

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 B2

PATENT OWNERS' SUR-REPLY

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EXHIBITS

- 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).
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- 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*

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- 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)
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- 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
- EX2021 Declaration of Dr. Casey M. Kraning in support of Motion for *Pro Hac Vice* Admission
- EX2022 Declaration of Deanna J. Reichel in support of Motion for *Pro Hac Vice* Admission
- EX2023 Melissa Bartel et al., *Enhancing the Clinical Potential of AAV Vectors by Capsid Engineering to Evade Pre-Existing Immunity*, 2 Front. Microbiol. 204 (Oct. 2011)

- EX2024 Jae-Hyung Jang et al., *Library Selection and Directed Evolution Approaches to Engineering Targeted Viral Vectors*, 98 Biotechnol. Bioeng. 3 (Oct. 2007)
- EX2025 David Schaffer, *AAV Shuffles to the Liver: Commentary on Lisowski et al.*, 1 Mol. Ther. Methods Clin. Dev. 14006 (2014)
- EX2026 David Ojala, *Adeno-Associated Virus Vectors and Neurological Gene Therapy*, Neuroscientist (2014)
- EX2027 Declaration of Dr. Richard Jude Samulski
- EX2028 Dr. Richard Jude Samulski's *Curriculum Vitae*
- EX2029 Chengwen Li and R. Jude Samulski, *Engineering adeno-associated virus vectors for gene therapy*, 21 Nat. Rev. 255 (April 2020)
- EX2030 Deposition Transcript of Dr. David Schaffer
- EX2031 Essential Amino Acids: Chart, Abbreviations and Structure
- EX2032 Sequence Alignments for AAVrh10, AAV7, AAV8, AAV1, AAV2, and AAV3
- EX2033 Michael Lochrie et al., *Mutations on the External Surfaces of Adeno-Associated Virus Type 2 Capsids That Affect Transduction and Neutralization*, 80:2 J. Virol. 821 (Jan. 2006)
- EX2034 Shaun Opie et al., *Identification of Amino Acid Residues in the Capsid Proteins of Adeno-Associated Virus Type 2 That Contribute to*

Heparan Sulfate Proteoglycan Binding, 77:12 J. Virol. 6995 (June 2003)

- EX2035 Xun Zhou et al., *Adeno-Associated Virus Engineering and Load Strategy for Tropism Modification, Immune Evasion, and Enhanced Transgene Expression*, 19 Int. J. Nanomedicine 7691 (July 2024)
- EX2036 Ziyu Jiang and Paul Dalby, *Challenges in scaling up AAV-based gene therapy manufacturing*, 41:10 Trends Biotechnol. 1268 (Oct. 2023)
- EX2037 Barath Jagadisan and Anil Dhawan, *Hepatotoxicity in Adeno-Associated Viral Vector Gene Therapy*, 22 Curr. Hepat. Rep. 276 (2023)
- EX2038 Dominique Larrey et al., *Drug-induced liver injury related to gene therapy: A new challenge to be managed*, 44 Liver Int. 3121 (2024)
- EX2039 Gemma Conroy, *How viruses are driving the gene-therapy renaissance*, 612 Nature S24 (Dec. 2022)
- EX2040 Eric Hoffman, *The discovery of dystrophin, the protein product of the Duchenne muscular dystrophy gene*, 287 FEBS J. 3879 (2020)
- EX2041 Quan Gao and Elizabeth McNally, *The Dystrophin Complex: structure, function and implications for therapy*, 5(3) Compr. Physiol. 1223 (July 2015)

- EX2042 Fengqi Jiang et al., *Bibliometric analysis of global research trends in adeno-associated virus vector for gene therapy (1991-2022)*, Front. Cell. Infect. Microbiol. (2023)
- EX2043 A Gene Therapy Pioneer: The Jude Samulski Story website printout, <https://www.askbio.com/the-jude-samulski-story/>, last accessed Dec. 5, 2024
- EX2044 Errata Sheet to Transcript of Dr. Jude Samulski's Deposition, taken on March 6, 2025 (EX1063)

I. INTRODUCTION

Petitioner's Reply fails to address the critical issue underlying this IPR—that claim 8 of the '274 Patent requires an adeno-associated virus (“AAV”) that delivers a dystrophin gene product to *muscle* tissue.¹ Instead, all of Petitioner's grounds are based on modifying an AAV vector to improve delivery to *liver* tissue. The Board pointed out Petitioner's failure and “invite[d] the parties to address this issue further at trial.” D.I., 28. Patent Owners subsequently put forth extensive evidence and explanation from a leading expert in gene therapy, Dr. Jude Samulski, describing why a POSITA intent on delivering dystrophin would have made different choices, such as choosing a known vector with better inherent delivery to *muscle*, or modifying a promising vector based on that known *muscle-specific* vector. POR, 22-35, 60-66. None of those paths would lead a POSITA to claim 8.

Petitioner failed to substantively address muscle delivery in its Reply—a tacit admission that the Petition's ground references and proffered motivation are

¹ To narrow the issues for the Board, Patent Owners have statutorily disclaimed claims 1 and 3-6 of the '274 Patent, leaving only claim 8 in this proceeding. Thus, Petitioner's Grounds 1-3 are no longer at issue apart from where Grounds 4-6 rely on them.

not directed at improving muscle-directed delivery. Petitioner's failure is highlighted by the scant evidence it points to regarding muscle delivery—just four paragraphs scattered throughout its expert's declaration and Petition. Reply, 18 (citing EX1005, ¶¶85, 89-90; EX1007, [0257]). To deflect from this fundamental omission, Petitioner's Reply resorts to attacking Patent Owners and their expert, inventing disputes irrelevant to its Petition. In doing so, Petitioner injects new references into the case—references omitted from the Petition and not established as prior art. Petitioner's attempt to backfill its Petition backfires, however, as even these new references support Patent Owners' arguments, not Petitioner's. Ultimately, Petitioner has not met its burden to demonstrate the unpatentability of claim 8, and the Board should confirm its patentability.

II. GROUNDS 1-6 FOCUS ON DELIVERY TO LIVER

A. The Motivation to Combine Identified in the Petition Is Improving Targeting to Liver, Not Muscle

As Patent Owners' expert explained, “[d]ystrophin is a protein that is predominantly expressed in muscle, and a skilled artisan creating a gene therapy to deliver dystrophin would seek to target the muscles.” EX2027, ¶60; *see also* EX1063, 270:9-15. Petitioner offers no meaningful dispute, and contends that its Petition addressed muscle targeting (though it did not). *See* Reply, 17-20 (“Petitioner and Dr. Schaffer Addressed Motivation to Target Muscle”). Thus,

there is no real dispute that claim 8 requires an AAV that can deliver dystrophin to muscle, as even Petitioner's ground reference, Fabb, confirms. *See, e.g.*, EX1010, abstract.

As addressed below, none of the Petition's arguments relate to muscle-specific targeting. Petitioner did not identify anywhere in its Petition or expert declarations that explained *how* a POSITA would engineer an AAV to target muscle. Nor could it, without going well beyond the scope of the Petition. Instead, Petitioner points to one overview paragraph in its Petition and a handful of paragraphs buried in the "technical background" section of its expert's declaration, which together only generically reference an alleged desire to improve targeting in a variety of tissues. Reply, 18 (citing Pet., 8; EX1005, ¶¶85, 89-90).

Petitioner does not meaningfully address Patent Owners' position that grounds 1-3 do not address muscle targeting. Indeed, by Petitioner's expert's own admission, the word "muscle" appears only once in these grounds, in one quote from the '772 publication underlying all six grounds. EX1005, ¶208; EX2030, 147:6-21, 350:1-359:7. The only other paragraph that uses the word "muscle" discusses Petitioner's Fabb reference in grounds 4-6. EX1005, ¶294. Paragraph 294, however, is merely focused on the size of the dystrophin gene, and whether a

truncated “micro-dystrophin” could be used. EX1005, ¶294.² Fabb is silent as to the AAV vector used.

Instead of addressing muscle-targeting, Petitioner’s expert doubles down on his argument that a POSITA would have been motivated to increase liver delivery:

- Discussing alleged motivation “to confer some of the favorable liver tropism of AAV8 onto AAVrh.10.” EX1072, ¶¶9, 11.
- Discussing alleged motivation “to make the S665N substitution to improve the tropism of AAVrh.10 in liver tissue.” *Id.*, ¶57.
- Arguing a POSITA “would have used the teachings of Snowdy, combined with those of the ’772 Publication...to improve liver tropism.” *Id.*, ¶195.
- Discussing “improving liver tropism by increasing the efficiency of expression of the transgene in liver tissue[.]” *Id.*, ¶¶325, 326.
- Arguing that “the superiority of AAV8 in liver would have motivated a POSA to try to improve the tropism of AAVrh.10 in liver[.]” *Id.*, ¶368.

See also id., ¶¶139, 308, 334, 336-337, 480.

² To the extent Petitioner suggests dystrophin is expressed outside muscle, (Reply, 20), it has not addressed delivery to those tissues—and has never argued dystrophin should be targeted to the liver, the sole stated motivation for modifying AAVrh10.

Petitioner's focus on liver targeting emphasizes its failure to address claim 8. Petitioner's only argument on claim 8 is new—that a POSITA would have been motivated to “preserve” targeting to muscle while improving targeting to liver.³ Nowhere, however, does the Petition explain why a POSITA with the goal of targeting a dystrophin gene to muscle would seek to improve liver targeting. Certainly nothing in the Petition, Reply, or cited references shows that a POSITA would have (i) selected position 665 to the exclusion of other positions, and (ii) substituted the serine at 665 with asparagine, if the goal was to deliver a gene therapy to muscle. And none of the references suggest that the specific S665N substitution would aid muscle delivery.

Nor does Petitioner meaningfully rebut Patent Owners' evidence that off-target delivery would increase manufacturing costs and risk life-threatening toxicity. *See* EX2027, ¶¶33-35. Tissue-specific promoters, (Reply, 22), do not mitigate immune responses to the AAV capsid itself, as the virus would still be everywhere, (EX2027, ¶35; EX1063, 214:15-19). Nor does local administration

³ Tellingly, Petitioner sets out to rewrite its Petition, injecting “muscle” where that word did not previously exist. *See* Reply, 19 (claiming that the “desirable properties” of AAVrh.10 included “its outstanding tropism in muscle and lung,” where the cited paragraph references only lung).

solve the problem, as multiple high-dose injections across the body are required to reach widespread muscle, increasing exposure and triggering immune responses. *See* EX1062, 1, 10 (discussing “the very large mass of target tissue...widely distributed throughout the body with layers of biological barriers”).

Rather than engage with these concerns, Petitioner attacks Dr. Samulski’s use of the term “tropism”—a red herring. Reply, 3-6. The word “tropism” is not in the claims. The concept of tropism is relevant here only because the sole motivation Petitioner offered for combining its ground references is to create an AAV vector “with even more efficient gene transfer *in liver*.” Pet., 27; *see also id.*, 49 (“A POSA, seeking to improve the transduction of AAVrh.10 *in liver* to approach that of AAV8...”). Patent Owners and Dr. Samulski are simply responding to this liver-specific motivation, not offering an “unusual” definition of tropism.⁴ But the experts here agree that whether a gene therapy vector reaches

⁴ Dr. Samulski explained that his definition of tropism is not “different” from the other definitions Petitioner’s counsel showed him. He explained that Petitioner’s counsel was misunderstanding him, and attempted to provide reasonable context about how the field uses the word “tropism,” including that it can be ambiguous which steps are specifically implicated by certain usages. *See* EX1063, 49:7-24; *see also id.*, 31:20-32:15, 49:25-50:5, 265:11-25.

and engages with a particular tissue is governed by steps that happen outside of the cells, not by the steps that occur after the vector enters the cells. EX1005, ¶85 (“[R]esearchers were working to improve the tropism (ability to target particular cell types) and transduction efficiency (efficiency of delivering a therapeutic gene and expressing it in targeted cells)[.]”); EX2027, ¶73 (“[T]ropism relates to the steps that occur that allow an AAV vector to reach and be taken up by the cell or tissue of interest”). Once the vector is inside the cells, the viral capsid’s impact on gene expression is generally not cell-type specific. EX2027, ¶73 (“Increasing intracellular infectivity, and in particular, the transport of the virus across the nuclear pore, would not have been expected to increase extracellularly-determined tropism to a particular tissue.”).

Petitioner pivots in Reply, arguing for the first time that a POSITA “would be motivated to combine [the ’772 Publication and Snowdy] to improve **transduction** of AAVrh.10” generally. Reply, 5-6. The Board should reject this new argument, *see Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1370 (Fed. Cir. 2016) (no abuse of discretion in excluding reply brief where petitioner “relied on an entirely new rationale to explain why [a POSITA] would have been motivated to combine” two ground references), which also fails substantively. The only motivation the Petition supplies for selecting AAV8 in the first place is its excellence in targeting liver. Pet., 26-27, 49. Petitioner relies on

that motivation to argue that a POSITA would have substituted the asparagine in AAV8 for the serine in AAVrh10 at position 665 to attempt to increase liver-targeting of AAVrh10. “Improving transduction” generally (i.e., not within a specific cell type) provides no motivation for a POSITA to select AAV8 specifically, as opposed to any other vector. Petitioner acknowledges as much in its Petition, citing Snowdy merely for improving transduction efficiency of an AAV—not for changing the tissue the AAV targets. Pet., 47-49.

B. Petitioner’s Proposed Substitution Would Not Target Muscle

Petitioner offers no substantive response to Patent Owners’ arguments addressing Grounds 1, 2, 4, or 5, each of which lacks any explanation for muscle targeting. This apparent retreat aligns with the Board’s Institution Decision, which identified the ’772 publication and Snowdy combination as Petitioner’s “strongest” ground. D.I., 13; *see also id.* (same for Ground 6 addressing claim 8). Petitioner’s silence signals a concession that these grounds cannot support unpatentability of claim 8.

1. The ’772 Publication Would Not Lead a POSITA to Use AAVrh10 to Target Muscle

As explained in Patent Owners’ Response, a POSITA seeking to deliver dystrophin to muscle would not have started with AAVrh10, given the ’772 publication’s praise for AAV7 and the public availability of AAV1. *See* POR, 30-

35, 60-66. Petitioner highlights a purported “unusual emphasis” placed on AAVrh.10, but ignores that AAV7 is described as “particularly well suited for use in muscle,” and performed roughly *three times better* than AAV1—then the best-known muscle vector. EX1007, [0142], [0251]; POR, 32-34; EX2027, ¶63.

Even assuming a POSITA started with AAVrh10, Petitioner fails to explain why she would then modify it in a way aimed solely at enhancing liver tropism. *See* Pet., 26-28, 49; POR, 12, 22. But enhancing liver tropism has no bearing on, and may even conflict with, claim 8’s requirement to deliver dystrophin to muscle. None of the Petition, Petitioner’s Reply, or Petitioner’s two expert declarations address why a POSITA seeking to deliver dystrophin to muscle would modify AAVrh10 to improve liver targeting.

Petitioner newly argues that a POSITA may have chosen AAVrh10 for reasons unrelated to targeting, such as “usefulness for targeting multiple tissues, safety, and ease of purification[.]” Reply, 16; *see also* EX1072, ¶397 (also identifying “ease and consistency of manufacturing, an established safety profile, and expedited review for regulatory approval”). But the ’772 publication does not disclose any human safety data or information regarding “ease of purification,” and FDA had not addressed AAVrh10. These considerations would have counseled a POSITA *away* from starting with AAVrh10. As Dr. Samulski explained, manufacturing, safety, and regulatory reasons in 2005 would have led (and in fact

did lead) a POSITA to choose a well-characterized serotype such as AAV2 as a starting point. *See, e.g.*, EX1063, 106:23-107:23, 257:21-259:2. A POSITA would have known that AAV2 was the only vector FDA had allowed in human testing by 2005. *See id.*, 107:1-5. Tellingly, Petitioner’s argument that a POSITA would have considered the “usefulness for targeting multiple tissues” is unsupported by record evidence beyond its own expert’s testimony, and should be accorded little weight. 37 C.F.R. § 42.65(a); *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (PTAB Aug. 24, 2022) (precedential).

2. Snowdy is Irrelevant to Tissue Targeting and Highlights Unpredictability of the Field of Gene Therapy in 2005

Petitioner contends that Patent Owners and Dr. Samulski, “improperly dismissed” Snowdy. Reply, 1. Not so. Rather, Dr. Samulski and Patent Owners thoroughly analyzed Snowdy for what it did and did not teach. As Snowdy’s thesis advisor, Dr. Samulski is uniquely positioned; he is the ideal source to understand what Snowdy’s experiment was designed to test, the reasons it was designed as it was, and the proper context in which to understand Snowdy’s results and implications (if any) for the field of gene therapy.

The issue is not whether Snowdy’s data are valid, but whether they are relevant. They are not. Snowdy provides no rationale for a POSITA to modify AAVrh10 to enhance liver targeting—Petitioner’s sole stated motivation. Far from

agreeing about any “import of Snowdy’s results” at his deposition, Dr. Samulski explained that Snowdy’s hypothesis was never validated—“our hypothesis was in flux.” EX1063, 95:12-24. The data could have been driven by unknown factors unrelated to nuclear localization. *Id.*, 94:20-95:7. As he put it, Snowdy “stumbled into something we didn’t understand.” *Id.*, 127:18-19. Petitioner still offers no explanation how Snowdy supports its proposed liver-targeting modification to AAVrh10—much less muscle targeting as required by claim.

Indeed, as Petitioner’s expert acknowledges, Snowdy’s study was done on HeLa cells in culture. *See, e.g.*, EX1072, ¶114; EX1064, 306:9-20. HeLa cells, however, were simply a tool to study the biology of AAV; their use was unrelated to targeting any specific tissue. EX1063, 55:19-24 (“I am saying definitively that cell culture cannot define things that are related to tropism.”). Thus, Snowdy used HeLa cells “because HeLa cells were the most permissive cell to study in a molecular step and be consistently able to reproduce it,” not because they were representative of or relevant to tissue-specific targeting. *Id.*, 92:5-13; *see also id.*, 91:12-15 (“We were studying a very specific step that we could only [confirm] that it worked in that cell type, until we could test it in other cell types. It may be unique to HeLa cells.”), 93:21-25 (“We’ve been burnt enough where if we made this assumption, it did the same thing, and it didn’t work...we study something unique to this cell type and...[i]t’s restricted to this cell type.”).

Even if any conclusions could be derived from Snowdy regarding transduction generally (they cannot) an increase in transduction would occur regardless of the tissue being targeted. Petitioner, however, cannot arrive at the four amino acids that a POSITA would purportedly modify, (*see* Pet., 49-51), without narrowing them down based on a comparison between AAVrh10 and AAV8, a comparison a POSITA would only do to increase liver targeting—a goal simply not found in Snowdy.

Even setting aside Snowdy’s irrelevance to improving liver targeting, the combination of Snowdy with the ’772 publication still fails. Petitioner does not argue—nor could it—that Snowdy modified position 665 in any AAV or taught that position 665 is relevant for any biological function. Nor does Snowdy teach making a serine to asparagine substitution. Petitioner’s only argument to the contrary is based on an incorrect interpretation of a reference that Snowdy cites, Jans & Jans (EX1017). POR, 56-58; EX2027, ¶¶79-85. Moreover, as Petitioner admits, (*see, e.g.*, Reply, 7-8), Snowdy’s results were “surprising”—the *opposite* of what was expected based on Jans & Jans, (*see* POR, 57). Taken together, Snowdy and Jans & Jans demonstrate the innate unpredictability of the effect of making amino acid substitutions. Such unpredictability undermines any attempt to apply Snowdy’s results here.

III. PETITIONER INTRODUCES UNTIMELY NEW REFERENCES AND ARGUMENTS THAT ULTIMATELY SUPPORT PATENTABILITY

Because Petitioner's ground references cannot support obviousness, Petitioner pivots from them in its Reply. Petitioner cites new references that it could have included with its Petition, and attempts to support them with a 165-page expert declaration. But these references are outside the scope of the Petition, and Petitioner made no attempt to show that many of them qualify as prior art. Moreover, Petitioner's second expert declaration grossly violates the scope of its Reply with its plethora of new evidence and arguments.

Even if these procedural violations were excused, Petitioner's new references fail on the merits. Petitioner devotes much of its Reply to arguing that single amino acid substitutions were generally known to affect AAV function. But that is not the issue here. To meet its burden, Petitioner must demonstrate that a POSITA in 2005 would have been motivated to make *one specific amino acid substitution*—asparagine for serine at position 665—to improve AAVrh10's targeting in liver. Given the inherent unpredictability in this art in 2005, a POSITA would not have had that motivation.

A. Petitioner's Reply Declaration Impermissibly Breaches the Board's Established Word Count Limitations

In contravention of the Reply word limit, Petitioner submitted a 165-page reply declaration from its expert—significantly longer than the opening declaration

(118 pages), and ***over three times*** the length of the 53-page declaration it purports to respond to, (EX1072, ¶1).⁵ See EX2027. Petitioner uses this reply declaration to present new arguments and evidence, then cites long portions of it in the Reply without meaningfully discussing the content. See, e.g., Reply, 24 n.6 (contending “Jans & Jans, which does not teach away from an S665N substitution in AAVrh.10 for multiple reasons,” citing 47 paragraphs across 15 pages of Dr. Schaffer’s declaration); see also Reply, 3 (citing 72 paragraphs across 27 pages to allegedly support that Snowdy was the “basis” for the ’126 provisional); Reply, 7 (citing 38 paragraphs across 14 pages to dispute Dr. Samulski’s characterization of Snowdy). In particular, Petitioner’s expert addresses ***1,049 lines*** of additional testimony of Patent Owners’ expert addressed nowhere in Petitioner’s Reply. Petitioner’s expert also includes significant analysis of the new references that could have been included in the Petition. See, e.g., EX1072, ¶¶127-264.

The Board’s rules prohibit arguments from being incorporated by reference into replies. See 37 C.F.R. §42.6(a)(3). Citations to “large portions of another document, without sufficient explanation of those portions, amounts to

⁵ Dr. Schaffer’s reply declaration has ***over 35,000 words***, more than six times the 5,600-word limit for Replies. Patent Owners cannot address even a fraction of this testimony here.

incorporation by reference.” *Cisco Systems, Inc. v. C-Cation Techs.*, IPR2014-00454, Paper 12, at 8 (PTAB Aug. 29, 2014) (informative). Additionally, the “practice of citing [a] Declaration to support conclusory statements that are not otherwise supported in the [brief] also amounts to incorporation by reference.” *Id.*, 9.⁶ Petitioner’s end-run around the word limit is particularly prejudicial here, as Patent Owners have no opportunity to address the new arguments with expert testimony. Therefore, the Board should disregard Dr. Schaffer’s reply declaration in reaching its conclusions here.

B. Petitioner’s New References Are Neither Prior Art Nor Relevant to a Person of Ordinary Skill’s Knowledge in 2005

Petitioner’s Reply and its expert rely on numerous references introduced for the first time, many of which are not prior art. All of these new references should be disregarded. For instance, Petitioner relies heavily on the ’126 provisional

⁶ *See also id.* at 10 (“[I]ncorporation by reference of numerous arguments from Dr. Roy’s 250-page Declaration into the Petition serves to circumvent the page limits imposed on petitions for *inter partes* review, while imposing on our time while asking us to sift through over 250 pages of Dr. Roy’s Declaration...to locate the specific arguments corresponding to the numerous paragraphs cited to support Petitioner’s assertions.”).

application filed near in time to the priority date of the '274 Patent. Reply, 10-11, 21, 25; EX1072, ¶¶127-199. But Petitioner made no showing, either legally or factually, that the '126 provisional application—not available to the public until it published in June 2006—qualifies as prior art to the '274 Patent. Even if it did, the '126 provisional is not a ground reference, and for that additional reason it would be legal error for the Board to rely on it in combination with the ground references in reaching a decision of unpatentability. Regardless, the '126 provisional approach would not lead to claim 8.

Similarly, Petitioner relies on a **2006** paper (“Wu”) that is undisputedly not prior art, and therefore cannot “contradict” what a POSITA knew or would have done in **2005**, as Petitioner alleges. *See* Reply, 11, 13 (citing EX1060). Other of Petitioner’s new references are not about tissue targeting at all. For example, Petitioner cites one of its expert’s patent applications that purportedly showed a single amino acid substitution “enhanced the ability of the rAAV to evade the immune system.” Reply, 10 (citing EX1066). But Petitioner fails to explain how evading the immune system relates to any issue in this case, let alone tissue targeting.

With respect to the '126 provisional application, Petitioner takes its disclosures out of context. The work in the '126 provisional brought together experts with different backgrounds and skillsets to create an *extraordinarily skilled*

team in an unprecedented collaboration. An extraordinarily skilled person or team is not a person of **ordinary** skill in the art. *See Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) (“A [POSITA] is also presumed to be one who thinks along the line of **conventional** wisdom in the art and is **not** one who undertakes to innovate, whether by patient, and often expensive, systematic research **or by extraordinary insights**[.]”). Dr. Mavis McKenna was an extraordinarily skilled crystallographer. As Dr. Samulski explained, she was the “goddess of the AAV crystal structure. She solved all the crystal structures for all the serotypes. So she was the mecca who understood AAV structure.” EX1063, 271:7-13. Dr. Samulski further testified that she “independently solved” a number of AAV crystal structures in the early 2000s, and that he relied on her to determine amino acids to change based on the crystal structure. EX1063, 271:14-272:20. When asked if a POSITA could do this kind of analysis, Dr. Samulski said that he “still can’t do it after 50 years of being in this space.” EX1063, 279:14-16; *see also id.*, 115:21-116:1 (“Mavis used the crystal structure. She was the only one qualified to do that analysis.”). Another inventor, Dr. Joseph Rabinowitz, was “an innovator that opened the field up to trying different serotypes,” and was “extraordinary in that he developed technology that enabled the whole field to go forward[.]” *Id.*, 272:21-273:15.

Finally, Dr. Samulski himself in 2005 was a person of extraordinary skill in the field. Dr. Samulski was the first scientist to clone an AAV in 1982, and by 2005 had been working in the field for over twenty-five years. *See* EX1063, 273:22-274:1; *see also id.*, 130:20-131:21; EX2027, ¶¶2-18; POR, 10-11; EX2043. As Dr. Samulski explained at his deposition, his team's collaborative and innovative process to arrive at the specific substitutions disclosed in the '126 provisional application was far from trivial:

[I]t's not identifying a single amino acid. It's a process of narrowing down which requires, from my perspective of 50 years of this, an expert who can do crystal structures and interpret them, an expert that can do virology, and an expert that can do molecular biology. I don't think that was ordinary skill of the art in the majority of the students that I trained, including myself. I wasn't capable of carrying that out by myself. If it wasn't an expert from the crystal capability to give us GPS coordinates, we would have stayed forever with mutating 83 amino acids in combinations.

EX1063, 126:7-18; *see also id.*, 142:24-143:4 ("These were extraordinary people skilled in the art, which was why we were the first to be able to do this and the only ones to do it. You can't find another publication during this time that demonstrates these outcomes.").

Thus, in 2005, Dr. Samulski and his colleagues were on the cutting edge of the gene therapy field. As he explained at his deposition, "I think we were the lead in this and essentially all the other efforts that were going on, which meant we had

like a three or four-year head start over everybody else.” EX1063, 283:18-21; *see also id.*, 127:4-6 (“In 2004 and [200]5, I think we were the cutting edge, because everybody else was doing fragment swapping.”), 130:12-131:21 (others in the field using natural serotypes instead of modifying known serotypes), 144:6-11, 258:18-259:2. The insights and capabilities of extraordinarily skilled artisans—working behind closed doors and relying on unpublished data—are not reflective of what a POSITA, without access to this information, would have known or done in 2005. *See Standard Oil*, 774 F.2d at 454.

C. Petitioner’s New References Support Patent Owners’ Contention that a POSITA Would Have Used AAV1 or AAV7 for Muscle Targeting

Even if considered, the ’126 provisional contradicts Petitioner’s theory. It shows a POSITA would not have followed Petitioner’s path to an asparagine substitution at position 665 in AAVrh10 if the goal was to target dystrophin to muscle. Instead, a POSITA would have followed a path similar to that described in Patent Owners’ Response. *See* POR, 30-35; EX2027, ¶¶60-70.

The premise of the work in the ’126 provisional was to take the best known and characterized AAV to date—AAV2—and confer muscle targeting onto it. EX1059, 4. At that time, AAV1, AAV6, and AAV7 were “the most promising for delivery to skeletal muscle.” *Id.*; EX1072, ¶129. Therefore, it was “desirable to engineer a variant of AAV2 that exhibits the enhanced muscle tropism of AAV1, 6

and 7 but still maintains its ease of purification.” EX1059, 4. In addition to AAV2’s ease of purification, Dr. Samulski testified that regulatory concerns were central—AAV2 was the only vector FDA would allow for use in clinical trials in 2005. *See* EX1063, 106:23-107:5, 257:21-258:17.

As Dr. Samulski explained, however, the field moved toward taking other *known AAV vectors* into the clinic instead of modifying AAV2. EX1063, 130:12-131:21 (“For clinical applications, everybody went from AAV2 serotypes to natural serotypes that had predilection to go into certain cell types, muscle, liver, lung, whatever they were.”); *see also id.*, 144:6-11, 258:18-259:2. In short, a POSITA would have chosen a vector already known to perform well in muscle—such as AAV1 or AAV7. EX2027, ¶¶62-63; *see also* POR, 30-33.

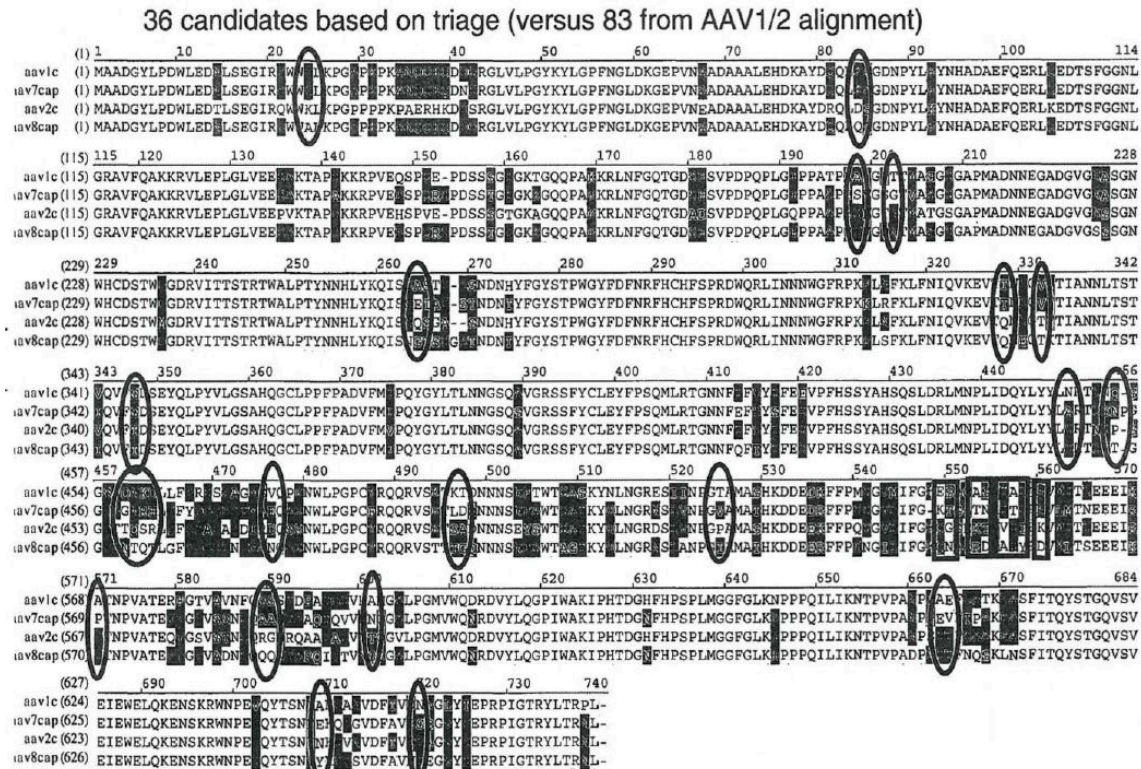
A POSITA would not have used AAV8 to target muscle. It was already known that AAV8 “provide[d] a substantial advantage over the other serotypes in terms of efficiency of gene transfer to liver[.]” EX1007, [0250]; EX2027, ¶40; POR, 14-16. A POSITA would have instead turned to either AAV1, “the best muscle transducer,” or AAV7, more recently discovered and showed “favorable tropism...for muscle[.]” EX1007, [0251], [0257]; EX2027, ¶63; POR, 32-34. In fact, AAV8 was used in Dr. Samulski’s ’126 provisional application as a *negative*

comparator because of its poor muscle performance. *See* EX1059, 5 (Fig. 1A).⁷ Specifically, the sequences of AAV1, AAV2, AAV7, and AAV8 were aligned, and “[a]mino acids similar in AAV1 and AAV7 *and distinct from AAV2 and AAV8*...were pinpointed as potential candidates.” *Id.*, 5:15-19 (emphasis added); *see also id.*, 15:9-17 (identifying AAV2 and AAV8 as serotypes “less effective in transducing skeletal muscle” than AAV1 and AAV7). Thus, a POSITA targeting muscle would have known to *avoid* amino acid substitutions from AAV8—the opposite of the path Petitioner advocates here. Notably, neither AAV1 nor AAV7 has an asparagine at position 665. *See* EX2032, 2; EX2027, ¶¶68-69.

Dr. Samulski’s team’s next steps further demonstrate that a POSITA seeking to target muscle would not have substituted an asparagine for a serine at position 665. As Dr. Samulski explained, they used sequence alignment to identify 83 amino acids that differed between AAV1 and AAV2. *See* EX1063, 113:6-17; EX1059, 64. Those 83 differences were culled to 36 by choosing amino acids found in both AAV1 and AAV7 but not found in AAV8, and based on whether the substitution would be non-conservative or conservative (more or less likely to have

⁷ References to EX1059 herein cite to the stamped exhibit page; in Dr. Samulski’s deposition, the provisional application’s filed page numbers are used.

an impact). *See* EX1063, 114:11-115:20. These 36 candidates are identified in Figure 1A, shown below by oval and rectangular boxes:



EX1059, 64 (Fig. 1A); *see also id.*, 44:21-26.

Next, Dr. McKenna used the crystal structure of AAV2 to narrow to 12 amino acids in positions likely to affect AAV biology. EX1063, 115:21-117:13. These 12 amino acids are identified in Figure 1B, noted in bullets and shown by arrows below:

12 candidates that tested based on amino acid and crystal structure analyses

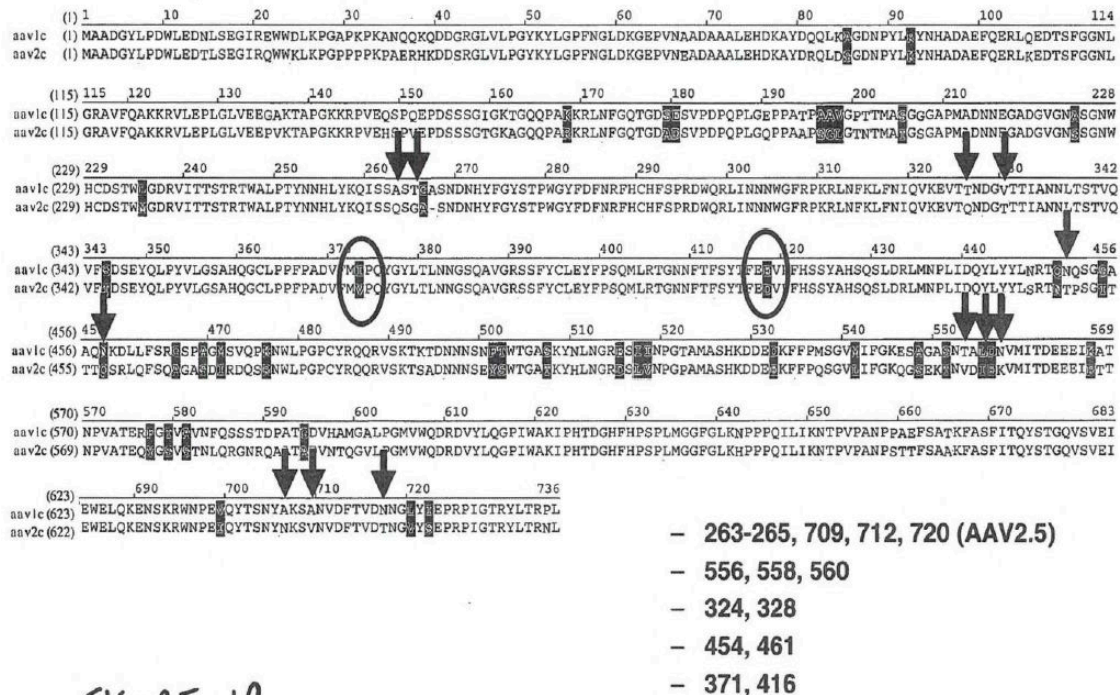


FIGURE 1B

EX1059, 65; *see also id.*, 44:26-27. Notably, no candidates were selected near position 665. EX1063, 279:17-280:4; *see also id.*, 119:23-120:21.

Further, when the twelve candidates were tested, many of them had no impact on AAV2's ability to target muscle, including a threonine to asparagine change at position 720. *See* EX1059, 45:10-19; *see also* EX1063, 186:20-188:9. In other words, changing a potentially phosphorylatable amino acid to an amino acid that cannot be phosphorylated, like the S665N substitution Petitioner proposes here, had no effect on improving muscle targeting.

Thus, the '126 provisional teaches a path different from the one Petitioner advocates—a path that would not lead to the invention of claim 8 of the '274 Patent.⁸

D. The Unpredictability of the Art in 2005 Would Not Have Motivated a POSITA to Make Petitioner's Modifications

Petitioner's argument is premised on a POSITA being motivated to make a serine to asparagine substitution at position 665 to improve AAVrh10 targeting to liver. But as described above, references like Snowdy, Jans & Jans (cited by Snowdy), the '126 provisional application, and other references demonstrate the unpredictability inherent in the field of AAV gene therapy in 2005. Petitioner's expert admits that Snowdy, "following...teachings" from Jans & Jans, found that the "results for the S181A and S181D mutations were the *opposite* of what he would have expected, based on Jans & Jans." EX1072, ¶¶461, 488 (emphasis

⁸ Petitioner's contention that Snowdy's graduate work formed the basis of the '126 provisional, (Reply, 2-3), is unsupported. Dr. Samulski—the person in the best position to know the contributions to his patents—testified specifically that Snowdy would have been a coinventor if he had contributed, and he did not. *See* EX1059, 1; EX1063, 195:13-23. Moreover, Snowdy is silent as to tissue targeting—the entire premise of the '126 provisional.

added); *see also* EX1005, ¶¶188-189. Armed with two contradictory results, a POSITA could not have predicted the results of similar mutations in different locations.

That unpredictability is reinforced by the contradictory results within Jans & Jans itself. In a separate experiment, when neighboring serines 111 and 112 were individually mutated to glycine, one substitution abolished phosphorylation while the other had no effect. EX1017, 6 (Fig. 5); *see also* EX2027, ¶¶82-85. As Dr. Samulski explained, “these contradictory effects highlight why relying on a specific substitution from one study to conclude generally that a skilled artisan would make a specific modification to a different AAV is tenuous and wholly speculative.” EX2027, ¶84. Put simply—the specific result could not have been reasonably predicted. *See* EX1063, 119:7-121:11, 125:12-133:2, 135:2-141:14, 142:12-149:6, 153:22-154:18, 186:20-191:17, 195:7-200:13, 281:11-282:13.

Petitioner’s new references further support this unpredictability. Petitioner relies on another of Dr. Samulski’s papers, Wu 2006, a non-prior art reference that investigates why AAV1 and AAV6 show different tissue targeting when they differ by only 6 amino acids. EX1060, 1; EX1063, 203:9-19. Wu created and tested twelve mutants, with each AAV mutant swapping in a different single amino acid from the other AAV. EX1060, 2 (Table 1); EX1063, 203:22-204:2. A year after the priority date of the ’274 Patent, Wu did not predict which residues would

affect targeting—he tested all twelve mutants. Nor could Wu have predicted that in three mutants, their “vector yields *exceeded those of both parent serotypes*.”

EX1060, 1. If anything, Wu taught a POSITA to mutate everything and determine the result—exactly what Patent Owners have argued was required in such an unpredictable field. POR, 30-35; EX2027, ¶¶60-70.

Kern, another new reference introduced by Petitioner (EX1068), investigated the region of AAV2 that was responsible for heparin binding. EX1068, Abstract. This investigation is entirely consistent with Dr. Samulski’s testimony regarding the state of the art at the time of the invention—that researchers were “figuring out how theses vectors worked, and determining which portions of the vectors were important for specific AAV functions.” EX2027, ¶27; *see also id.*, ¶¶25-26. Kern’s study, like Dr. Samulski’s studies, compared AAV sequences, identified regions of interest, and then made 33 different mutants, each with 1-4 amino acid substitutions, and tested each in HeLa cells. *See* EX1068, 4 (Table 1). Kern’s work is irrelevant to claim 8: it does not relate to targeting dystrophin to muscle tissue, to AAVrh10 or AAV8, to serine to asparagine mutations, or to the region of the capsid with position 665. *See* EX1068, 3 (mutants identified between amino acids 443 and 602). The incidental discovery in Kern—a non-ground reference absent from the Petition—that specific mutations at positions 484 and 585 in AAV2 *de-targeted* liver and instead targeted heart is irrelevant to

Petitioner's burden to show a motivation to make the specific S665N substitution in AAVrh10 with the purpose of *targeting* liver. Given the unpredictability underlying all of Petitioner's references and the field of gene therapy at large, a POSITA would not have been motivated to arrive at the claimed invention.

IV. CONCLUSION

For each reason stated herein, the Petitioner has not shown by a preponderance of the evidence that claim 8 of the '274 Patent is unpatentable.

Respectfully submitted,

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CERTIFICATION UNDER 37 CFR § 42.24

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Patent Owners' Sur-Reply totals 5,578 words, which is less than the 5,600 allowed under 37 CFR § 42.24(c)(4).

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e), the undersigned certifies that on April 24, 2025, a complete and entire copy of this Patent Owners' Sur-Reply and accompanying exhibit were provided via email to the Petitioner by serving the email correspondence addresses of record as follows:

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