle in Ground 1. EX2030, 349:9-359:7. Nor does he address such targeting in other Grounds. Critically, Grounds 4-6 only address the creation of a micro-dystrophin

³ Dr. Schaffer's feigned ignorance of where in the body dystrophin should be targeted in gene therapy further serves to discredit his testimony. The references he cited state that dystrophin is found in, and targeted to, muscle.

or mini-dystrophin gene product, that Petitioner contends is disclosed in Fabb. Nothing in Grounds 4-6 addresses targeting or delivering the micro-dystrophin gene product to its desired location in the body—*muscle*. See Pet., 53-59; EX1005, ¶¶112-118. Instead, these Grounds implicitly rely on the modifications proposed in Grounds 1-3, which, as discussed above, were made solely for the purposes of targeting liver.

As Dr. Samulski explains, a POSITA desiring to target muscle would have applied a different approach. Assuming, as Petitioner does, that a POSITA would have used the '772 Publication as a starting point, a POSITA would first have identified the capsids that are the best muscle transducers. EX2027, ¶¶62-63. Specifically, she would have first identified AAV1, which the '772 Publication describes as “the most efficient in skeletal muscle of the previously described serotypes.” EX1007, [0243]; EX2027, ¶63; *see also* EX1052, 1 (“In particular, AAV1 is a much more efficient vector for gene delivery to muscle than is AAV2.”). But then a POSITA would have looked to the data in Table 6 and Table 8, just as Petitioner contends a POSITA would have done for identifying vectors of interest for improving tropism to liver. From Table 6, a POSITA would have learned that the performance of the novel AAV7 was *nearly triple* that of AAV1 in muscle:

TABLE 6

Expression of β -unit of Rhesus Monkey Chorionic Gonadotropin (rhCG)		
Vector	Muscle	Liver
AAV2/1	4.5 $\pm$ 2.1	1.6 $\pm$ 1.0
AAV2	0.5 $\pm$ 0.1	0.7 $\pm$ 0.3
AAV2/5	ND*	4.8 $\pm$ 0.8
AAV2/7	14.2 $\pm$ 2.4	8.2 $\pm$ 4.3
AAV2/8	4.0 $\pm$ 0.7	76.0 $\pm$ 22.8

*Not determined in this experiment.

EX1007, [0244] (Table 6); EX2027, ¶63. By contrast, from Table 8, a POSITA would have learned that the performance of the novel AAVrh10 was “close to that of...the [prior] best muscle transducer AAV1”:

TABLE 8

Vector	Target Tissue		
	Lung	Liver	Muscle
AAV2/1	ND	ND	45 $\pm$ 11
AAV2/5	0.6 $\pm$ 0.2	ND	ND
AAV2/8	ND	84 $\pm$ 30	ND
AAV2/rh.2 (43.1)	14 $\pm$ 7	25 $\pm$ 7.4	35 $\pm$ 14
AAV2/rh.10 (44.2)	23 $\pm$ 6	53 $\pm$ 19	46 $\pm$ 11
AAV2/rh.13 (42.2)	3.5 $\pm$ 2	2 $\pm$ 0.8	3.5 $\pm$ 1.7
AAV2/rh.21 (42.10)	3.1 $\pm$ 2	2 $\pm$ 1.4	4.3 $\pm$ 2

EX1007, [0253] (Table 8), [0257]; EX2027, ¶64. Thus, a POSITA seeking to maximize targeting to muscle would have selected the vector with the strongest expression in muscle tissue: AAV7. See EX1007, [0142] (“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*.”); *id.*, [0251] (“The lack of pre-existing immunity to AAV7 and the *favorable tropism of the vectors for muscle* indicates that AAV7 is

suitable for use as a vector in human gene therapy and other in vivo applications.”); EX2027, ¶65.

Even if a POSITA seeking to improve tropism to muscle would have started with AAVrh10—which Petitioner has not even attempted to show—based on Petitioner’s logic, she would have sought to make changes based on AAV7, as the vector showing the best tropism to muscle, not AAV8, which has weak tropism to muscle. EX1007, [0244] (Table 6); EX2027, ¶¶66-68. To do so, a POSITA would have aligned the sequences for AAVrh10 and AAV7, and found that the two vectors are 88.6% identical, with 655 amino acids the same and 84 amino acids that differ. EX2027, ¶68. A POSITA would have looked at the 84 amino acids that differ, and made modifications to AAVrh10 based on those amino acids to target muscle. Even if she were motivated to alter position 665, notably, at position 665, where AAVrh10 has a serine, AAV7 has a threonine. Thus, this pathway does not get a POSITA to the vector claimed in the ’274 Patent.

Finally, a POSITA seeking to target muscle would have looked to articles available at the time that had the same goal, such as EX1052, an article by Hauck and Xiao (“Hauck”) cited by Petitioner’s expert. Not only do the authors in Hauck substitute large fragments of AAV2 with fragments of AAV1 in order to attempt to confer muscle tropism to AAV2 as discussed above, the authors also concluded that one particular section of AAV1 appears to be largely responsible for muscle

targeting. EX1052, 3-5. In particular, based on several substitutions of several different fragments of AAV1 into an AAV2 vector, the authors concluded that “amino acids 350 to 423 corresponding to AAV1 VP1 contribute significantly to the high performance of AAV1 vectors in the transduction of muscle.” EX1052, 4-5. And the longer fragment 213 to 423 was required to confer tropism for muscle. *Id.*, 4. A POSITA seeking to improve muscle tropism would have thus looked to the teaching of Hauck, and would not have sought to make changes at position 665 (where AAV1, like AAVrh10, had a serine).

VII. THE CHALLENGED CLAIMS OF THE '274 PATENT ARE PATENTABLE

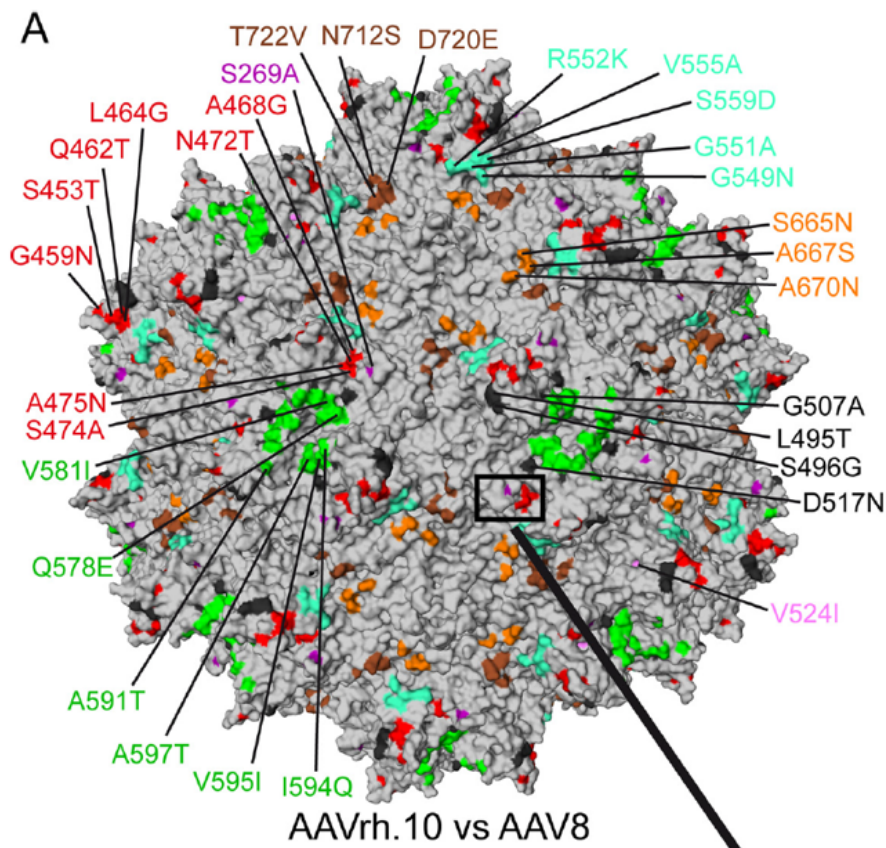
A. Claims 1-3 and 6 Are Patentable Over Ground 1 ('772 Publication)

It is undisputed that the '772 Publication does not disclose any AAV capsid with a sequence that is 95% identical to AAVrh46 with an asparagine (N) located at position 665, as required by the claims of the '274 Patent. *See* Pet., 25-28. To reach the claims, Petitioner plucks AAVrh10 out of the '772 Publication and argues that a POSITA would have made a single amino acid substitution at position 665 of AAVrh10 based on AAV8 in an effort to obtain “even more efficient gene transfer in liver.” *Id.*, 27-28. But as the Board correctly recognized, the Petition “does not appear to offer sufficient evidence and reasoning as to why a POSA would have modified AAVrh.10 at position 665 as described as opposed to

other modifications based solely on the disclosure of the '772 Publication.” D.I.,
26.

Indeed, of the many flaws in Ground 1, the flaw pointed out by the Board is the most egregious; the Petition fails to identify any rationale in the '772 Publication for why a POSITA “seeking to improve the transduction of AAVrh.10 in liver to approach that of AAV8,” (Pet., 49), would have chosen to modify the amino acid at position 665, as opposed to any of the other 47 positions where AAVrh10 and AAV8 have different amino acids. This oversight alone condemns Ground 1. Additionally, the Petition fails to explain why a POSITA would have expected changing a single amino acid to have any effect on tropism to liver. As explained by Dr. Samulski and discussed above in Section VI(A), a POSITA in 2005 would have had no such expectation, because at that time, no one had shown or even suggested that a single amino acid change could confer different tissue tropism. EX2027, ¶¶28, 32, 42, 44, 48-49.

Put simply, Petitioner fails to explain why a POSITA would have been motivated to specifically modify amino acid residue 665 to improve liver tropism. Petitioner admits there are 48 positions where the residues of AAV8 and AAVrh10 differ. Pet., 28 (citing EX1019, 1); *see also* EX2030, 149:12-14. A visual representation of a subset of the positions where AAV8 and AAVrh10 differ is shown below, from a paper published in 2020:



EX2019, 11.

Of the other 47 positions, the Petition *fails to address a single one*. Pet., 28; EX1005, ¶213. Neither Petitioner nor Petitioner’s expert attempts to explain why a POSITA would modify residue 665, as opposed to one of the other 47, to improve tropism to liver. Additionally, as Dr. Samulski explains, that method is inconsistent with what a POSITA would have done in 2005. Instead, a POSITA would have used alanine scanning to change each residue to an alanine and test each mutant to determine which residues were important to tropism, a technique Dr. Samulski refers to as “wreck and check.” EX2027, ¶¶46, 49. Critically, he

explains that a POSITA would have had *no way of predicting* which of the 48 residues would affect tissue tropism; a POSITA would have had to make each mutation and then check it. EX2027, ¶¶47-48. And that's only if a POSITA only compares AAVrh10 to AAV8. If AAVrh10 is modified based on any of the other preferred capsids of the '772 Publication—or if any other preferred capsid is selected to modify instead of AAVrh10—the number of potential residues that could be modified increases exponentially.

Additionally, as described above, Petitioner has cited no evidence that a single amino acid change would be expected to alter tissue tropism. In contrast, all the literature that Petitioner cites shows that a POSITA would instead have been motivated to modify multiple amino acids at once or insert a fragment if altering tissue tropism was the goal. For example, both Petitioner's Wu reference and the '772 Publication describe using fragments to change or improve tropism. EX1032, 9 (results from peptide fragment insertion “suggested...that the tropism of the mutant rAAVs had been changed” from kidney to lung epithelium); EX1007, [0091] (describing how using fragments of AAV sequences “may be to increase expression, yield, and/or to improve purification in the selected expression systems, or for another desired purpose (e.g., to change tropism or alter neutralizing antibody epitopes.)”); EX2027, ¶¶52-53, 58. Petitioner ignores these teachings.

Modifying even *a single additional* amino acid (a total of two) from the sequence of AAVrh10 to match AAV8 increases the number of potential combinations dramatically to **1,128**.⁴ For each additional amino acid that is modified, the number of possibilities increases exponentially; for example, modifying three sites yields a possible **17,296** combinations, and modifying four sites yields a possible **194,580**. And that is if only substitutions are considered; if a POSITA considers other possible mutations, such as additions, deletions, or the insertion of a fragment as recommended by the Wu article and Petitioner's expert, these numbers dramatically increase. Petitioner does not address these possibilities, as they eviscerate Petitioner's obviousness case.

Indeed, nothing in the '772 Publication teaches a POSITA to start with the sequence of AAVrh10, focus solely on position 665 to the exclusion of all other modifiable positions, and then modify the amino acid residue at that position based upon the corresponding residue found in AAV8. Petitioner has not met its burden as to Ground 1.

⁴ The formula to calculate the number of possible combinations is as follows, where "n" is the number of modified sites:

$$Combinations = \frac{48!}{(n! * (48 - n)!)}$$

B. Claims 1-3 and 6 are Patentable Over Ground 2 ('772 Publication + Xie)

Petitioner does not contend—nor could it—that either the '772 Publication or Xie discloses any AAV capsid with a sequence that is 95% identical to AAVrh46 with an asparagine (N) located at position 665, as required by the claims. *See* Pet., 42-43. Instead, Petitioner contends that a POSITA would start with the 48 “artificial variants” of AAVrh10 allegedly identified in the '772 Publication and narrow those variants to 18 based on Xie in order to “confer some of the favorable properties of AAV8 on AAVrh.10,” i.e., improved targeting to liver. *Id.*

Setting aside that the number of mutations possible by modifying AAVrh10 based on AAV8 is exponential (3.86×10^{14} total potential combinations), Petitioner does not explain why a POSITA, if she started with AAVrh10 at all, would have been motivated to modify AAVrh10 by looking to **both** AAV8 **and** AAV2, the focus of Xie. Petitioner also mischaracterizes Xie’s disclosures regarding which residues appear on the surface to reach the position 665 in the '274 Patent’s claims. Fatally, the Petition also fails to explain why a POSITA would have been specifically motivated to modify position 665 to an **asparagine** (N) based on Xie, when Xie discloses that AAV2, like AAVrh10, has a **serine** (S) at position 665. The combination of the '772 Publication and Xie does not render claims 1 and 3-6

of the '274 Patent obvious.

1. Ground 2 Introduces Yet Another AAV Into the Combination Without Sufficient Motivation

Petitioner's only motivation for combining Xie with the '772 Publication is reliance on a statement made by Patent Owner's expert in a separate litigation, Dr. Michael Metzker, that a POSITA "would have consulted known crystal structures of related sequences to guide where to introduce mutations to a sequence." Pet., 43-44 (citing EX1013, ¶306). As with Petitioner's reliance on Dr. Leone's statements in Ground 1, this argument again conflates the legal inquiries underlying *enablement* versus *obviousness*. Dr. Metzker did not opine that, based on the '772 Publication, a POSITA *would* have actually performed any specific mutations. Instead, his opinion was tethered to whether a POSITA would have understood such a structure to inform the scope of the claims of the issued '617 Patent, which differ materially from the claims of the '274 Patent. Understanding the scope of an invention is not the same thing as rendering each potential embodiment obvious. *Belden*, 805 F.3d at 1073. Petitioner has made no showing that a POSITA would have been motivated to modify AAVrh10 based on either the '772 Publication or Xie, which is silent as to AAVrh10.

2. Xie Provides No Motivation to Modify Position 665

Even if a POSITA would have been motivated to consult Xie for the

structure of AAV2, the Petition erroneously concludes that a POSITA would have been motivated to modify position 665 from serine (S) to asparagine (N) based upon its teachings. But Xie provides no such motivation.

As Petitioner's EX1023 notes, the serine at position 665 (SER665) in AAVrh10 corresponds to the exact same amino acid, serine, at that *same position* in AAV2 (SER525 using Xie's numbering). EX1023; EX2030, 275:21-277:8. That identity would *dissuade* a POSITA from changing that amino acid, particularly where there are many other possible residues to modify. Xie therefore provides no basis for Petitioner's conclusion that a POSITA "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." Pet., 45; EX1005, ¶262.

Petitioner's argument here suffers from the same deficiencies that the Board recently identified in *Kelonia Therapeutics, Inc. v. Interius Biotherapeutics, Inc.*, PGR2024-00008, Paper No. 11 (PTAB May 17, 2024). In *Kelonia*, the challenged patent claimed proteins with site-specific mutations. *Id.* at 7. *Kelonia*, like Petitioner here, argued that a POSITA would have been motivated to make a mutation at a specific site by recognizing the possibility of mutations from a base prior art reference and by consulting crystal structures to determine that the mutation purported to be "nearby aspartic acid residues...that may be negatively

charged.” *Id.* at 28. The Board squarely rejected Kelonia’s argument. Noting that the prior art disclosed certain mutations, the Board nonetheless found that “a POSA would have no direction for selecting the route to create the...mutations specified by the challenged claims among the various unpredictable alternatives suggested.” *Id.* at 35. This was true even though the crystal structures provided some data, because that data “does not itself contain any teaching or suggestion directing a POSA to create the [mutation] specified by the challenged claims.” *Id.* at 36. Petitioner here, as in *Kelonia*, “comes to the claimed...mutations by retracing the path of the inventor with hindsight accuracy supported only by the bare testimony of [its expert].” *Id.* at 38. This flawed approach cannot support an obviousness finding.

3. The Petition Mischaracterizes Xie’s Disclosures Regarding Surface Residues

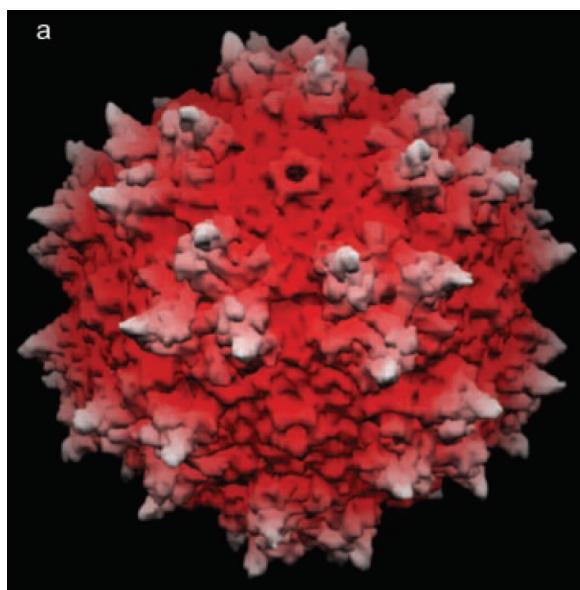
The Petition states that “Xie teaches that the *amino acids* that lie on the surface of the capsid ‘govern interactions with antibodies and cellular receptors.’” Pet., 44 (citing EX1008, 3); *see also* EX1005, ¶256. But that is not what Xie says. Instead, Xie explains that “[t]hese loops constitute the surface features of the virus that govern interactions with antibodies and cellular receptors,” referring to the “long interstrand loops of AAV ... contain[ing] β -ribbons and other additional elements of secondary structure.” EX1008, 2-3. In other words, Xie teaches that

the *secondary structure*, i.e. the three-dimensional folding of the protein, governs AAV2's interactions with antibodies and cellular receptors. Petitioner's expert admitted this at his deposition. EX2030, 280:11-281:3 ("Those loops are very important determinants of the interactions with antibodies and cellular receptors"). Thus, Xie does not stand for the proposition that *individual amino acids* "govern characteristics of AAV such as tropism, transduction efficiency, and immunogenicity," as the Petition suggests. Pet., 44. Indeed, as discussed at length above, a POSITA in 2005 would not have expected a single amino acid to control or even affect tropism. See Sections VI(A), VII(A), *supra*.

Even if Petitioner is correct to assume that amino acids at the surface are desirable targets, the Petition does not explain how it arrives at the eighteen amino acids "that differ between AAVrh.10 and AAV8 [that] lie on the surface of the capsid." Pet., 44. Petitioner's expert alleges that "[t]he red triangle underneath this serine (S) indicates that it is on the surface of the capsid." EX1005, ¶261. But Figure 2's caption explains that the triangles are "shaded according to each residue's accessibility," where red indicates the *least amount of accessibility* at the surface, compared to the cyan, green, or blue triangles. EX1008, 3 ("20 Å² < red < 50 Å² < cyan < 80 Å² < green < 100 Å² < blue"). Petitioner's expert agreed with this interpretation at his deposition. EX2030, 284:5-285:8. Applying this color mapping to the eighteen "surface" residues that the Petitioner contends differ

between AAVrh10 and AAV8, (*see* EX1023), Figure 2 shows that twelve of these residues are either cyan, green, or blue, indicating that the serine at 665 is *less accessible* than at least twelve other residues. EX2016, 1; EX2030, 285:9-287:4.

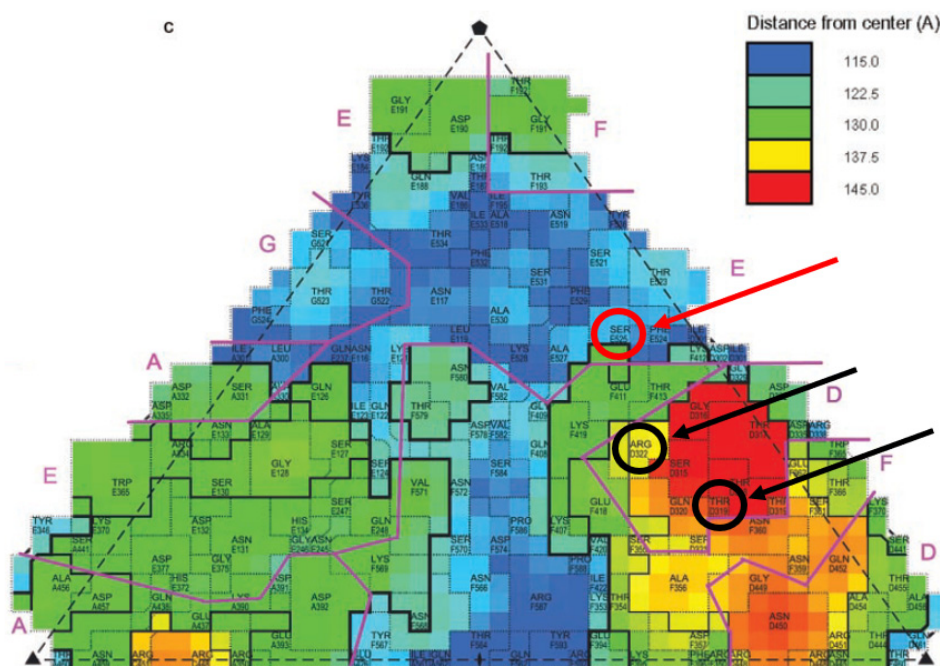
Xie further shows that the other identified “surface” residues are more accessible than serine 665. Figure 3 shows that AAV2’s surface has a series of protruding peaks from the center:



EX1008, 4.

Xie’s Figure 4, below, shows the location of amino acids by their distance from the center of AAV2. *Id.* (Fig. 4). Blue amino acids are “closest to the virus center” and red are farthest, located in the protruding peaks. *Id.*; EX2030, 287:6-13. The amino acid in Xie that corresponds to AAVrh10’s position 665 is serine 525 (SER525). *See* EX1023. SER525 is shown as blue in Figure 4, meaning that

it is *closest* to the virus center—i.e., not wholly on the surface. EX1008, 4 (Fig. 4) (red arrow):



See also EX2030, 287:14-21. In contrast, other surface-level amino acids that EX1023 identifies—including, for example, THR319 and ARG322—are yellow and orange (black arrows above), meaning they are *farther* from the virus center and *closer* to the surface, i.e. at the peaks. EX1008, 4 (Fig. 4). Indeed, *fourteen* of the eighteen residues are either green, yellow, orange, or red, indicating they are closer to the surface than the serine at 665:

Label	AAVrh10	AAV2 corresponding position	Xie numbering (-137)	Fig. 4 Color ²
1	GLY 459	THR 456	THR (T) 319	Red
2	GLN 462	ARG 459	ARG (R) 322	Yellow
3	ASN 472	ASP 469	ASP (D) 332	Green
4	SER 474	ARG 471	ARG (R) 334	Green
5	LEU 495	SER 492	SER (S) 355	Yellow
6	SER 496	ALA 493	ALA (A) 356	Orange
7	GLY 551	GLU 548	GLU (E) 411	Green
8	LYS 552	LYS 549	LYS (K) 412	Green
9	SER 559	LYS 556	LYS (K) 419	Green
10	ALA 591	ARG 588	ARG (R) 451	Yellow
11	VAL 595	THR 592	THR (T) 455	Green
12	ALA 597	ASP 594	ASP (D) 457	Green
13	SER 665	SER 662	SER (S) 525	Blue
14	ALA 667	ALA 664	ALA (A) 527	Blue
15	ALA 670	ALA 667	ALA (A) 530	Blue
16	ASN 712	ASN 709	ASN (N) 572	Green
17	ASP 720	ASN 717	ASN (N) 580	Green
18	THR 722	VAL 719	VAL (V) 582	Blue

EX2016, 2.

Additionally, Petitioner ignores the fact that Xie discloses specific mutations at several residues of interest on the surface that coincide with residues that Petitioner identified as being different between AAVrh10 and AAV8. Xie describes mutants identified in the Wu article discussed above (EX1032), including an alanine substitution at residues 448-451 and a hemagglutinin epitope insertion at 454. EX1008, 5; EX2030, 288:22-291:1. As Petitioner's expert admitted at his deposition, both residue 451 and residue 454 are on the surface of AAV2 and are

residues that are different between AAVrh10 and AAV8. EX1023, 2; EX2030, 290:13-291:1.

The Petition does not explain why a POSITA would ignore the other fourteen known surface-level amino acid possibilities (and particularly the two identified in Xie by Wu) in favor of position 665. With each of the fourteen possibilities being on the surface of the capsid, according to the logic in the Petition, they would be areas of focus for a POSITA. *See* Pet., 44-45. The Petition fails to explain why a POSITA would cast aside amino acids that are located closer to the capsid surface in favor of one buried deeper within the capsid's structure. And then having chosen that single amino acid residue based on Xie, the Petition does not contend with why a POSITA would further modify it when Xie's AAV2, like AAVrh10, has a serine there. Petitioner has not met its burden as to Ground 2.

C. Claims 1-3 and 6 are Patentable Over Ground 3 ('772 Publication + Snowdy)

As with previous grounds, Petitioner does not assert that either the '772 Publication or Snowdy discloses any AAV capsid with a sequence that is 95% identical to AAVrh46 with an asparagine (N) located at position 665, as required by the claims of the '274 Patent. *See* Pet., 47-49. Instead, Petitioner asserts that a POSITA reading the '772 Publication would have sought to improve the expression of AAVrh10 in liver by changing phosphorylatable amino acids near

putative nuclear localization signals in AAVrh10 to non-phosphorylatable amino acids, based on the sequence of AAV8 “to improve the transduction of AAVrh.10 in liver to approach that of AAV8[.]” Pet., 49. Petitioner further states that a POSITA would make this assessment on the basis of Snowdy’s disclosures relating to AAV2. Finally, Petitioner once again suggests a POSITA would focus on the serine at position 665 in AAVrh10, to the exclusion of all other results from this analysis. Pet., 47-49.

At the outset, Petitioner’s initial premise is flawed, as it assumes, without basis, that nuclear localization signals have any relationship to tissue tropism. As Patent Owners’ expert (and Snowdy’s thesis advisor), Dr. Samulski, explains, they do not. EX2027, ¶¶71-74. The portions of Snowdy that Petitioner relies upon—a mere seven pages out of a 132-page dissertation—do not teach or suggest that the modification of one amino acid can affect tissue tropism, let alone that the modification of a serine to an asparagine improves tropism to liver—Petitioner’s sole motivation for combining Snowdy with the ’772 Publication. Snowdy is completely silent on tissue tropism. Instead, Snowdy is focused on increasing *infectivity*, a different step distinct from tissue tropism. *Id.*

Moreover, Petitioner’s entire reliance on Snowdy to teach a serine to asparagine substitution fails. Snowdy (1) used alanine and aspartic acid substitutions to mimic phosphorylation states, not asparagine, (2) cites a reference

that demonstrated that asparagine substitutions can *negatively* affect functionality, and (3) disclosed how nascent AAV research was in 2005. Additionally, the work that Snowdy relied upon showed how mutating a serine can have conflicting (and unpredictable) results.

1. Petitioner Improperly Conflates Infectivity with Tissue Tropism

Dr. Samulski explains that Snowdy's study in Chapter IV of the dissertation, completed under Dr. Samulski's supervision, had a purpose entirely unrelated to improving or changing tissue tropism. EX2027, ¶¶71-74. Rather, Snowdy's work investigated nuclear localization signals, meaning the signals that control the ability of an AAV vector to be transported into the nucleus once inside a cell. *Id.* Critically, that step only happens *after* the AAV vector has reached the target tissue and been taken up by the target cell. The difference in these steps is shown in the below graphic:

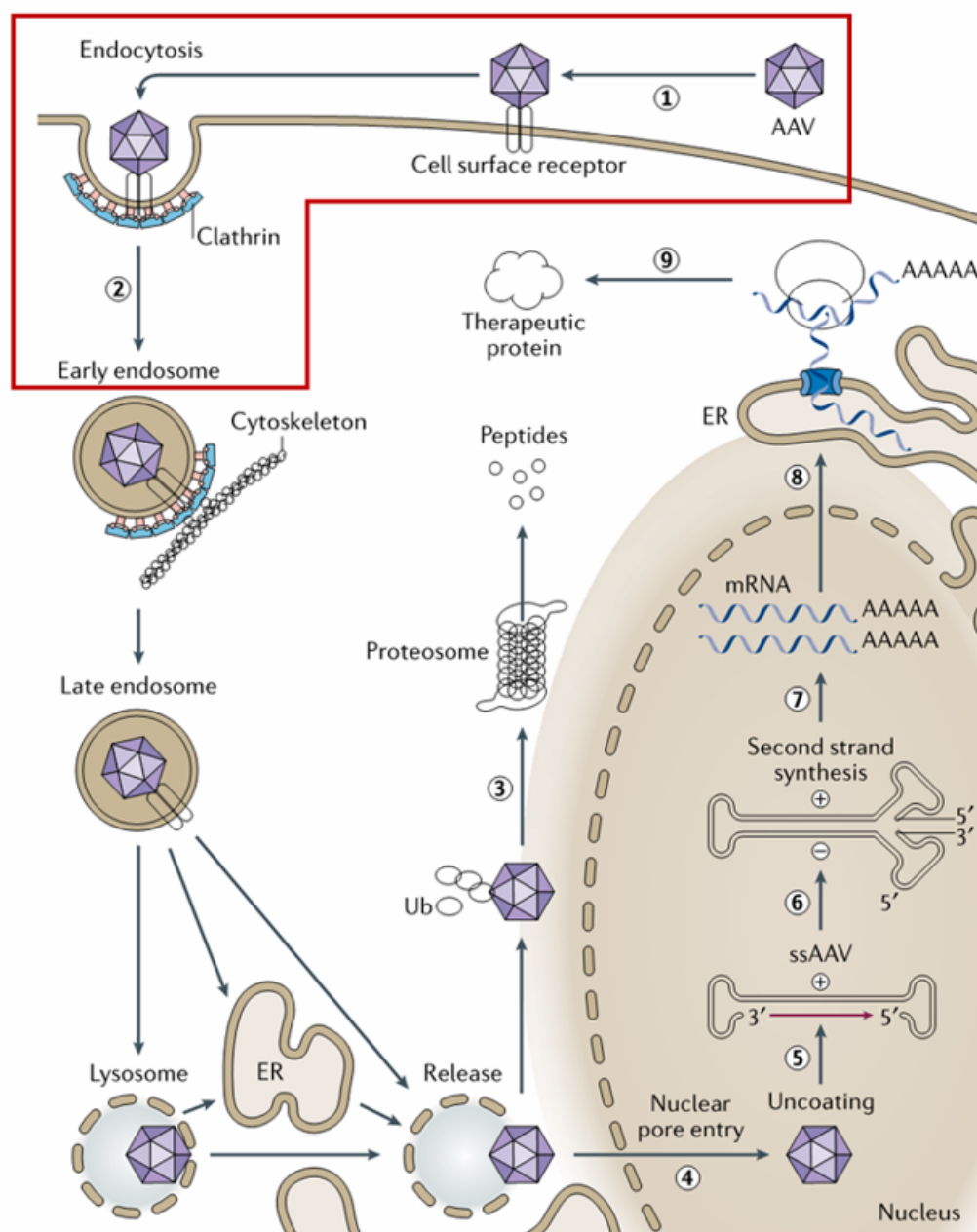


Fig. 1 | AAV vector transduction pathway. Adeno-associated virus (AAV) vector virions bind to receptors and co-receptors on the surface of target cells (step 1) and are taken into endosomes within these cells through endocytosis (step 2). Following their release from endosomes, AAV virions are either ubiquitinated and targeted for proteasome-mediated degradation (step 3) or intracellularly trafficked to the nucleus (step 4). Once in the nucleus, AAV virions are uncoated and the AAV genome is released (step 5). The AAV single-stranded DNA genome then is converted into double-stranded DNA (step 6), followed by transcription (step 7) and the nuclear export of mRNA (step 8) for translation and expression of the therapeutic transgene (step 9). Engineering AAV vectors to affect any step of their transduction pathway impacts their transduction efficiency. ER, endoplasmic reticulum; ssAAV, single-stranded AAV; Ub, ubiquitin.

EX2027, ¶¶30, 73 (explaining EX2029, 4 (Fig. 1)). Here, Dr. Samulski explains that tissue tropism is implicated by the steps that occur extracellularly, meaning the steps that facilitate the AAV's ability to reach and bind to the cell or tissue type of interest. These are steps one and two in the diagram (red box): (1) the AAV's interaction with cell surface receptors and (2) entry into the cell by the creation of an endosome, or lipid compartment. EX2027, ¶¶30, 73. Steps that occur *after* the AAV enters the cell (i.e., intracellularly) drive infectivity, meaning the AAV's ability to enter the nucleus and ultimately have its genetic payload be expressed by the cell as a protein. *Id.* A POSITA in 2005 would not have expected a modification that affected the *intracellular* steps, such as the virus's transport across the nuclear pore (controlled by nuclear localization signals) to also have affected the *extracellularly*-determined tropism to a specific tissue. EX2027, ¶73.

At his deposition, Petitioner's expert, Dr. Schaffer, expressly conflated these steps in a manner to suggest that "tropism" includes every step of gene delivery, (*see* EX2030, 81:2-82:6, 234:11-13, 312:5-313:4). But, as Dr. Samulski explains, that is not how a POSITA would understand the term, (EX2027, ¶¶37-38, 73), nor is it consistent with the Petition, which clearly relied on a motivation to increase targeting to liver—i.e., tissue tropism—as the reason to modify AAVrh10 based on AAV8, (*see* Pet., 27, 43, 49). Dr. Schaffer's own declaration further makes this distinction clear. *See, e.g.*, EX1005, ¶85 (noting that "*tropism*" means the "*ability*

to target particular cell types,” while “transduction efficiency” means “efficiency of delivering a therapeutic gene and expressing it in targeted cells”).

Moreover, even if nuclear localization signals or phosphorylation sites near nuclear localization signals were of possible relevance to tissue tropism (they are not)—Petitioner assumes, again without basis, that the putative (i.e., possible) phosphorylation sites Petitioner’s expert identifies in Exhibit 1022 are actual phosphorylation sites, and that they are actually phosphorylated on AAV2. But Snowdy never showed either possibility to be true. EX2027, ¶74. In fact, two of the three sites that Snowdy identified had no impact on infectivity, as will be discussed in more detail below. That is why Snowdy cautioned against making a “premature” “assum[ption] that a given phosphorylation status will have the same effect on all NLSs, as there is insufficient evidence in the literature to support this assumption.” EX1009, 129; EX2027, ¶75. Thus, at most, Snowdy’s study, which Dr. Samulski notes was never published and never peer-reviewed, would have taught a POSITA about three potential phosphorylation sites on AAV2, none of which were at position 665, and all were irrelevant to tissue tropism. EX2027, ¶¶71-72, 74.

For the same reason, Dr. Schaffer’s testimony that he would have used the NetPhos program to identify the phosphorylation sites in AAVrh10 is misguided. EX1005, ¶¶278-279; I.D., 26-27. Even if a POSITA had been motivated to

identify four potential phosphorylation sites where AAV8 had non-phosphorylatable amino acids, that is only the first step. A POSITA would have had no way of knowing which, if any, of those four sites were actually phosphorylated. EX2027, ¶74; EX2030, 312:4-316:18. And, if phosphorylated, a POSITA would have had no way of knowing what impact, if any, phosphorylation had on functionality. EX2027, ¶74; *see also* EX2030, 304:20-305:6. As Snowdy showed, a phosphorylation site was just as likely to have no effect, or a negative effect, on function, as a positive one. Further, as discussed above, in 2005 there was no evidence that showed phosphorylation would have any impact on tropism. EX2027, ¶¶73-74

2. Petitioner's Reliance on Alanine and Aspartic Acid Substitutions Fails

In the portion of Snowdy that Petitioner cites, Snowdy modifies a phosphorylatable residue, like a serine, to “either a nonphosphorylatable *alanine*, to simulate an unphosphorylated serine, or to an *aspartic acid* to simulate a constitutively [i.e. always] phosphorylated serine[.]” EX1009, 125. Neither substitution is to an asparagine. EX2027, ¶76. While Petitioner alleges that “Snowdy also teaches the substitution of asparagine (N) as a nonphosphorylatable amino acid to remove a phosphorylation site,” (Pet., 48 (citing EX1009, 28-29; EX1005, ¶274)), Petitioner's own expert directly rebuts this. Earlier in his

declaration, Petitioner's expert explains that Snowdy's reference to "asparagine" here is a typo, because "a POSA at the time would immediately understand that the term 'asparagine' is a *typographical error* and that the correct term should be 'aspartic acid.'" EX1005, ¶¶178-179; EX2027, ¶77. In other words, "asparagine" does not make sense in the context of the sentence, which discusses a substitution "resulting in a *constitutively phosphorylated* residue," i.e., *aspartic acid*. EX1009, 29. Thus, *none* of the disclosures Petitioner relies upon in Snowdy involved modifying serine to *asparagine*. Nor do they teach the specific S665N modification required by the claims. EX2027, ¶77. If anything, Snowdy teaches an alanine substitution, not an asparagine substitution. *Id.*; *see also* EX1009, 125. Petitioner provides no rational explanation for why, if a POSITA were to modify a serine to a nonphosphorylatable amino acid, a POSITA would have chosen asparagine specifically over alanine or any of the other possibilities. EX2027, ¶77.

Additionally, Snowdy highlights the unpredictability in mutating possible phosphorylation sites. In addition to the serine at position 181 that Petitioner focuses its attention on (where the alanine mutation improved the transduction efficiency of the virus), Snowdy tested two other amino acids at different putative phosphorylation sites, namely a threonine at position 159 and a different serine at position 148. EX1009, 125-126; EX2027, ¶78. Mutating either of these two amino acids "had no effect, or little effect on the virus' ability to infect the HeLa

cells and to deliver the eGFP gene carried as their cargo.” EX1009, 126. Thus, even within Snowdy’s limited experiment, mutating serines at two different positions yielded significantly different results. EX2027, ¶78. Thus, Petitioner’s alleged motivation in mutating the serine at position 665 in AAVrh10 to remove a phosphorylation site fails, because doing so would not have been reasonably expected to have any impact on the function of AAVrh10, let alone any impact on AAVrh10’s tropism to liver. *Id.*

3. Petitioner’s Prior Art Shows Asparagine “Abrogates” (Destroys) Functionality

Far from showing that substituting with asparagine would have been expected to improve functionality, Petitioner’s own prior art demonstrates exactly the opposite—that it “*abrogates*” functionality. EX1009, 78; EX2027, ¶79. Petitioner’s expert asserts that “Snowdy, in citing Jans & Jans, teaches substituting asparagine for aspartic acid to remove the potential for phosphorylation.” EX1005, ¶181. But that is not what Jans & Jans discloses. First, Jans & Jans is not about AAV at all; rather, Jans & Jans is focused on nuclear localization sequences in cellular proteins. EX1017, 2. Second, Jans & Jans discloses that, in one particular protein (SV40 large T-antigen), substituting asparagine for aspartic acid had a negative effect, “result[ing] in nuclear import rates *less than 4%* wild type.” *Id.* In other words, Jans & Jans teaches that substituting in asparagine could have a

dramatic **negative** impact on functionality, contradicting Petitioner’s argument.

EX2027, ¶80. Moreover, any relevance of Jans & Jans to AAV2, or any AAV in general, goes unsaid in the Petition, and would be speculative.

Snowdy further confirms that it was known that asparagine can impart a negative effect. In a section of Snowdy that Petitioner does not cite, Snowdy echoes the Jans & Jans finding, stating that “[i]t has been shown previously that mutation of basic residues to asparagines **abrogates** [i.e., destroys] the function of NLSs.” EX1009, 78; *see* EX1017, 2; EX2027, ¶81. Snowdy then goes on to perform an asparagine mutation, finding that while, “[t]o our surprise” the modified AAV2 “made recombinant virus at wild-type levels,” (EX1009, 72-79), it nevertheless **failed to successfully infect** cells, (*id.*, 81, 108-109), rendering it useless as a vector for gene therapy. Therefore, Snowdy provides no reason for a POSITA to modify any residue to asparagine, let alone the serine at 665, and particularly where Snowdy’s other tested alternatives—i.e., the mutations Snowdy *does* teach—were known. EX2027, ¶81.

4. Petitioner’s Prior Art Shows Amino Acid Substitutions Can Have Contradictory Effects

Notably, the same prior art that Snowdy cites for the asparagine substitution also discloses mutating serines, but with notably different results. While Snowdy itself showed that mutating one particular serine (S181) to alanine improved

transduction, Jans & Jans also taught that substituting serine (i.e., the native residue of AAVrh10 at position 665) in place of aspartic acid in the T-antigen protein actually “enhanced nuclear import,” suggesting that a POSITA seeking to improve functionality may not seek to change the serine at all. EX1017, 2; EX2027, ¶82.

Additionally, in a separate experiment, Jans & Jans identified a phosphorylation site containing two serines, at positions 111 and 112. EX1017, 4-6. Jans & Jans found that, while mutating the serine at position 111 to a nonphosphorylatable glycine had very little effect on phosphorylation of the protein as a whole, mutating the serine at position 112 reduced phosphorylation by ~80%. *Id.*, 6 (Figure 5); EX2027, ¶83. These conflicting results, coupled with Snowdy’s results, demonstrate why a POSITA would not rely on a specific substitution from one study in a different AAV vector at a different amino acid to predict or make assumptions about what would happen if that substitution were applied in a different study and in a different vector. EX2027, ¶84. A POSITA would be particularly skeptical about the effect of a substitution on tissue tropism, which neither Snowdy nor Jans & Jans addresses. EX2027, ¶85.

5. AAV Research was Relatively Nascent and Unpredictable in 2005

Snowdy discloses that unpredictability was inherent in modifying amino acids to reach a desired improvement in functionality. For example, as the Petition admits, in the very experiment that Petitioner relies on in Snowdy, the result was the opposite of what had been expected. Pet., 19-20; EX1009, 128-29 (explaining “we expected the serine to alanine mutations to result in lowered transduction efficiency” but the result “was a virus that transduces target cells with greater efficiency”). Thus, Snowdy itself cautioned against making a “premature” “assum[ption] that a given phosphorylation status will have the same effect on all NLSs, as there is insufficient evidence in the literature to support this assumption.” EX1009, 129. Instead, Snowdy states this “issue will be better understood with future studies on other nuclear localization signals.” *Id.*

Indeed, the future studies Snowdy suggests highlight that research into AAVs was relatively nascent in 2003. Snowdy explains that “[v]ery little of the pathway from receptor binding to gene expression has been unequivocally determined for the virus,” meaning that a “***great deal of work remains*** in establish the mechanisms through which AAV virions and capsid proteins traffic through their host cells.” EX1009, 132. Further, as noted above, it was “unknown what receptor mediates infection by AAV1, AAV3, AAV7, and AAV8,” (*id.*)—that is,

only AAV2 was beginning to be understood. And even AAV2 was not well characterized. Snowdy explained that “[s]ome confusion remains as to whether AAV2 escapes from early or late endosomes, though evidence is starting to accumulate that point towards a late endosomal escape for the virus,” and further, “[t]he mechanism through which AAV virions escape from the endosomal compartment is *completely unknown*.” *Id.* Also unknown was “how the incoming AAV virus targets the nucleus, and how it mediates transfer of its genome across the nuclear envelope.” *Id.*

Placed in context of this nascent technology, the Petition fails to meet its burden to provide sufficient evidence showing that a POSITA would have been motivated to substitute a specific serine at position 665 for an asparagine based on Snowdy’s limited disclosures.

D. Claim 8 is Independently Patentable Over Grounds 4-6

Grounds 4-6 of the Petition all fail for one simple reason—Claim 8 requires tropism to *muscle* tissue, not to lung or liver—a fact that the Petition entirely fails to address. Following Petitioner’s own logic, a POSITA starting with the ’772 Publication would have used the information in Figure 2 to arrive at a different vector to target muscle—a vector different from the one claimed by the ’274 Patent.

1. The Petition Does Not Address or Support Change in Motivation From Targeting Liver to Targeting Muscle Required By Claim 8

Claim 8 depends from claim 6, and specifies that the “heterologous gene” must be a “mini-dystrophin or micro-dystrophin.” EX1001, cl. 8. As discussed above in Section VI(C), it is undisputed that dystrophin is a key protein in muscle tissue. *See, e.g.*, EX1010, 1 (“Duchenne **muscular** dystrophy is a severe life-threatening X-linked recessive disorder, caused by mutations in the dystrophin gene); *id.* (describing how previous vector options were “less than ideal for gene transfer to **skeletal muscle**”); *id.*, 6 (“AAV vectors remain one of the most attractive systems for **muscle** gene transfer, and the studies described here further confirm the feasibility of using highly engineered **micro-dystrophin** AAV vectors as an approach towards gene therapy of DMD”). An AAV-based gene therapy delivering a dystrophin or mini-dystrophin / micro-dystrophin gene consequently requires **muscle-based** tropism. EX2027, ¶¶60-61; *see also* EX1010, 1-6; EX2040, 4-5; EX2041, 1.

As discussed above, however, the Petition contends that a POSITA would have been motivated to modify AAVrh10 based on AAV8 to improve gene transfer of AAVrh10 to **liver**, by stating that “[t]he ’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.” Pet., 27. The Petition similarly concludes that “a POSA would have considered substitutions between AAVrh.10 (best overall and best in lung) and AAV8 (best in liver) *as a promising strategy* for obtaining an artificial variant of AAVrh.10 *with even more efficient gene transfer in liver.*” *Id.*; *see also id.*, 43 (discussing how “to confer some of the favorable properties of AAV8 on AAVrh.10”), 49 (“A POSA, seeking to improve the transduction of AAVrh.10 *in liver* to approach that of AAV8...”). The Petition is silent about gene transfer in muscle. EX2027, ¶¶60-61. Instead, Petitioner’s Grounds 1-3 are all premised on the motivation to modify AAVrh10 based on AAV8 due to AAV8’s superior tropism in *liver*, because improving tropism to *liver* was allegedly the desired result.

Nothing in Grounds 4-6 speaks to why a POSITA would have now expected the modified AAVrh10 to achieve tropism to *muscle*; in fact, tropism is not mentioned once in these Grounds. *See* Pet., 53-59. But specific tropism to the muscle is critical to claim 8, because mini-dystrophin/micro-dystrophin is used to correct deficiencies in dystrophin, a protein predominantly found in muscle tissue. EX2018, 1; *see also* EX1010, 1; EX1027, 15:33-17:39, Figs. 7-10; EX2027, ¶¶60-61; EX1010, 1-6; EX2040, 4-5; EX2041, 1. A POSITA in 2005 with the goal of expressing dystrophin for the treatment of disease would not have targeted the liver. If anything, a POSITA would have wanted to avoid delivery to the liver, as

discussed above in Section VI(B).

Instead of addressing the importance of muscle tropism to claim 8, Petitioner uses its new reference, Fabb (EX1010), only to support that a mini- or micro-dystrophin gene product can be *made* in an AAV vector generally. Indeed, the only motivation to combine the '772 publication with Fabb that the Petition advances is to reduce the large dystrophin gene down to a size that could be packaged in an AAV vector. Pet., 53-55, 57-59. Likewise, the only reasonable expectation of success that the Petition identifies is the expectation to succeed in “creat[ing] a micro-dystrophin that could fit within an AAV capsid.” *Id.*, 55; *see also id.*, 56, 58-59. Thus, the Petition is silent as to why an AAV that was modified to have alleged improved liver tropism would have been used to carry a mini or micro-dystrophin and target muscle. EX2027, ¶¶60-68.

The Petition’s statement that “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,” (Pet., 55) says nothing about the expected tropism (or success) of AAVrh10, and certainly not AAVrh10 with the AAV8/liver tropism-based modifications the Petition suggests. Indeed, Fabb used only a portion of AAV2 in its dystrophin gene therapy experiments and is silent as to AAVrh10 and AAV8. *See* EX1010, 7. But Fabb does teach that *other* AAV serotypes, such as AAV1,

AAV3, and AAV5 “can increase levels of protein production by 100-1000-fold,” which could “greatly enhance the therapeutic potential of micro-dystrophin AAV vectors[.]” EX1010, 6. Thus Fabb provides no reason to select the modified AAVrh10 set forth in the Petition over the other promising AAVs Fabb identifies. EX2027, ¶69.

Given that mini-dystrophin or micro-dystrophin are genes that must be delivered to *muscle* tissue, the Petition fails to sufficiently explain why a POSITA, viewing the '772 Publication in view of Fabb, would seek to maximize *liver* function to supply a *muscle*-based dystrophin gene product by modifying AAVrh10 in view of a *liver*-based AAV. Because Petitioner failed to make any such showing, it would be reversible error for the Board to supply the missing motivation now. *See TQ Delta, LLC v. Cisco Sys.*, 942 F.3d 1352, n.8 (Fed. Cir. 2019) (finding factual determination on motivation to combine unsupported by substantial evidence where “cited paragraph is not referenced by [Petitioner] in support of motivation to combine”); *see also* I.D., 28. For at least this reason, all three Grounds challenging claim 8 fail.

2. A POSITA Applying Petitioner’s Logic to Obtain an AAV Vector with Favorable Muscle Tropism Would Not Have Used AAV8

If, instead of targeting the liver, as Petitioner contends a POSITA would have done in all six grounds of the Petition, a POSITA sought to develop an AAV

vector that targeted *muscle*, a POSITA would have arrived at a different vector than the one claimed in the '274 Patent. As discussed above in Section VI(C), assuming that a POSITA would have started with the '772 Publication, she would have first looked for the vectors that showed good expression in muscle tissue, such as AAV1 or AAV7, and either used those vectors or, if a POSITA insisted on using AAVrh10, would have aligned AAVrh10 with AAV1 or AAV7 and made mutations to AAVrh10 based on the amino acids that differ. EX2027, ¶¶60-68; *see also* EX1052 (inserting fragments of AAV1 capsid into AAV2 capsid to confer AAV1's muscle tropism). No such mutation would lead a POSITA to replace AAVrh10's serine at position 665 with an asparagine. EX2027, ¶¶68-69.

Petitioner only gets to an asparagine at position 665 by modifying AAVrh10 based on AAV8. But AAV8 was reported in the '772 Publication to be a poor muscle transducer that a POSITA in 2005 would not have selected for gene delivery in muscle. EX1007, [0244], (showing 4.0 ± 0.7 expression in muscle, compared to 76.0 ± 22.8 in liver).

Ultimately, the Petition does not address why a POSITA in 2005, starting with the '772 Publication and looking to target a therapy delivering a dystrophin gene product (thus targeting muscle tissue) would modify an already-promising AAV serotype (AAVrh10) by looking at a poor muscle transducer (AAV8) rather than a higher-performing example (e.g., AAV1 or AAV7). Thus, Petitioner has

failed to meet its burden to show why a POSITA would have been motivated to modify AAVrh10 based on AAV8. Ground 4 fails.

Grounds 5 and 6 similarly fail, because neither Xie nor Snowdy cures the Petition's deficiency of showing how a POSITA would target muscle. Both Xie and Snowdy use AAV2, which the '772 Publication showed had even *worse* expression in muscle than AAV8. *See* EX1007, [0244] (Table 6 showing 0.5 ± 0.1 AAV2 expression in muscle, compared to AAV8's 4.0 ± 0.7 expression in muscle). Petitioner fails to address this disclosure, which suggests a POSITA would in fact be counseled *against* modifying AAVrh10—or any AAV for that matter—based on AAV2 when the goal is muscle tropism. Moreover, even if a POSITA relied on AAV2, AAV2 has a serine at position 665 just like AAVrh10. Thus, a POSITA would not have arrived at the vector in claim 8 of the '274 Patent.

VIII. CONCLUSION

For each reason stated herein, the Petitioner has not shown by a preponderance of the evidence that any claim of the '274 Patent is unpatentable.

Respectfully submitted,

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CERTIFICATION UNDER 37 CFR § 42.24

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Patent Owner's Response to Petition totals 14,000 words, which is equal to the 14,000 allowed under 37 CFR § 42.24(c)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e), the undersigned certifies that on December 5, 2024, a complete and entire copy of this Patent Owner's Response and accompanying exhibits were provided via email to the Petitioner by serving the email correspondence addresses of record as follows:

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