

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 OWNER'S PRELIMINARY RESPONSE

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PATENT OWNER'S EXHIBIT LIST

- EX2001 Roman Gardlík et al., *Vectors and Delivery Systems in Gene Therapy*, 11(4): Med. Sci. Monitor RA110 (2005)
- EX2002 Terence R. Flotte, *Gene Therapy: The First Two Decades and the Current State-of-the-Art*, 213(2): J. Cellular Physiology 301 (Nov. 2007)
- EX2003 Guangping Gao et al., *Clades of Adeno-Associated Viruses Are Widely Disseminated in Human Tissues*, 78(12): J. Virology 6381 (June 2004).
- EX2004 Guang-Ping Gao et al., *Novel Adeno-Associated Viruses from Rhesus Monkeys as Vectors for Human Gene Therapy*, 99(18): Proc. Nat'l Acad. Scis. 11854 (Sept. 2002)
- EX2005 C.J. Leonard & Kenneth I. Berns, *Adeno-Associated Virus Type 2: A Latent Life Cycle*, 48 Prog. Nucleic Acid Res. & Molecular Bio. 29 (1994)
- EX2006 Joshua C. Grieger & Richard J. Samulski, *Adeno-Associated Virus as a Gene Therapy Vector: Vector Development, Production and Clinical Applications*, 99 Adv. Biochem. Eng'g/Biotech. 119 (Oct. 2005)
- EX2007 Ekaterina Minskaia et al., *Viral Vectors in Gene Replacement*

Therapy, 88(12-13): Biochem. (Moscow) 2157 (2023)

- EX2008 Alejandra E. Arbetman et al., *Novel Caprine Adeno-Associated Virus (AAV) Capsid (AAV-Go.1) Is Closely Related to the Primate AAV-5 and Has Unique Tropism and Neutralization Properties*, 79(24): J. Virology 15238 (Dec. 2005)
- EX2009 Dawn E. Bowles et al., *Marker Rescue of Adeno-Associated Virus (AAV) Capsid Mutants: A Novel Approach for Chimeric AAV Production*, 77(1): J. Virology 423 (Jan. 2003)
- EX2010 Pierce J. Ogden et al., *Comprehensive AAV Capsid Fitness Landscape Reveals a Viral Gene and Enables Machine-Guided Design*, 366 Sci. 1139 (Nov. 2019)
- EX2011 Derek J. Blake et al., *Function and Genetics of Dystrophin and Dystrophin-Related Proteins in Muscle*, 82 Physio. Revs. 291 (2002)
- EX2012 Joshua C. Grieger & Richard J. Samulski, *Packaging Capacity of Adeno-Associated Virus Serotypes: Impact of Larger Genomes on Infectivity and Postentry Steps*, 79(15) J. Virology 9933 (Aug. 2005)
- EX2013 Hengjun Chao et al., *Several Log Increase in Therapeutic Transgene Delivery by Distinct Adeno-Associated Viral Serotype Vectors*, 2(6) Molecular Therapy 619 (Dec. 2000)
- EX2014 United States Patent No. 7,282,199 to Gao et al.

- EX2015 United States Patent No. 7,198,951 to Gao et al.
- EX2016 Summary of Figures 2 and 4 in EX1008
- EX2017 Philip Cohen, *The Origins of Protein Phosphorylation*, 4 Nature Cell Bio. E127 (May 2002)
- 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).
- EX2019 Mario Mietzsch et al., *Comparative Analysis of the Capsid Structures of AAVrh.10, AAVrh.39, and AAV8*, 94(6) J. Virology 6 (March 2020)
- EX2020 Clustal Omega Sequence Alignment of rh46, rh2, rh4, rh14, rh24, rh12, rh18, bb2, bb1, rh25, rh20, rh9, rh10, and rh11

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 AAVrh46, or an AAV with a sequence at least 95% identical to AAVrh46, with an asparagine at amino acid residue 665. EX1001, cl. 1. Petitioner infringes these claims with its \$3.2 million-per treatment gene therapy product, Elevidys, and turns to this forum to attempt to invalidate them. But Petitioner’s obviousness arguments use the challenged claims to propose a series of modifications to other capsid proteins to arrive at the claimed invention—modifications that are made for scattershot and at times outright contradictory reasons, all aimed solely at arriving at the claimed invention in violation of the law. *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991) (“It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant’s structure as a template and selecting elements from references to fill the gaps.”). Petitioner cannot meet its burden through this approach.

Petitioner’s flawed analysis begins with the ’772 Publication, which discloses 55 AAV capsids, 49 of which were novel. Petitioner chooses AAVrh10 from among these, but AAVrh10 has a serine at residue 665, not the claimed asparagine, as do the other 12 capsids in the ’772 Publication that are at least 95% identical to

AAVrh46. So Petitioner looks for a sequence with asparagine at residue 665—and for that sole reason, lands on AAV8. But AAV8 and AAVrh10 target different tissues: AAV8 is superior in liver, while AAVrh10 is superior in lung and muscle. And AAV8 and AAVrh10 differ at **48** separate residues. Yet Ground 1 of the Petition fails to provide any explanation for why a POSITA would have picked position 665, or why a POSITA would *only* have modified position 665, and expected any improved functionality. When a POSITA accounts for all the possible permutations of mutations available within those 48 different residues, the number of possible combinations increases exponentially, to hundreds of thousands of possibilities—and that is if a POSITA only considers substitutions, as opposed to other types of modifications like additions or deletions. The Petition fails to articulate how, of those hundreds of thousands of possibilities, a POSITA would have recognized the sole modification that would yield the invention of the '274 Patent.

Petitioner's remaining grounds compound the flaws in Petitioner's arguments. In Ground 2, Petitioner purports to modify the AAVrh10/AAV8 combination with yet another AAV, AAV2, as disclosed in Xie. The Petition provides no evidence of how similar or dissimilar AAV2 is to either AAVrh10 or AAV8, but argues that a POSITA would have looked to the crystalline structure of AAV2 in Xie anyway. Ground 3 similarly relies upon a disclosure related to AAV2, a graduate thesis by

Snowdy. In addition to failing to grapple with the differences between AAV2, AAV8, and AAVrh10, Petitioner's reliance on one experiment in Snowdy is further flawed because it merely disclosed substituting amino acids in AAV2 to mimic individual phosphorylated and unphosphorylated residues and, critically, discloses only alanine and aspartic acid substitutions, *not* asparagine, as claimed. Finally, Grounds 4-6, which challenge claim 8, all fail for the same reason—claim 8 is specific to micro-dystrophin and mini-dystrophin, which are targeted to muscle tissue. The Petition utterly fails to grapple with the difference in tropism between the AAVs it relies upon.

Accordingly, the Board should deny institution.

II. BACKGROUND AND STATE OF THE ART

A. Gene Therapy Overview

Gene therapy is a cutting-edge approach to treat genetic diseases and disorders by altering the genetic makeup of cells. EX1046. It involves the introduction, alteration, or replacement of specific genes within a patient's cells to correct or compensate for an absent or malfunctioning gene causing the disease or disorder, or to introduce a gene encoding a therapeutic product, such as an antibody. *Id.* Today, there are several methods for delivering therapeutic genes into the body, including viral “vectors,” or carriers, which are genetically engineered viruses that can carry the desired gene into target cells, and non-viral methods like direct injection of naked

DNA or RNA into the body. EX2001, 2, 6. Non-viral vectors are simpler and comparatively safer than viral vectors, but they often result in weaker entry or expression of the gene within a patient's cells, meaning they can be less effective than desired. *Id.* By contrast, genes enclosed in viral vectors can be strongly expressed in a patient's cells and have the potential to be very effective. *Id.*, 2. Viral vectors are extensively studied to ensure that they can deliver gene therapy safely and to the correct genetic location without adverse side effects.

B. Early Gene Therapy and Discovery of AAVs

Gene therapy first emerged as a potential way to cure disease in the 1990s, but with limited success. Non-viral vectors, such as direct, naked DNA injection, were tried first, but attained little clinical efficacy. EX2002, 1. To improve the efficacy of gene therapy, scientists turned to viral vectors for delivering therapeutic proteins. Some early approaches included the use of recombinant adenovirus, lentivirus, or recombinant herpesvirus vectors. *Id.* In the late 1990s, however, approaches using these kinds of viral vectors resulted in mixed safety outcomes that stalled efforts to develop clinically viable gene therapies. *Id.*, 2. Specifically, the viral vectors being used triggered inflammation and often severe side effects. *Id.* Believing in the promise in gene therapy, scientists focused their efforts on identifying new viral vectors that could be used both safely and effectively. EX2001, 2.

Adeno-associated virus (AAV) was first discovered in 1965 as a contaminant from laboratory preparations of adenoviruses. EX2003, 1. Unlike the adenoviruses with which they were associated, AAVs were found to be non-pathogenic, meaning they did not cause infectious disease on their own and were therefore considered safer than other viral vectors. For decades, only six different AAVs had been identified: AAV1, AAV2, AAV3, AAV4, AAV5, and AAV6. *Id.*

In late 2002, more than thirty years after the discovery of AAVs, Dr. James Wilson, a physician and researcher at the University of Pennsylvania, discovered previously unknown serotypes of AAV DNA in monkey tissue not otherwise known to be infected with AAV or adenovirus. EX2003, 1, 7. This AAV DNA existed in a cell without causing symptomatic infection in the monkey. EX2004, 2; EX2005, 1-2 (distinguishing this type of infection from “productive infection”). Unlike the discovery of AAVs 1-6, which were generally found in the presence of adenoviruses (which can cause symptomatic infection), Dr. Wilson discovered that AAVs would persist in a subject’s cells without being associated with disease or associated adverse effects, making them an attractive option for gene therapy. EX2001, 5. Further research by Dr. Wilson and his colleagues revealed the presence of additional AAV sequences in primate tissues, resulting in the discovery of a “total of 108 new and unique isolates” sharing phylogenetic similarities with known AAVs 1-6. EX2003, 2. Following Dr. Wilson’s research, scientists continued to screen for

additional novel AAVs, employing the techniques his group pioneered. Many of these serotypes were disclosed in the specification of the '274 Patent.

C. AAVs as Viral Vectors and Vector Modification

As of the '274 Patent's priority date in 2005, the use of AAVs for gene therapy was an emerging practice. *See, e.g.*, EX2006, 1. ("AAV virologists and gene therapists alike have just begun to scratch the surface in terms of the utility of this small virus in a clinical setting."). Indeed, the first AAV-based gene therapy, Glybera, was approved in 2012, in Europe. EX2007, 3. Five years later, Luxturna became the first AAV-based gene therapy approved in the United States. *Id.*, 4.

In 2005, knowledge of the biology of AAV infections, including about AAV's structure and mechanism of action, was in its infancy. The study of AAV for use in gene therapy at that time was limited to the previously identified AAVs, AAV1-6. EX2003, 1. At a high level, it was known that the outer protein shell of AAV—known as the AAV capsid—was composed of a combination of three proteins, called capsid proteins, vp1, vp2, and vp3. EX2008, 1. These three proteins, encoded by the AAV cap gene, are expressed as "splice variants," i.e., subsets of the largest protein, vp1, which contains the complete amino acid sequence. EX2009, 1. The smaller vp2 and vp3 proteins each contain a subset of vp1's sequence. *Id.* The AAV vector that is used for gene therapy comprises a capsid protein shell that houses the genetic material, such as the DNA of a transgene or "minigene." The term

“serotype” is generally used when referring to a specific AAV capsid, such as AAV1, AAVrh10, or AAVrh46. Different AAV serotypes have different efficacy in infecting and delivering genetic material to different tissues, a concept sometimes referred to as “tissue tropism.” *See, e.g., id.*; EX2002, 2; EX2007, 2; EX1032, 1; EX1052, 1.

Initial research on how AAVs worked was performed on AAV2, one of the earliest identified AAVs. EX2002, 4. Researchers had begun characterizing the functional domains of the vp1, 2, and 3 capsid proteins of AAV2 by generating a “comprehensive genetic map.” *See* EX1032, 1. The atomic structure of AAV2 was published in 2002, allowing researchers to further investigate the relationship between the structure and functions of AAV2. *See* EX1008, 1, 5.

As of 2005, AAV research relating to genetic engineering and mutagenesis was largely for basic science research purposes. Neither had been implemented as a general strategy to improve specific functions of AAV capsids. Research at that time addressed basic questions about how the biology and structure of AAVs influenced functionality. For example, one reference Petitioner relies on, Hauck (EX1052), describes this type of basic research: scientists swapped out regions of the genetic code of AAVs to test which regions influenced tropism and functionality. EX1052, 1-2 (“In the present study, a series of AAV capsid mutants were generated to identify the major regions affecting AAV transduction efficiency in muscle.”).

Hauck was not an example of modifying AAVs with the goal of creating capsids with specific improved functions; rather, it was designed to study which parts of the AAV capsid proteins affect certain functions. *See, e.g., id.*, 6 (“[W]e draw the conclusion that amino acids 350 to 423 are important in determining AAV1 tropism.”).

The type of modification that Petitioner proposes—i.e., changing a single amino acid of an AAV with the goal of significantly improving tropism or other functionality—was not reported in 2005. The literature demonstrates that such modifications were not reported until much later. *See, e.g.,* EX2010, 1 (reporting in 2019 that “recent high-throughput AAV mutagenesis studies have focused on limited capsid regions” and that their study generated “all single-codon insertions and deletions”). AAV-based gene therapy vectors were only beginning to be explored in 2005.

III. 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 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 aligning the capsid sequence of the weakly performing AAV 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, either singleton-corrected or lacking singletons. *Id.*, 8:41-44, 8:49-55.

The claims of the '274 Patent are directed to the second invention, i.e., gene therapy using the novel AAVs, and, in particular, using 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 nomenclature for the taxa is ... a reference to the species source...”). 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

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's only rejection of the claims was 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 remaining 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 was allowed on December 7, 2022, (EX1002, 363), with later minor amendments incorporating dependent claims directed to

¹ All emphasis added herein unless otherwise noted.

recombinant AAVs, (*id.*, 504-506).

IV. 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 application which discloses a method for detecting novel AAV serotypes, and host cells encoding them. As discussed above, in 2001 only six serotypes of AAVs had been identified: AAV1-6. EX1007, [0003]. While it was believed at the time that AAV could be a 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. *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.*

Noting that “experimental atomic structure has been a high priority for development of viral gene therapy vectors,” Xie sought to perform “high-order noncrystallographic redundancy” to create an “electronic density map for the protein capsid shell” of AAV2. *Id.*, 2. Xie does not disclose any AAV apart from AAV2, and discloses 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 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.” EX1009, 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.*

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 via an AAV2 vector and achieved promising results, suggesting that use of other 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.

V. LEVEL OF ORDINARY SKILL IN THE ART

For purposes of this Preliminary Response, Patent Owner does not dispute Petitioner’s definition of the qualifications of a person of skill in the art. Patent Owner reserves its right to challenge Petitioner’s definition and to provide its own definition, should trial be instituted.

VI. CLAIM CONSTRUCTION

For purposes of this Preliminary Response, Patent Owner does not challenge Petitioner’s articulation of the lack of a need for claim construction, and reserves its right to address any construction proposed by Petitioner or the Board, or to propose its own construction should trial be instituted.

VII. PETITIONER CANNOT PREVAIL AS TO ANY CHALLENGED CLAIM

A. Ground 1: Claims 1 and 3-6 Are Not Obvious Over ’772 Publication

Sarepta’s Petition suffers from a fatal flaw that precludes institution—it is premised on the idea that a POSITA would start her work toward developing a better AAV capsid with a sequence that was 95% identical to the claimed sequence for the novel AAVrh46 capsid. But Petitioner does not dispute that sequence was *not yet known* in the art at the time of the invention in 2005.

The '772 Publication does not disclose the AAVrh46 capsid (SEQ ID NO:4) or any AAV capsid that has a sequence with 95% identity to AAVrh46 with an asparagine (N) located at residue position 665, as the claims of the '274 Patent require. *See* Pet., 3 (acknowledging in '772 Publication that “AAVrh.10 has a serine (S) at position 665”). The only way a POSITA could have attempted to arrive at the invention from the '772 Publication would have been to somehow modify one of the 55 sequences disclosed (*see* EX1007, [0066], Table 1). The Petition, however, ignores the numerous steps and decisions a POSITA would have had to make to choose and alter one of the AAV capsids in the '772 Publication to arrive at the AAV capsids claimed in the '274 Patent.

To arrive at the sequence of the novel AAVrh46 capsid, the Petitioner starts by choosing just one of the more than fifty sequences disclosed in the '772 Publication, AAVrh10—a choice it makes based on the sequence covered by the challenged claims. Petitioner then aligns that sequence with just one of the more than fifty other sequences in that publication, AAV8, to determine that there are more than forty differences between those sequences. Petitioner then replaces only a single amino acid, AAVrh10's serine at position 665, with the asparagine that AAV8 has at that position. This strategy suffers from at least three fundamental flaws, any one of which preclude Petitioner from meeting its burden for Ground 1.

First, the Petition fails to show why a POSITA would have selected AAVrh10

as its starting point out of the dozens of AAV capsids disclosed in the '772 Publication. Second, the Petition fails to explain why a POSITA would have sought to modify AAVrh10 at all, when it was already a superior performer in lung and muscle tissue, and, to the extent liver targeting was desired, AAV8 already performed substantially better than AAVrh10 in liver tissue. Third, the Petition fails to show why a POSITA would have modified AAVrh10 in the specific manner suggested by Petitioner, as opposed to making any one of many available modifications.

Ultimately, a POSITA would have made the selections Petitioner suggests only if she had the claims of the '274 Patent in hand to use as a guide. Claims 1 and 3-6 of the '274 Patent are not obvious over the '772 Publication. The Board should reject Petitioner's attempt to work backwards from the claims of the '274 Patent to argue otherwise. *See In re Gorman*, 933 F.2d at 987.

1. The Petition Does Not Demonstrate Why a POSITA Would Have Selected AAVrh10 from the '772 Publication

The only rationale the Petition provides for a POSITA to select AAVrh10 from the '772 Publication is because it is allegedly “the preferred embodiment” and because it has 97.29% identity to AAVrh46. Pet., 25-26. But Petitioner does not address the fact that the '772 Publication discloses **49 novel capsids** in addition to the six capsids that had already been identified, a number of which are described as

“preferred embodiments,” and thirteen of which are at least 95% identical to the then-unknown AAVrh46. *See* EX1007, [0066] (Table 1); EX2020, 4.

Apart from allegedly being “the preferred embodiment,” the Petition provides little other basis for why AAVrh10 was selected from the 55 disclosed capsids. And Petitioner ignores that the ’772 Publication discloses numerous other preferred embodiments. For example, AAV2 is described as a “widely used” capsid “for efficient gene transfer experiments in different target tissues and animal models.” EX1007, [0003]. Table 1 shows *forty-eight* other novel AAVs useful for tissues including heart, liver, mesenteric lymph nodes (MLN), spleen, duodenum, kidney, liver, and blood. *Id.*, [0066] (Table 1). All are considered “[p]articularly desirable[.]” *Id.*, [0080]. Additionally, the ’772 Publication claims many, if not most, of the novel capsids disclosed in the specification; AAVrh10 is only one. *See id.*, cls. 25, 29, 46, 53, 59. Critically, the only AAV capsid that is singled out in the ’772 Publication’s claims is **AAV7**, which is claimed in two independent claims (cls. 65, 67) and one dependent claim (cl. 49). If anything, AAV7 appears to be the more preferred capsid.

Petitioner’s reliance on AAVrh10’s superior gene transfer in a specific tissue (i.e., tropism, or the ability to target a specific tissue type), (Pet., 25-26), is not persuasive. The ’772 Publication shows that other capsids have equal or superior targeting than AAVrh10 depending on the tissue type. For example, the ’772

Publication specifically notes that “vectors based on AAV7 capsids ... are particularly well suited for use in muscle; where vectors based on rh.10 (44-2) capsids ... are particularly well suited for use in lung.” EX1007, [0142]. Moreover, contemporaneous prior art pointed to many other promising capsids that could have been selected as well. *See, e.g.*, EX2014; EX2015.

The experiments in the '772 Publication also show that multiple desirable capsids exist. For example, AAV7 is described as being as efficient in skeletal muscle as AAV1, “the serotype that confers the highest level of transduction in skeletal muscle.” EX1007, [0250]. Table 8 shows the results of gene transfer into lung, liver, and muscle target tissues by known capsids AAV1, AAV5, AAV8, and novel capsids AAVrh2, AAVrh10, AAVrh13, and AAVrh21:

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

Id., [0253] (Table 8). Notably, AAV8 shows the highest gene transfer in liver tissue, surpassing AAVrh10 by over fifty percent. *See also* EX1007, [0246] (“AAV8 is the **most efficient vector for liver-directed gene transfer....**”). Petitioner acknowledges AAV8’s superiority in liver—noting that AAV8 provides “a substantial advantage

over the other serotypes in terms of efficiency of gene transfer to liver”—but only later in its Petition when it better fits its narrative. Pet., 26 (quoting EX1007, [0250]). In muscle tissue, on the other hand, AAV1 and AAVrh10 show roughly equivalent gene transfer. EX1007, [0253] (Table 8). And AAVrh2 is not far behind. *Id.* While AAVrh10 showed the highest gene transfer in lung, this transfer was markedly lower than the highest performers in liver and muscle. *Id.*

To the extent Petitioner contends a POSITA would have selected AAVrh10 because its sequence was 97.2% (i.e. greater than 95%) identical to AAVrh46’s sequence, that argument also fails. Petitioner ***does not dispute*** that the sequence of AAVrh46 was ***unknown*** to a POSITA at the time of the ’274 Patent. Using the novel, claimed AAVrh46 sequence as the starting point of the obviousness analysis is prohibited. *See Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) (“Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.”) (citation omitted); *see also Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004) (prohibiting using “the invention as a roadmap” to find prior art components in an obviousness analysis).

Using the AAVrh46 sequence also would ***not*** lead a POSITA to AAVrh10. Of the 49 novel AAV capsids disclosed in the ’772 Publication, thirteen have sequences that are at least 95% identical to AAVrh46: AAVrh2, AAVrh4, AAVrh9, AAVrh10,

AAVrh11, AAVrh12, AAVrh14, AAVrh18, AAVrh20, AAVrh24, AAVrh25, AAVbb.1 and AAVbb.2. EX2020, 4. The Petition does not mention, let alone address, the other twelve capsids at all, nor does it contain any discussion of why a POSITA would have picked AAVrh10 instead of any of those other twelve capsids. Not one of these thirteen capsids has an asparagine (N) at residue 665; each has a serine (S) instead. EX1007, Fig. 2. Thus, none provide the asparagine residue that Petitioner needs to reach the AAVrh46 in the '274 Patent claims. Additionally, if anything, the apparent conservation of residue 665 among the sequences that are at least 95% identical to AAVrh46 would have counseled a POSITA *against* changing it from a serine.

2. The Petition Does Not Demonstrate Why a POSITA Would Have Modified AAVrh10

Setting aside how and whether a POSITA would have arrived at AAVrh10 as a starting point, the Petition also does not explain *why* a POSITA would have modified AAVrh10 at all. The Petition cites nothing in the '772 Publication that suggests specific modifications to AAVrh10. Indeed, the purpose of the '772 Publication was *not* to modify known capsids, but rather to detect and isolate new AAV sequences from DNA samples, and construct host cells and viral vectors from those sequences. *See, e.g.*, EX1007, abstract.

The Petition argues 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).

In other words, a suitable capsid had already been identified for gene transfer to liver: AAV8. AAV8’s superiority is shown by the gene transfer data, discussed above, as AAV8 surpassed all other vectors in gene transfer to liver tissue. *Id.*, [0253] (Table 8). Petitioner provides no explanation for why a POSITA would not simply have selected AAV8, rather than modifying AAVrh10, if the problem the

POSITA sought to solve was maximizing efficiency of gene transfer in liver. Indeed, the effects of AAVrh10 modification would have been unknown, whereas AAV8 was already known for superior gene transfer in liver. 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.

Moreover, the '772 Publication's description of AAVrh10 indicates it was already a high performer in ***lung*** tissue. EX1007, [0254] (confirming "the superior tropism of AAV 44.2 [AAVrh10] in lung tissue"); [0142] ("vectors based on rh.10 (44-2) capsids of the invention are particularly well suited for use in lung"); *see also supra* at VII.A.1-2 (discussing the results in Table 8). Petitioner fails to explain why a POSITA, armed with such results, would have modified AAVrh10 for liver tropism when it already commanded high tropism in lung tissue.

Thus, the Petition fails to provide a cogent reason for why a POSITA would have been motivated to modify the '772 Publication's AAVrh10 sequence at all. *See In re Stepan Co.*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017) (for single-reference obviousness, "there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan would not arrive at the claimed combination").

3. The Petition Does Not Demonstrate Why a POSITA Would Modify AAVrh10 as It Suggests

Even if a POSITA were motivated to modify AAVrh10—which Petitioner has not shown—the Petition fails to explain why a POSITA would have modified AAVrh10 in the way the Petition suggests, as opposed to one of the many other modification options she could have chosen across multiple steps. 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 Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008). The same logic applies here.

(i) ***Why Modify Based on AAV8?***

As discussed above, the Petition contends that a POSITA would have modified AAVrh10 based on AAV8 to improve AAVrh10’s gene transfer in the liver. Pet., 27. Petitioner then argues, however, that a POSITA “would not have sought to make sweeping substitutions throughout the AAVrh.10 sequence” “given the already superior performance of AAVrh.10 *in lung*.” *Id.* By this, Petitioner admits that a POSITA would have been motivated to ***maintain*** AAVrh10’s superior tropism to lung tissue. *Id.*

The '772 Publication similarly highlights AAVrh10's ability to target lung tissue. Indeed, it repeatedly touts the superiority of AAVrh10 in lung tissue compared to other known and novel capsids, in addition to those shown in Table 8:

- AAVrh10 was a “**very potent** gene transfer vehicle ... with a **big lead** in the lung tissue particularly,” (EX1007, [0253]);
- “[V]ectors based on rh.10 (44-2) capsids of the invention are **particularly well suited** for use in lung,” (*id.*, [0142]);
- Additional experiments “confirm the **superior tropism** of AAV 44.2 [AAVrh10] in lung tissue,” (*id.*, [0254]);
- Table 9 showing relative gene transfer in lung in immune-deficient mice as compared to AAVrh10 (100), with closest comparison AAVrh8 (13.7), (*id.*);
- Table 10 showing relative gene transfer in lung in immune-competent as compared to AAVrh10 (100), with closest comparison AAV43.25 (58) (*id.*, [0255]);
- “The data from both experiments confirmed the **superb tropism** of clone 44.2 [AAVrh10] in lung-directed gene transfer,” (*id.*, [0256]).

Thus, Petitioner's suggestion of maintaining AAVrh10's “superior performance” in lung is consistent with the teachings of the '772 Publication. But Petitioner then suggests combining AAVrh10 with AAV8. But the data in Table 8 show AAV8 was “ND,” or “not determined” in lung tissue. EX1007, [0253] (Table 8); *see id.*, [0244] (Table 6 stating “ND” means “Not determined in this

experiment”). It is nonsensical that a POSITA, seeing this result, would have picked AAV8, not determined in lung, as a basis to modify the capsid “*particularly well-suited*” for lung, namely, AAVrh10. Moreover, Petitioner never addresses that modifying AAVrh10 based on AAV8, with its reported superior tropism for liver, could *negatively* impact AAVrh10’s tropism in the lung, and could do so *without* improving performance in other tissues.

The Petition relies on a single sentence from the ’772 Publication as a reason to modify AAVrh10 based on AAV8:

Interestingly, performance of clone 44.2 in liver and muscle directed gene transfer was also outstanding, close to that of the best liver transducer, AAV8 and the best muscle transducer AAV1, suggesting that this novel AAV has some intriguing biological significance.

Pet., 26-27 (citing EX1007, [0257]). But this is merely a statement of results, not an invitation to combine the two, as Petitioner argues. As the ’772 Publication explains, “[i]t will be readily apparent to one of skill in the art ... that certain serotypes of the invention will be particularly well suited for certain uses.” EX1007, [0142]. Indeed, the ’772 Publication describes other comparisons throughout. But Petitioner does not argue that any of those provide a reason to combine, because they do not reach the two AAVs that Petitioner *must combine* to arrive at the claimed sequence. *See*,

e.g., id. (comparing AAV7 and AAVrh10); [0243] (comparing pseudotyped² AAV2/1 and AAV2/7 vectors against AAV2/2 and AAV 2/8 vectors in muscle, as well as AAV2/7 and AAV2/1 in skeletal muscle); [0244] (Table 6) (comparing pseudotyped AAV2/1, AAV2/5, AAV2/7, AAV2/8 and AAV 2 vectors in liver); [0245] (noting pseudotyped AAV2/8 vectors performed best over intermediate expression from AAV2/5 and AAV2/7 vectors in liver); [0246] (noting AAV8 as the “most efficient vector for liver-directed gene transfer”); [0250] (identifying AAV2/7 as close to AAV2/1 in efficiency in muscle and AAV2/8 as best for liver); [0251] (identifying AAV7 as having “favorable tropism of the vectors for muscle”); [0253] (Table 8) (comparing AAV2/1, AAV2/5, AAV2/8, AAV2/rh.2, AAV2/rh.10, AAV2/rh.13, and AAV2/rh.21 vectors in lung, liver, and muscle).

At bottom, the ’772 Publication shows that AAVrh10 and AAV8 have different tropisms, and the Petition points to nothing that teaches or even hints at modifying one sequence based on the other, or that doing so would achieve any particular benefit.

² “Pseudotyped” vectors combine the rep gene from one serotype with a capsid gene from another serotype. For example, an AAV2/1 pseudotyped vector uses the AAV2 rep gene and the AAV1 capsid gene.

(ii) ***Why Modify One Residue Instead of a Fragment?***

The Petition next 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, Petitioner asserts a POSITA would have “modif[ied] a single amino acid residue at a time.” *Id.* 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 modifying specific amino acid residues in this manner.

Instead, to support modifying one residue at a time, Petitioner cites two secondary references. The first reference is its expert’s declaration (EX1005). That declaration, however, “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.”). The second reference, (EX1032), is an article published in 2000 that describes a study that used individual mutations to “obtain a comprehensive genetic map of the [AAV2] capsid gene.” EX1032, abstract. That is not what the ’772 Publication taught.

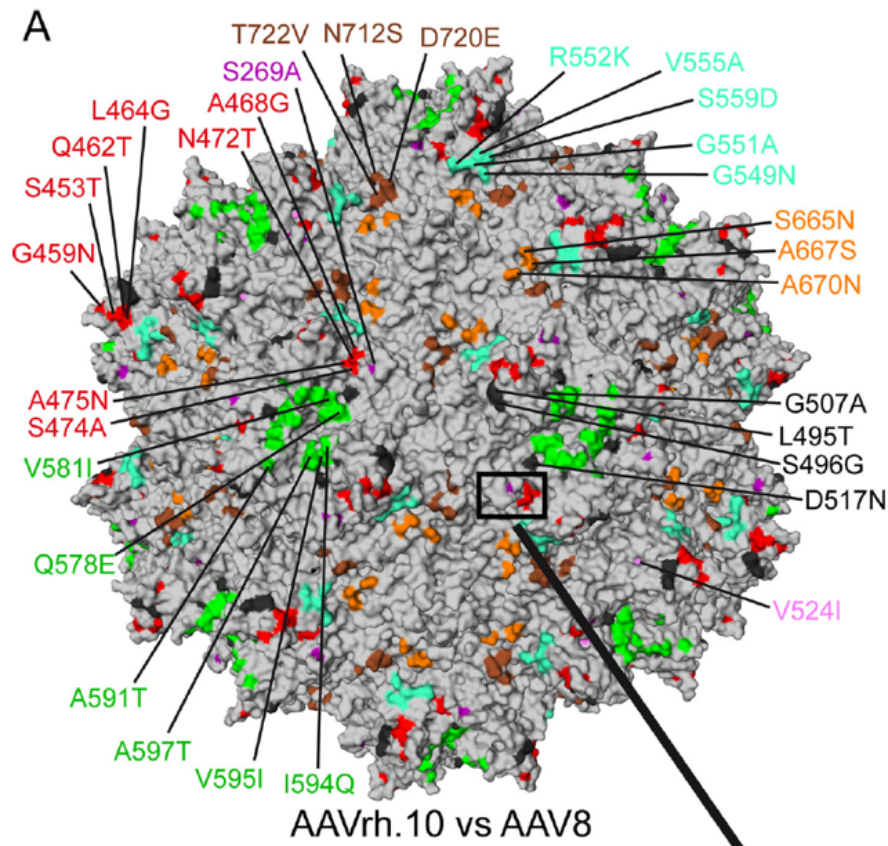
The '772 Publication teaches modifying AAV fragments instead of individual residues, teaching that fragments of AAV sequences can be used and combined with other portions of AAVs to form an “artificial capsid.” EX1007, [0075]; *see also id.*, [0071]-[0073], [0081], [0083]-[0085], [0118], [0141]. The '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]. 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.” *Id.*, [0017]. The Petition acknowledges this. Pet., 14-15 (citing EX1007, [0067]).

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—fails to meet Petitioner’s burden.

(iii) *Why Modify Residue 665?*

Next, in perhaps the most egregious of the Petition’s deficiencies, Petitioner fails explain why a POSITA would have been motivated to specifically modify amino acid residue 665. Petitioner admits there are 48 positions where the residues

of AAV8 and AAVrh10 differ. Pet., 28 (citing EX1019, 1). 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*. The Petition makes no attempt whatsoever to explain why a POSITA would modify residue 665, as opposed to one of the other 47. 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.

Keeping with Petitioner’s proposed AAVrh10 to AAV8 modification, the ’772 Publication also shows that many of those 48 sites can be modified in multiple ways. Figure 2 of the ’772 Publication shows that AAVs other than AAV8 have different amino acids at those 48 sites, any one of which could have been selected. The Petition acknowledges this understanding. *See* Pet., 29-32; EX1012, ¶¶313-319. For example, while position 665 of AAVrh10 contains a serine (S) and position 665 of AAV8 contains an asparagine (N), other AAVs contain a threonine (T) at that same position. *See* Pet., 34. Despite acknowledging that the 665 residue could also be a threonine (T), the Petition does not address why a POSITA would select asparagine over threonine. Petitioner also ignores that this same variability applies to *each of the other 47 sites*: multiple amino acids could be substituted at each of them. According to Figure 2, the sum total of possible single-site modifications for the 48 sites that differ between AAVrh10 and AAV8 is **163**. Thus, even if a POSITA wanted to change only a single AAVrh10 residue based on AAV8 to avoid “damaging or destroying the desirable properties of AAVrh.10,” (Pet., 27), a POSITA would have had to choose one modification over the 162 other possible modifications, meaning they would have a **0.6% chance** of selecting the S665N modification advocated by the Petition. The Petition provides no reason for a

POSITA to make this choice. *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994) (“The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious.”); *In re Deuel*, 51 F.3d 1552, 1558-59 (Fed. Cir. 1995) (“[A] broad genus does not necessarily render obvious each compound within its scope.”).

Further, Petitioner has not explained why a POSITA would have had a reasonable expectation that a mutation at a single residue, at 665, would work to ***solve the purported problem***—namely, improving AAVrh10’s targeting to liver—or that such a change would not have damaged the favorable properties of AAVrh10. Pet., 27. In fact, Petitioner has set forth ***no evidence*** of what effect, if any, a mutation at residue 665 would be expected to have on tissue targeting, undermining any argument that a POSITA would have selected that particular residue. And the same is true of any of the other 162 possible modifications.

(iv) ***Why Only Modify Residue 665?***

Petitioner relies on EX1032 for its allegation that a POSITA would only modify “a single amino acid residue at a time.” Pet., 27. As discussed above, however, the purpose of EX1032 was to create a genetic map of AAV2, not to modify targeting of an AAV capsid. EX1032, abstract. The Petition provides no reason why a POSITA would modify only one residue—indeed, as just discussed, the ’772 Publication discloses modifying whole ***fragments***.

The '274 Patent teaches that a POSITA would modify more than just one amino acid at a time, stating that “where a parental AAV contains multiple singletons and functional improvement is observed altered of a first singleton, it may be desirable to optimize function by altering the remaining singleton(s).” EX1001, 7:4-7. In other words, the '274 Patent teaches that a POSITA could keep going and modify multiple amino acids to improve a certain function. The Petition provides no reason why a POSITA would stop after a single amino acid modification.

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**.³ 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 or deletions, these

³ The formula to calculate the number of possible combinations is as follows, where “n” is the number of modified sites:

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

numbers dramatically increase. Petitioner does not address these possibilities, as they eviscerate Petitioner's obviousness case.

Further, Petitioner cites to *no evidence*, from the '772 Publication or elsewhere, that indicates that changing a single amino acid residue would have been expected to materially alter *any* functionality in the AAV capsid, let alone to alter tissue targeting.

(v) *Why Modify Residue 665 to Asparagine?*

Finally, as noted above, despite later acknowledging that residue 665 can also be a threonine (T), (Pet., 34), the Petition makes no attempt to explain why a POSITA would have selected asparagine (N) over threonine (T). Instead, the Petition makes a conclusory argument that "a POSA would have been motivated to make this single amino acid change in AAVrh.10 – namely, substituting an N for the S at position 665." Pet., 28. Petitioner cites to its expert, (EX1005, ¶213), but the expert again recites the Petition verbatim, and is of little value. *Xerox*, Paper 9 at 15-16. Therefore, Petitioner has not met its burden for Ground 1 to show that a POSITA would have been motivated to arrive at the final claim limitation, which requires that the "amino acid residue corresponding to position 665 ... is N." EX1001, cl. 1.

4. The Petition Misapplies Dr. Leone's Enablement Opinions to its Obviousness Analysis

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 (Ex. 1014), a patent that claims priority to the application published as the '772 Publication. The opinions Petitioner relies upon relate to Dr. Leone's written description and enablement analysis, and Petitioner misconstrues those opinions to attempt to support its obviousness analysis.

Petitioner alleges that it "[a]ppl[ied] Dr. Leone's analysis" and found the '772 Publication "teaches the creation of artificial variants ... including the substitution of N for S at the 665 position, resulting in the sequence recited in claim 1." Pet., 34. Petitioner's analysis misses the mark.

Dr. Leone's litigation report related to enablement, and specifically addressed 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) (explaining that obviousness "turns on what the prior art would have taught a [POSITA] and whether the claimed invention would have been obvious in view of the prior art," while enablement "turns on whether the skilled artisan, after reading the specification, would be able to make and use the claimed invention without undue experimentation"). Thus, 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. Pet., 29-30; EX1012, ¶¶310-11

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) ("It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus."); *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) ("A disclosure of millions of compounds does not render obvious a claim to three compounds[.]"). 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 would understand that there are an overwhelming number of possible combinations of modifications that could be made to AAVrh10. Based on Dr. Leone's analysis of Figure 2, of the 738 amino acids in the AAVrh10 vp1 sequence, 353 are conserved and 385 are variable. 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 of 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 is enormous, but can 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).⁴ The number of combinations increases exponentially, 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
6	2.674*10 ¹⁴
7	2.8762*10 ¹⁶
8	2.6996*10 ¹⁸
9	2.24697*10 ²⁰
10	1.67853*10 ²²
100	1.88589*10 ¹²⁴
250	1.73053*10 ¹⁸²
385	6.27401*10 ¹⁸²

⁴ 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:

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

The total number of possible combinations disclosed within the '772 Publication is 6.274×10^{182} . While a POSITA would have understood the scope of the '772 Publication's disclosure, she nevertheless would have had little chance of picking the *only* modification that yields the invention. Thus, even if a POSITA started with AAVrh10 because it is 95% similar to AAVrh46 (a position only possible through the disclosure of the challenged patent itself), it is mathematically improbable that she would select the one modification that yields the claimed invention.

Next, applying Petitioner's assumption that a POSITA would further select AAV8 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. That yields a total of 3.86×10^{14} combinations informed by the combination of AAVrh10 and AAV8. A POSITA would not instantly recognize a single site modification of S665N to be one of those, and so it would not have been obvious from the '772 Publication.

Indeed, nothing in the '772 Publication or Dr. Leone's declaration teaches a POSITA to start with the sequence of AAVrh10, focus solely on position 665 to the exclusion of all other positions that could be modified, 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.

B. Ground 2: Claims 1 and 3-6 Are Not Obvious Over the Combination of the '772 Publication and 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 of the '274 Patent. *See* Pet. at 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. *Id.* As discussed above, Petitioner fails to grapple with the fact that those 48 “variant” capsids actually amount to at least 163 different capsids when a POSITA considers all of the individual mutations that Figure 2 of the '772 Publication suggests could occur at those 48 positions, or with the fact that if more than one amino acid residue is changed, the number of potential capsids increases exponentially. *See* §VII(A)(3)(iii)-(iv), *supra*.

Further, Petitioner’s argument that a POSITA would require further motivation to narrow the possible changes to 18 residues highlights the lack of motivation in the '772 Publication itself, discussed above in Ground 1. Ground 2 of the Petition also fails, because 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 from the claims of the '274 Patent at issue here. Understanding the scope of an invention is not the same thing as rendering each potential embodiment obvious. "[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.” *Belden*, 805 F.3d at 1073 (emphasis in original). 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.

Even if a POSITA would have consulted the crystal structures of other AAVs, the Petition does not address why a POSITA would have chosen AAV2, in addition to AAV8, and as opposed to other AAVs. The ’772 Publication shows that AAV2 has poor expression in both muscle and liver cells. EX1007, [0244]-[0245] (Table 6). The Petition ignores this and offers no rationale for why a POSITA would consider AAV2 sufficiently “related.” The Petition does not even address how similar, if at all, AAV2 and AAVrh10 or AAV8 are. The ’772 Publication, which discloses pairwise alignments for certain capsids, does not compare AAV2 with either AAVrh10 or AAV8. *See* EX1007, [0188] (Table 3). Under Petitioner’s rationale, then, *any* AAV crystalline structure could be a reference point. The Board should reject Petitioner’s attempt to inject a *third* AAV into the combination to arrive at the AAV of the invention.

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 be motivated to

modify position 665 from serine (S) to asparagine (N) based upon its teachings. Xie provides no such motivation. First, Xie does not meaningfully narrow a POSITA's focus to "18 of the 48 variants" that differ between AAVrh10 and AAV8, (Pet., 44-45), because there are *more* than 18 variants taught by the '772 Publication. Even if a POSITA would have focused on the 18 positions that allegedly "involve amino acids that lie on the surface of the capsid," a POSITA would understand that, according to Figure 2 of the '772 Publication, **multiple** substitutions are possible at each individual position, and multiple substitutions at other locations are also possible, as discussed above. *See supra*, §VII(A)(3)(iv)-(v). Based on Figure 2 in the '772 Publication, the eighteen residues the Petition identifies can contain a sum total of seventy-three different possible amino acids, meaning that there are **seventy-three** possible single-mutation capsids to choose from, not the 18 Petitioner identifies. *Id.* The Petition erroneously plucks out just **one** of those possible capsids—a scant 1.4%, ignoring the **98.6%** of other possible substitutions without explanation or comment.

Moreover, nothing in Xie teaches that a POSITA would select a serine-to-asparagine modification out of the seventy-three possible modifications. As Petitioner's Exhibit 1023 notes, the serine at position 665 (SER665) in AAVrh10 corresponds to the exact same amino acid, serine, at that **same position** in AAV2 525 (SER525 using Xie's numbering). EX1023. That identity would dissuade

a POSITA from changing that amino acid, particularly where there are many other possible modifications to choose from. Thus, Xie 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.

Indeed, 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, such as an I182E or I182D mutation. *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

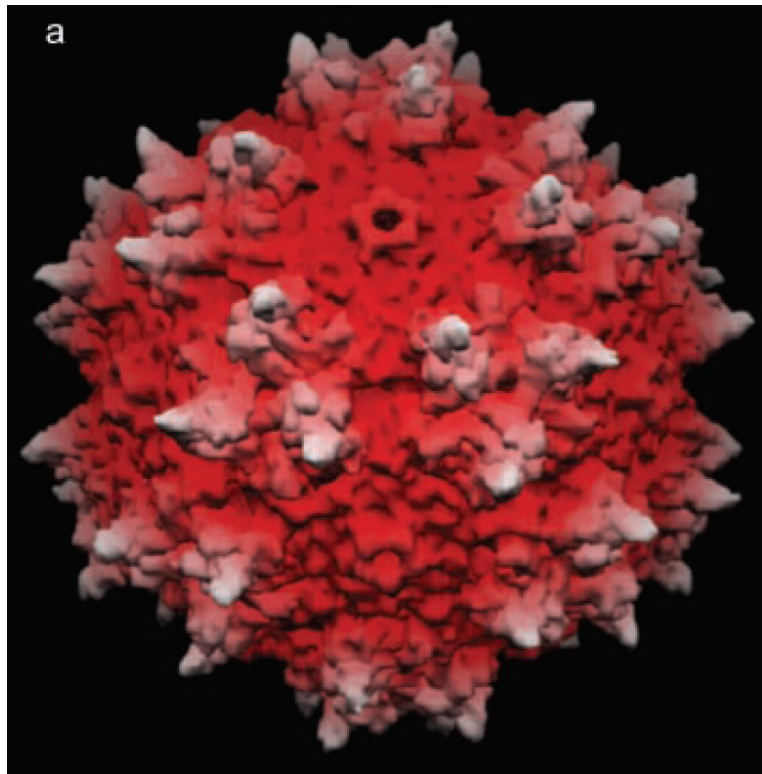
challenged claims.” *Id.* at 36. Petitioner here, as in *Kelonia*, “comes to the claimed ... mutations by retracing the path of the inventor with hindsight accuracy supported only by the bare testimony of [its expert].” *Id.* at 38. This flawed approach cannot support an obviousness finding.

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). But what Xie actually says is 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, it is the *secondary structure*, i.e. the three-dimensional folding of the protein, that Xie teaches governs AAV2’s 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. Nor does Petitioner’s expert provide any additional support for this statement, as his declaration again parrots the Petition verbatim. Compare Pet., 44, with EX1005, ¶256; Xerox, Paper 9 at 15-16.

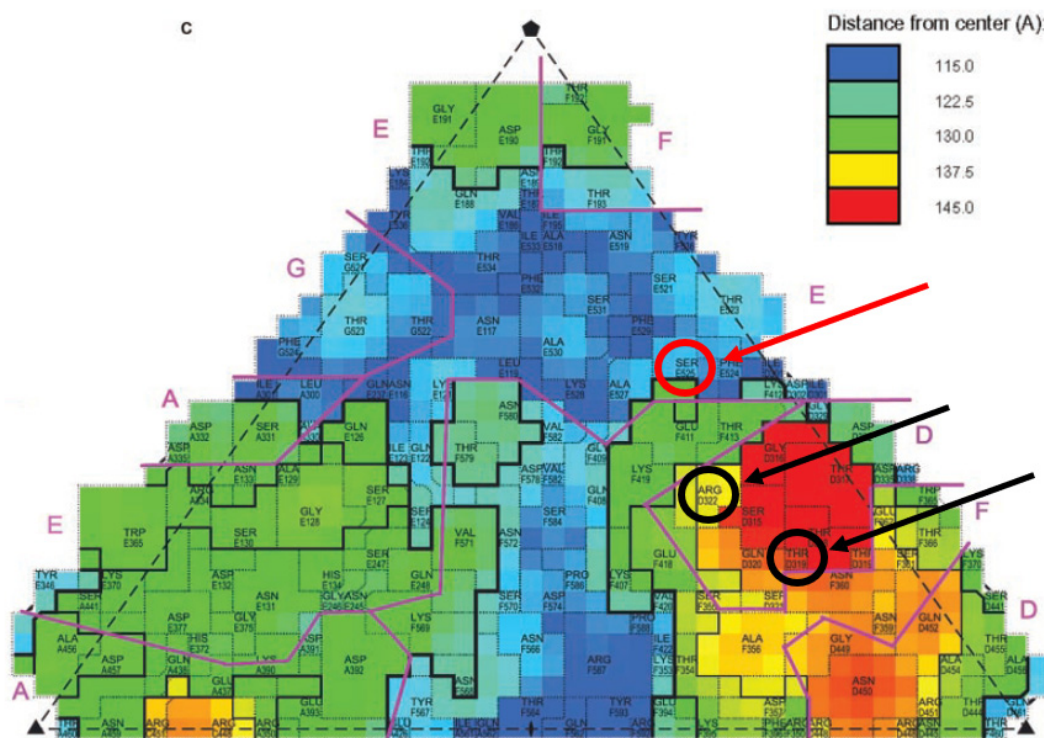
Even if Petitioner is correct to assume that amino acids at the surface are desirable targets, the Petition does not explain how it arrives at the eighteen amino acids “that differ between AAVrh.10 and AAV8 [that] lie on the surface of the capsid.” Pet., 44. Petitioner’s expert alleges that “[t]he red 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 (“ $20 \text{ \AA}^2 < \text{red} < 50 \text{ \AA}^2 < \text{cyan} < 80 \text{ \AA}^2 < \text{green} < 100 \text{ \AA}^2 < \text{blue}$ ”). 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.

Xie’s Figure 4, which Petitioner also purports to rely on, further shows that the other identified “surface” residues are more accessible than serine 665. For context, the overall structure of AAV2, shown in Figure 3 and replicated below, shows that the surface of AAV2 is characterized by a series of peaks that protrude from the AAV’s center:



EX1008, 4 (Fig. 3a).

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.* 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):



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. *Id.* 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.

The Petition does not explain why a POSITA would *ignore* these other known surface-level amino acid possibilities in favor of position 665. With each of those 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. at 44-45. The Petition fails to explain why a POSITA, having determined that surface amino acids are allegedly preferred, 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. Ground 3: Claims 1 and 3-6 are Not Obvious Over the Combination of the '772 Publication and 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 in AAVrh10 to non-phosphorylatable amino acids, based on the sequence of AAV8. 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 the serine at position 665 is in fact phosphorylated, and if it is, that its phosphorylation (or abrogation thereof) would have any effect on functionality.

Moreover, Ground 3 fails because Snowdy does not provide any reason to

combine AAVrh10 with AAV8 based on AAV2. The Petition fails to contend with the fact that, as with Xie in Ground 2, Snowdy's disclosures relate to AAV2, **not** to AAVrh10 or to AAV8. Snowdy does not suggest that the AAV2 results could directly apply to other AAVs. Instead, Snowdy suggests just the opposite. For example, while some understanding of the source of a virus's multiple functions had been established for certain AAVs, like AAV2, AAV4, and AAV5, for others the sources were entirely unknown in 2005. Specifically, while Snowdy notes that for AAV2, "it is widely accepted that the virus depends on heparin proteoglycans for initial attachment to the target cell and depends on $\alpha_v\beta_5$ integrin as a coreceptor that enhances the virus' internalization," it also notes that how AAV4 and AAV5 function differs from how AAV2 functions and that "[i]t is **unknown** what receptor mediates infection by AAV1, AAV3, AAV7, **and AAV8**." EX1009, 132.⁵ Snowdy does not mention AAVrh10, let alone attempt to speculate on how it functions.

The portions of Snowdy that Petitioner relies upon—a mere seven pages out of a 132-page dissertation—do not teach the modification of a serine to an asparagine. Instead, Petitioner (1) relies on alanine and aspartic acid substitutions,

⁵ Citations herein to Snowdy cite to the stamped numbers at the bottom right, consistent with Petitioner's convention.

(2) ignores that asparagine substitutions had been demonstrated to ***negatively*** affect functionality, and (3) fails to grapple with Snowdy’s own disclosures of how nascent AAV research was at the time of the invention.

1. 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. 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. 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. If anything, Snowdy teaches an alanine substitution, not an asparagine substitution. *Id.*, 125. Petitioner provides no cogent explanation for why, if a POSITA were to modify a serine to a nonphosphorylatable amino acid, a POSITA would choose asparagine over alanine or any of the other possibilities.

2. Prior Art Shows Asparagine “Abrogates” (Destroys) Functionality

Far from showing that substituting an asparagine would have been expected to improve functionality, Petitioner’s own prior art demonstrates exactly the opposite—that it “**abrogates**” functionality. EX1009, 78. 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. Moreover, any relevance of Jans & Jans to AAV2, or any AAV in general, goes unsaid in the Petition, and would be speculative. Notably, Jans & Jans also teaches 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,” further rebutting the idea that a POSITA seeking to improve functionality would seek to change the serine at all. *Id.*

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. 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.

3. AAV Research was Nascent and Unpredictable

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 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 for an asparagine based on Snowdy's limited disclosures.

D. Grounds 4-6: Petitioner's Addition of Fabb Does Not Render Claim 8 Obvious

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

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. Claim 8 depends from claim 6. Claim 6 includes an extensive list of different proteins that could be encoded by the “heterologous gene,” one of which is “a dystrophin gene product.” EX1001, cl. 6. Claim 8 specifies that the dystrophin gene product is a “mini-dystrophin or micro-dystrophin.” *Id.*, cl. 8. 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. *Id.*

As discussed above, however, the Petition suggests that a POSITA would have started with AAVrh10 because of its superior tropism in ***lung*** tissue. Pet., 26 (“The ’772 Publication singles out AAVrh.10 as a particularly preferred embodiment, and touts ‘the superb tropism of clone 44.2 [AAVrh.10] in ***lung-directed*** gene transfer.”); *see also id.*, 27 (“given the already superior performance of AAVrh.10 in ***lung***, a POSA would not have sought to make sweeping substitutions”). And the Petition then 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.* The Petition is silent about gene transfer in muscle. 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 found primarily in muscle tissue. EX2018, 1; *see also* EX1010, 1; EX1027, 15:33-17:39, Figs. 7-10.

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. *Id.*, 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.

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 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.

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. For at least this reason, all three Grounds challenging claim 8 fail. Additional Ground-specific reasons are addressed in turn below.

2. Ground 4 Fails Because Petitioner Did Not Include Limitation-By-Limitation Analysis and Ignored Better Tropism of AAV1 in Muscle

Ground 4 includes no limitation-by-limitation analysis of claim 8.⁶ Therefore, at the outset, Petitioner has failed to meet its burden to show that Ground 4 discloses each and every element of claim 8. For example, Ground 4 itself contains no explanation whatsoever of how the combination of the '772 Publication and Fabb teaches “[t]he 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.” Under 35 U.S.C. §312(a), a Petition must “identif[y], in writing and **with particularity**, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim.” *See also* 37 C.F.R. §42.104(b)(5); 37 C.F.R. §42.22(a)(2); *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (“In an IPR, the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.”).

Even setting that omission aside, the Petition ignores that the '772 Publication discloses that AAV8 has poor gene transfer in muscle tissue. Table 6 shows that AAV8 showed **minimal** expression in muscle. EX1007, [0244], (showing 4.0 ± 0.7

⁶ Petitioner’s Ground 4 does not cite back to Ground 1. *See* Pet., 53-56.

expression in muscle, compared to 76.0 ± 22.8 in liver). In Table 8, the applicants did not determine the tropism of AAV8 to muscle. *Id.*, [0253] (Table 8); *id.*, [0244] (Table 6 showing “ND” means “Not determined in this experiment”). Thus, the ’772 Publication provides no support for using AAV8 to improve muscle targeting.

Instead, the ’772 Publication notes that other AAVs known in the prior art, such as AAV1, were understood to be better transducers in muscle tissue than AAV8. *Id.*, [0257] (identifying AAV1 as “the best muscle transducer”); *see also id.*, [0244] (Table 6), [0253] (Table 8). As noted above, Fabb similarly identified AAV1 as a promising candidate that “could greatly enhance the therapeutic potential of micro-dystrophin AAV vectors[.]” EX1010, 6. Notably, AAV1, like AAVrh10, contains a serine at position 665. *See* EX1012, 34.⁷ Thus, neither the ’772 Publication alone nor in combination with Fabb provides any motivation to look to AAV8 at all with respect to claim 8, given AAV8’s poor expression in muscle.

Ultimately, the Petition does not address why a POSITA, starting with the ’772 Publication and looking to target a therapy delivering a dystrophin gene product

⁷ The Petition explains that position 665 in AAVrh10 corresponds to position 678 in the alignment in Figure 2. Pet., 32-33 (citing EX1005, ¶223). At position 678 in Figure 2, AAV1 (5th row) has a serine (S).

(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). 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.

3. Ground 5 Fails Because Xie Does Not Cure the Muscle Tropism Deficiency

Petitioner's Ground 5 expressly incorporates "the reasons discussed above regarding Ground 2," (Pet., 57), and is therefore deficient for the same reasons as Ground 2 discussed in Section VII(B). Moreover, the Petition does nothing to address the muscle tropism that a vector would need to deliver the mini-dystrophin/micro-dystrophin gene recited by claim 8, citing no additional evidence from Xie that addresses this issue. The Petition shows neither a reason to combine nor a reasonable expectation of success in achieving the tropism to muscle that is required to target claim 8's "mini-dystrophin or micro-dystrophin" gene product using the AAV8 and AAV2-modified AAVrh10 described in Ground 2 of the Petition.

Indeed, the '772 Publication shows that Xie's AAV2 has 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.

Thus, Xie does not cure the deficiencies of Ground 4. Ground 5 fails.

4. Ground 6 Fails Because Snowdy Does Not Cure the Muscle Tropism Deficiency

Similar to Ground 5, Petitioner’s Ground 6 expressly incorporates “the reasons discussed above regarding Ground 3,” (Pet., 58), and is therefore deficient for the same reasons as Ground 3 discussed in Section VII(C). As with Ground 5, the Petition cites no additional evidence from Snowdy that addresses the muscle tropism issue. Again, the Petition shows neither a reason to combine nor a reasonable expectation of success in achieving the tropism to muscle that is required to target claim 8’s “mini-dystrophin or micro-dystrophin” gene product using the AAV8 and AAV2-modified AAVrh10 described in Ground 3 of the Petition. Snowdy adds nothing of substance to Ground 5, and thus it too fails.

VIII. CONCLUSION

For the foregoing reasons, Patent Owner respectfully requests that the Board deny institution of Grounds 1-6 of the Petition, and thus decline to institute *inter partes* review of any claim of the ’274 patent.

Respectfully submitted,

Date: May 24, 2024

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CERTIFICATION UNDER 37 C.F.R. §42.24(d)

Under the provisions of 37 C.F.R. §42.24(d), the undersigned hereby certifies that the word count for the foregoing Patent Owner's Preliminary Response to Petition totals 13,993, which is less than the 14,000 allowed under C.F.R. §42.24(b)(1).

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e), the undersigned certifies that on May 24, 2024, a complete and entire copy of this Patent Owner's Preliminary Response was provided via email to Petitioners by serving the correspondence email address of record as follows:

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