

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

IPR2024-00580
Patent 11,680,274 B2

Held: May 27, 2025

BEFORE: JEFFREY N. FREDMAN, ULRIKE W. JENKS, and
SUSAN L. C. MITCHELL, Administrative Patent Judges.

IPR2024-00580
Patent 11,680,274 B2

APPEARANCES:

ON BEHALF OF THE PETITIONER:

ROBERT B. WILSON, ESQUIRE
ANNE S. TOKER, ESQUIRE
Quinn Emanuel Urquhart & Sullivan LLP
295 5th Avenue, 9th Floor
New York, NY 10016
(213) 430-8212
robertwilson@quinnemanuel.com
annetoker@quinnemanuel.com

ON BEHALF OF THE PATENT OWNER:

SUSAN E. MORRISON, ESQUIRE
CASEY M. KRANING, Ph.D., ESQUIRE
Fish & Richardson, P.C.
222 Delaware Avenue
17th Floor
Wilmington, DE 19801
(302) 778-8434
morrison@fr.com
cmk@fr.com

JULIE S. GOLDEMBERG, ESQUIRE
Morgan, Lewis & Bockius LLP
2222 Market Street
Philadelphia, PA 19103
(215) 963-5095
julie.goldemberg@morganlewis.com

The above-entitled matter came on for hearing on May 27, 2025,
commencing at 1:00 p.m., via video teleconference.

P R O C E E D I N G S

- - - - -

JUDGE MITCHELL: Good afternoon, everyone. You can be seated. So, good afternoon again, everyone. We have a final hearing this afternoon in IPR2024-00580. I am Judge Mitchell, and to my right is Judge Fredman, and with us by videoconference is Judge Jenks.

So, I'd like to get appearances before we get started. So, who do we have for Petitioner?

MR. WILSON: Good afternoon, Your Honor. My name is Robert Wilson from Quinn Emanuel Urquhart & Sullivan, and I'm here on behalf of Petitioner, Sarepta Therapeutics. And with me at counsel table is my colleague, Anne Toker.

JUDGE MITCHELL: Great, thank you, and welcome. And who do we have for the Patent Owner?

MS. MORRISON: Good afternoon. Susan Morrison from Fish & Richardson on behalf of Patent Owner. And with me today at counsel table is Casey Kraning, also of Fish & Richardson, and also present is Julie Goldemberg from Morgan Lewis, who represents the University of Pennsylvania.

JUDGE MITCHELL: Great, thank you, and welcome. So, as set forth in our oral hearing order, each side has 60 minutes to present its case. Just a reminder to assist us in following along with your argument and for the clarity of the record when we go back and take a look, if you would refer to an exhibit by number and what page you're on or what demonstrative you're on, just so we can sort of follow the flow too, when we go back and

1 read through the transcript. Petitioner will present its arguments first, as it
2 bears the burden of showing unpatentability of the challenged claims. So
3 Petitioner, would you like to reserve some time for rebuttal?

4 MR. WILSON: I would, Your Honor. I'd like to reserve 15
5 minutes as my time for rebuttal, please.

6 JUDGE MITCHELL: Great. And let me go ahead and ask Patent
7 Owner, because you will have the last word, if you wish. Would you like to
8 reserve any of your time?

9 MS. MORRISON: I would, Your Honor. I'd like to also reserve
10 15 minutes. Thank you.

11 JUDGE MITCHELL: Great, and I'll just set up the clock, and
12 whenever you're ready.

13 MR. WILSON: Thank you, Your Honor. Also, I brought hard
14 copies of our demonstratives if that would be helpful for the Court, if there
15 are any clerks or if any other additional copies are necessary.

16 JUDGE MITCHELL: I would take one. I'm a little old school, so
17 hard copies are nice.

18 MR. WILSON: And I don't know if the court reporter needs a
19 copy or if she has a copy? Okay.

20 So, good afternoon, Your Honors. I'd like to start by really
21 focusing on the specific issue that remains for the Panel to decide in this
22 case. As you're aware, there have been some developments, particularly
23 since the surreply was filed, and so I would like to focus on what counts are
24 still at issue, and then what issue the Panel specifically needs to decide in
25 order to resolve that count. So first, I'd just like to turn to Slide 2 in our slide
26 deck. Slide 2 summarizes the grounds that were asserted in the Petition.

1 And as the Panel is aware, there were six grounds that were
2 originally asserted, and there were six challenged claims. In the surreply,
3 Patent Owner has disclaimed five of the claims, Claims 1, 3, 4, 5, and 6. So
4 they have been disclaimed. So I've shaded in this slide Grounds 1, 2, and 3,
5 which address those claims, and the remaining counts are 4, 5, and 6. And
6 there's one claim at issue, Claim 8.

7 In the Institution Decision, the Panel considered all six of the
8 grounds and found that actually Grounds 3 and Ground 6, which involve the
9 references of the '772 Publication and the Snowdy thesis to be the strongest
10 arguments. So taking the guidance of the Panel in the Institution Decision, I
11 will focus my arguments on the one remaining ground, Ground 6, that
12 relates to Claim 8. And the references for Ground 6 are the combination of
13 the '772 Publication, the Snowdy thesis, and Fabb.

14 So, turning to Slide 4, Slide 4 reproduces the language of Claim 8.
15 And I'll just be very brief here but Claim 8 is a dependent claim from Claim
16 6, and Claim 6 in turn is dependent from Claim 1. And Claim 1 is directed
17 to a recombinant AAV vector, and the vector has a capsid and a mini-gene,
18 and the mini-gene has a heterologous gene within in it. Claim 1 also talks
19 about the amino acid sequence of the vp1 proteins in the capsid and specifies
20 a sequence that is the same as a variant called rh.46, or a sequence that's 95
21 percent identical to that sequence, and Claim 1 also specifies that a position
22 665 in the vp1 capsids, the amino acid is asparagine, or M.

23 Claim 6 depends from Claim 1 and specifies a long list of possible
24 heterologous genes that can be packaged into the AAV capsid. And one of
25 those genes is referenced way down at the bottom, it's highlighted in the
26 slide, it's a dystrophin gene product. And then Claim 8 further narrows

1 Claim 6 and specifies that the dystrophin gene product is either a mini-
2 dystrophin or a micro-dystrophin.

3 So there's really only one issue left for the Panel to decide, given
4 the disclaimer of Claim 1 and Claim 6. And Patent Owner is not defending
5 the patentability of the vector as it's recited in Claim 1. They're not
6 defending the patentability of the list of heterologous genes that's recited in
7 Claim 6. Instead, Patent Owner's argument is about the specific
8 combination in Claim 8. And Patent Owner --

9 JUDGE FREDMAN: Let's go back, because that may be the case,
10 but you still have to prove that Claim 1 is obvious, and the fact that they've
11 disclaimed it doesn't mean that limitation doesn't matter. So let me first ask,
12 you talk a lot, and I think both parties talk a lot, about transduction and
13 tropism. Can you explain what you think the difference between those two
14 terms is?

15 MR. WILSON: Yes. So that's actually referred to in one of the
16 primary references, the '772 Publication, and I will fast forward to that. This
17 is Slide 8, which talks about the motivation to select rh.10. And in the '772
18 Publication, it talks about testing for tropism. And tropism is described -- is
19 discussed in terms of the rh.10 variant, which is referenced in Slide 8. And
20 tropism here, it's talking about the superb tropism of rh.10 in lung-directed
21 gene transfer. And so tropism refers to or encompasses transduction.

22 JUDGE FREDMAN: Right, so tropism is typically understood by
23 virologists as the cell type to which the virus would bind, right? Whether it's
24 a lung cell, a kidney cell, a liver cell, or whatever. Transduction is the
25 process by which the virus gets into the cell and has nuclear translocation,
26 for example, in this case.

1 MR. WILSON: Well, I think that the way that the '772 Publication
2 uses those terms is that transduction efficiency, transduction is a part or is a
3 component of tropism. So tropism, the way that it's used in the primary
4 reference, is not only the targeting of a particular cell type, but it's also the
5 expression of the heterologous gene in the cell. So when the applicants in
6 the '772 Publication are talking about tropism, they also refer to how much
7 expression am I getting. That's how they measure the expression in that
8 example.

9 JUDGE FREDMAN: So the argument you're making is that
10 essentially if you bind to the cell, but you don't express in the cell, it doesn't
11 do you any good?

12 MR. WILSON: I would say that it doesn't do you any good and it
13 doesn't do you any good in the way that the applicants in the '772
14 Publication defined and measured tropism. So they were looking for
15 expression in particular cells and looking at the level of expression as the
16 measure or the gauge of tropism.

17 JUDGE FREDMAN: Well, the claim actually doesn't require any
18 particular tropism, does it?

19 MR. WILSON: That's a very good point, Your Honor. Yes, that's
20 correct. So the claim is a construct. The claim is directed to the AAV
21 construct and Claim 8 specifically is then directed to that vector with a
22 dystrophin mini-gene or micro-gene packaged within it. It doesn't require --

23 JUDGE MITCHELL: I hate to interrupt you, but I think I just lost
24 one of our judges.

25 MR. WILSON: Understood.

26 JUDGE FREDMAN: Are you pausing the time for them?

1 JUDGE MITCHELL: That's fine, yes.

2 JUDGE FREDMAN: Commercial break.

3 (Whereupon, the above-entitled matter went off the record at 1:15
4 p.m. and returned at 1:17 p.m.)

5 JUDGE MITCHELL: Sorry about the interruption. Go ahead and
6 proceed.

7 MR. WILSON: Thank you. So, Your Honor, you were asking
8 about Claim 8, and I've put Slide 4 back up on the screen, which is the
9 summary of Claim 8. And as you say, Claim 8 does not require expression,
10 it doesn't require any kind of tropism in particular, it doesn't specify that
11 there has to be some sort of clinical application or effect. It's the construct;
12 it is an AAV vector that has a mini or micro-dystrophin gene packaged in it.
13 And so if a POSA would be motivated to make that construct, which they
14 would be in light of the primary references in Ground 6 --

15 JUDGE FREDMAN: So let me ask that question, let's jump to that
16 motivation.

17 MR. WILSON: Yes, sir.

18 JUDGE FREDMAN: So, you certainly have the AAV vector in
19 your prior art, you then have the 95 percent identity in the prior art, it
20 appears to me. What specifically targets us to the position 665 in the
21 sequence, in particular making an asparagine substitution at that location?

22 MR. WILSON: Yes, sir. So let me put up the Slide 5, which is
23 Ground 6. And what this slide shows is the combination of the three
24 references that are asserted in Ground 6, and on the left-hand side is the '772
25 Publication, and on the right-hand side is Snowdy and Fabb.

26 Starting with the '772 Publication, that publication really directs

1 you to the rh.10 variant. It describes it as having intriguing biological
2 significance, and it says that that vector is a potent vector in three different
3 tissues. So it's highlighting this unique quality of rh.10. In particular, it
4 talks about rh.10 having superb tropism in lung, and outstanding tropism in
5 liver and muscle.

6 And then it goes on and compares rh.10 with this outstanding
7 tropism in all three different tissues, it compares it to other variants, and it
8 talks about rh.10 is close to the best liver transducer, AAV8, and the best
9 muscle transducer, AAV1.

10 And then the '772 Publication teaches -- has an additional teaching
11 about liver tropism in particular, and it basically says, tropism in liver has
12 been relatively disappointing. And so it's been difficult for researchers to
13 get vectors or define vectors with good liver tropism. So that provides a
14 motivation for a person of ordinary skill in the art to take rh.10, which has
15 this intriguing significance and this excellent tropism in all three of these
16 tissues, and see if it can dial up the transduction or the tropism in liver to
17 make it as good, or at least to confer some of the additional liver tropism of
18 AAV8 onto rh.10. And what that would motivate a person of skill in the art
19 to do is to align the two sequences, align the rh.10 sequence and the AAV8
20 sequence and look at differences.

21 JUDGE FREDMAN: Right, so when you do the alignment, there
22 are 48 differences, is that correct?

23 MR. WILSON: Correct, Your Honor.

24 JUDGE FREDMAN: Okay, and how many of those are cross
25 phosphorylatable or whatever?

26 MR. WILSON: Right, so that's the application of the teaching in

1 Snowdy. So Snowdy says, look, I found that if I substitute a
2 phosphorylatable amino acid for a non-phosphorylatable amino acid, my
3 transduction goes sky high, way up. And so a person of skill in the art
4 applying that principle from Snowdy to the '772 Publication would then look
5 at those 48 positions where there's a difference between rh.10 and AAV8,
6 but then they would be more specific than that.

7 Instead of just looking for a difference, they would be looking for
8 positions where rh.10 has a phosphorylatable amino acid, and AAV8 has a
9 non-phosphorylatable amino acid. That's applying the teaching of Snowdy.
10 And to your question, Your Honor, out of the 48, there are four positions
11 that have that unique difference.

12 JUDGE FREDMAN: And would a motivation be to remove the
13 phosphorylatable, or would it be to add it?

14 MR. WILSON: To remove the phosphorylatable amino acid. So
15 Snowdy removed a phosphorylatable amino acid, replaced it with a non-
16 phosphorylatable amino acid and saw transduction efficiency go up. So a
17 POSA motivated to confer additional liver tropism --

18 JUDGE FREDMAN: How many amino acids are
19 phosphorylatable?

20 MR. WILSON: There would be four positions --

21 JUDGE FREDMAN: Four positions. How many of the 20 amino
22 acids would be phosphorylatable?

23 MR. WILSON: Well, there are four positions in the rh.10 in the --

24 JUDGE FREDMAN: Right, you wouldn't want to substitute any
25 of the other 19?

26 MR. WILSON: Right, but you would be looking to substitute the

1 amino acid from AAV8. Not just a non-phosphorylatable --

2 JUDGE FREDMAN: Why, necessarily?

3 MR. WILSON: Because AAV8 works. AAV8 is taught to have
4 this additional liver tropism, and so the '772 Publication is saying oh look,
5 we've got really good liver tropism in AAV8, so a POSA would be
6 motivated not just to substitute it with any non-phosphorylatable amino acid,
7 but would look specifically to the AAV8 sequence --

8 JUDGE FREDMAN: And AAV8 has an asparagine at that
9 position.

10 MR. WILSON: And it has an asparagine at position 665 as one of
11 the four positions that a POSA would identify where rh.10 is
12 phosphorylatable and AAV8 is not. So the motivation would be to take the
13 amino acids from AAV8 and put it into rh.10 in each of those vector
14 constructs. And so a POSA would be motivated to make all four of those
15 vector constructs, and as you say, Your Honor, one of those vector
16 constructs would be a serine substitution to an asparagine substitution at
17 position 665. Okay?

18 So the issue that really remains for the Panel to decide, and what
19 Patent Owners argue, is would a POSA be motivated now that they have
20 created these four vectors. They've created these modified vectors based on
21 the teaching of the '772 Publication, would a POSA be motivated to package
22 a micro-dystrophin or a mini-dystrophin gene into that construct? And the
23 answer is absolutely yes, there is that motivation.

24 The POSA is motivated to make the modified rh.10, that's what
25 '772 and Snowdy teach us, and a POSA is thinking -- when they're thinking
26 about rh.10, they're thinking about tropism in all three of these tissues,

1 because that's what the '772 Publication teaches us. It highlights that it has
2 excellent tropism in liver, muscle, and lung.

3 So that's the intriguing biological significance that the '772
4 Publication identifies. So when a POSA has modified rh.10 in order to dial
5 up the lung tropism and to preserve tropism in muscle and in lung, then a
6 POSA would naturally be motivated to use that modified or that improved
7 rh.10 in all three tissues. And basically putting a dystrophin gene in a
8 modified rh.10 vector, which has been designed to preserve its excellent
9 muscle tropism, is an obvious combination. And that's not a patentable
10 distinction for Claim 8.

11 JUDGE MITCHELL: Let me ask you this, because I know Patent
12 Owner argued that, hey, you really kind of shifted your motivation to, you
13 know, combine the teachings to get to Claim 8. So I think they were saying
14 that, you know, when you're talking about preserving excellent tropism in
15 muscle in lung at the same time that you're improving liver, because you
16 know there's not a great vector for liver according to this '772 Publication, so
17 where is that in the original declaration from your expert, to sort of walk us
18 through that motivation?

19 MR. WILSON: Yes, let me walk you through that, Your Honor.
20 So the motivation has always been to improve liver transduction but also
21 maintain transduction in muscle and lung. And it makes no sense, as an
22 initial matter, it makes no sense to improve one of these tropisms at the
23 expense of the other, because the '772 Publication highlights the unique
24 biological significance as tropism in all three tissues.

25 JUDGE FREDMAN: Can you point to where the Petition and the
26 experts say that?

1 MR. WILSON: Yes. So if we turn to Slide 12, Your Honor. I
2 have Slide 12 up on the screen, and Slide 12 is an excerpt from the Petition,
3 and what the Petition says is that a POSA would be motivated to make
4 single amino acid substitutions from AAV8 to rh.10 in order to preserve the
5 existing desirable properties, or the way the Petition frames it, for fear of
6 damaging or destroying the desirable properties of AAV rh.10. And so the
7 motivation is that you don't want to take a wrecking ball to rh.10; you want
8 to use single amino acid substitutions, because you don't want to destroy,
9 you don't want to lose the already excellent tropism that it has in liver --

10 JUDGE FREDMAN: Does the word tropism show up there?

11 MR. WILSON: Well, we have the desirable properties in the
12 Petition, and if you turn to Slide 13, this is an excerpt from the reply
13 declaration of our expert --

14 JUDGE FREDMAN: Do you have it in the original declaration?

15 MR. WILSON: And he has, in the original declaration, and it's
16 cited here, he talks about for fear of damaging or destroying the desirable
17 properties. When he was asked at his deposition about this, he said fear of
18 the desirable properties includes muscle and --

19 JUDGE FREDMAN: He still didn't respond to the question that
20 was -- he knew that after, that that was an issue, he didn't say before, though.

21 MR. WILSON: He did say that before, Your Honor. He said that
22 in terms of the, his opinions regarding making single amino --

23 JUDGE FREDMAN: Does he define the desirable properties in
24 his original declaration?

25 MR. WILSON: He does not -- here, he does not. He defines it
26 here as in all the desirable properties --

1 JUDGE FREDMAN: As a --

2 MR. WILSON: He's saying that that's what he meant.

3 JUDGE FREDMAN: Okay.

4 MR. WILSON: But he's focused, in his original declaration and
5 the Petition, on the unique characteristic of rh.10. So there hasn't been a
6 shift in motivation. It's always been about the three tropisms in that
7 particular variant. There's been no shift, and there was no shift at his
8 deposition, and there's no shift in his reply declaration. He included and
9 includes the excellent tropism in muscle and lung in the desirable properties
10 that a POSA would want to preserve, even as they're making changes to
11 rh.10. And again, the unique biological characteristics and his references to
12 rh.10, when he was asked about those at his deposition, he also testified that
13 that includes all of the properties. When you're thinking about rh.10, in light
14 of the '772 Publication, you're thinking about the multiple tropism in all
15 three tissues. That's what makes it so unique for a person of ordinary skill in
16 the art, and that's what makes it unusual, and why a POSA would start with
17 that in the first place. But a POSA is not going to want to lose those unique
18 characteristics in favor of one tropism or another.

19 The motivation in the '772 Publication, and this is discussed
20 throughout the Petition and throughout Dr. Schaffer's declaration, is to dial
21 up or just increase that incremental amount of liver tropism, to see if you can
22 take some of that property from AAV8 and confer it onto rh.10. So implicit
23 within that motivation is that you want to maintain the already excellent and
24 interesting properties of rh.10 without destroying that in a modified version.

25 JUDGE MITCHELL: Let me ask you this. So, the claims are to
26 the particular construct, right? So we're not talking about actually treatment,

1 getting it into the cells to treat any diseases. So should we be as concerned
2 at all that we're looking at whether it's muscle, lung, liver, do we need to
3 worry about the tropism, or can we look and say it's a good vector, you
4 might want to make this, you know, produce it in a lab, and that would be
5 within the Claim 2? So do we have to be -- how concerned do I have to be
6 about where this is potentially going?

7 MR. WILSON: I think that's an excellent point, Your Honor, and I
8 don't think you have to be concerned about where it's going. Really, the
9 obviousness analysis is, would a person be motivated to make this construct
10 for whatever reason? It could be for scientific interest, it could be for
11 research interest, it could be in vivo, in vitro, but it doesn't have to have a
12 clinical effect, it doesn't have to have some sort of expression, and we lay
13 this out in the reasonable expectation of success.

14 It's really just forming the construct is all Claim 8 is directed to
15 here. There's no requirement of any particular use, and a POSA doesn't have
16 to be motivated to use it for anything; they just have to be motivated to put
17 these two things together. And as you say, rh.10 is already excellent in these
18 three tissue types. A modified rh.10, a POSA motivated to modify rh.10 to
19 increase that liver tropism and at the same time maintain tropism in muscle
20 and lung, of course they would use it on all three types. They would be
21 motivated to combine it with all sorts of potential genes in all three of those
22 tissues.

23 And again, as you say, they don't have to obtain an effect. They
24 don't have to show any particular clinical result or any threshold of tropism
25 in any tissue. The motivation to make that combination is there, and that's
26 what rendered Claim 8 obvious.

1 JUDGE MITCHELL: Thank you.

2 MR. WILSON: All right. Patent Owners also argue that the
3 person of ordinary skill would just use the best vector in a particular tissue,
4 and for muscle they point to AAV1 and AAV7, and they say, oh, you just
5 use the best naturally occurring vector. And that's inconsistent with the
6 disclosure in the '772 Publication and what it teaches. And if we take a look
7 at Slide 15, this Slide 15 is paragraph 142 of the '772 Publication, and the
8 first two sentences in this paragraph talk about certain vectors being
9 particularly useful in particular tissues.

10 And Patent Owner interestingly quotes these two sentences, the
11 two sentences that are not highlighted at the beginning, in their response, but
12 they don't cite the following two sentences in the '772 Publication. And
13 that's important because the '772 Publication teaches that the use of these
14 vectors is not limited just to the best natural transducers.

15 What the first sentence says, in the highlighted section, is that uses
16 of the vectors are not so limited. So AAV7 can be used in more than just
17 muscle, rh.10 can be used in more than just lung, and more specifically than
18 that, it talks about one of skill in the art may utilize these vectors for delivery
19 to other cell types, tissues or organs. So AAVs may be used in more than
20 just the tissues where they are the best transducer. And more than that, a
21 person of ordinary skill would be able to do that. So it's well within the
22 level of ordinary skill for a POSA to use AAVs in different tissues or organs.
23 They would not just necessarily use the best transducer in a particular tissue.

24 JUDGE FREDMAN: So if we could jump back. This is
25 interesting, but not really what my focus wants to be on. Can we go back to
26 Snowdy for a minute?

1 MR. WILSON: Yes, sir.

2 JUDGE FREDMAN: Okay, Exhibit 1009, page 111 of the
3 reference, page 125 of the exhibit, it talks about the phosphorylation of the
4 protein as the reason to knock it down. That was phosphorylation in the
5 nuclear localization signal, right?

6 MR. WILSON: It was phosphorylation, it was a substitution in
7 three particular positions --

8 JUDGE FREDMAN: And all three of those are located in the
9 NLS, correct?

10 MR. WILSON: Well, Dr. Snowdy was looking at those positions
11 because he felt that they might be associated with an NLS, but --

12 JUDGE FREDMAN: And all those positions, they were 148, 159,
13 and 181?

14 MR. WILSON: Correct.

15 JUDGE FREDMAN: Okay, and those aren't anywhere near the
16 position you're changing, right?

17 MR. WILSON: That's correct, but Snowdy teaches something
18 more general than that. Snowdy is not focusing, in this experiment, the
19 result doesn't relate just to an NLS. What Snowdy is seeing is he's
20 substituting these phosphorylatable amino acids with non-phosphorylatable
21 amino acids, and he's seeing at position 181 a marked increase in
22 transduction. That's surprising to me.

23 JUDGE FREDMAN: Right, but the transduction could be due to
24 nuclear localization, because it's in the nuclear localization signal.

25 MR. WILSON: It could be due to nuclear localization --

26 JUDGE FREDMAN: It may be relevant to position -- 66-whatever

1 position?

2 MR. WILSON: It could be due to anything. Dr. Snowdy doesn't
3 specify what --

4 JUDGE FREDMAN: But so you're trying to carry -- change at
5 one position to a position that's 400, 500 amino acids away?

6 MR. WILSON: But I think, again, the teaching is more
7 generalizable than that.

8 JUDGE FREDMAN: Where do you have that in there?

9 MR. WILSON: Because Dr. Snowdy talks about it in his thesis,
10 Your Honor.

11 JUDGE FREDMAN: Where does he say that?

12 MR. WILSON: Let me just jump to that slide. Right, and --

13 JUDGE FREDMAN: If he says we examined -- in that page 114
14 of this thesis, we examined the importance of several possible
15 phosphorylatable cites near punitive nuclear localization signal of AAV2. It
16 doesn't say that this was necessarily effective for other locations of that
17 protein.

18 MR. WILSON: Well, a couple of points. So I've put up Slide 30
19 from the Snowdy thesis, and this describes the three positions and what
20 happened when Dr. Snowdy substituted phosphorylatable amino acids for a
21 non-phosphorylatable amino acid and then substituted the phosphorylatable
22 amino acid for an amino acid that appears to be constitutively
23 phosphorylated. And this section, this experiment in the Snowdy thesis is in
24 a separate section from the nuclear localization discussion that you're
25 referring to in Snowdy's thesis.

26 JUDGE FREDMAN: So why did Dr. Snowdy choose these three

1 or four?

2 MR. WILSON: They're near the nuclear localization signal, but
3 they're not in the NLS, and Dr. Snowdy was looking to see if it would have
4 an effect on nuclear localization, but he got an unexpected result. He
5 expected that if it had to do with nuclear localization, that substituting the
6 phosphorylatable amino acid for a non-phosphorylatable amino acid would
7 destroy functionality. And he got actually the opposite result. So that -- he
8 talks about it in his thesis --

9 JUDGE FREDMAN: So you're saying that essentially when it was
10 within the nuclear localization signal, you eliminated the function, but when
11 you were outside of the nuclear localization signal it still had the function.
12 Is that what you're trying to say?

13 MR. WILSON: Well, none of the substitutions were made in the
14 nuclear localization signals. He was looking at regions around what he
15 thought was a punitive nuclear localization signal. He got the unexpected
16 result for position 181 and said, oh, well this is not related to the nuclear
17 localization signal in the way that I thought it was. It's a more generalizable
18 principle, that by substituting this phosphorylatable amino acid for a non-
19 phosphorylatable amino acid, I'm getting an increase in transduction
20 efficiency, and that's not necessarily related. He says specifically in this
21 thesis, that's not -- we can't attribute that to a nuclear localization signal;
22 that's just something that's happening independent of that.

23 JUDGE FREDMAN: You could say that that would happen,
24 there's a presumption it would happen at other spots? Or just these spots?

25 MR. WILSON: Yes, because --

26 JUDGE FREDMAN: Based on what?

1 MR. WILSON: Well, based on the fact that it wasn't something
2 that he thought was going to be keyed into the nuclear localization signal,
3 and he's seeing that independent of that. Also, a person of skill in the art
4 would understand also that phosphorylation is important for stability, and
5 that removing potential phosphorylation site would improve potentially the
6 stability of the AAV capsid. So those two things are --

7 JUDGE FREDMAN: Where is that supported?

8 MR. WILSON: That's the state of the art, Your Honor, that's --

9 JUDGE FREDMAN: Is it in the record as that, or that's just your
10 statement?

11 MR. WILSON: Yes, yes. So, again, it's in Snowdy, when he's
12 talking about --

13 JUDGE FREDMAN: Is there a specific teaching?

14 MR. WILSON: That's in the Petition at 47 to 48, Your Honor.

15 JUDGE FREDMAN: Petition, thank you. Because I guess my
16 question is, I mean, with 48 different possible changes, you're making an
17 assumption that I think it's the phosphorylation at this additional site would
18 have the same effect as the one near the nuclear localization signal. And I'm
19 not 100 percent sure I believe that, having worked on other virus proteins,
20 and I'm not 100 percent sure that given the number of possible changes --
21 we're in a *Baird* situation, right? And *In re Baird*, as you probably
22 remember, a long time ago, it was a clinical case, but it was, a large genus
23 did not render a species obvious. And now it seems to me that we're at least
24 somewhat close to that in some cases here.

25 MR. WILSON: Well, I don't think that we're looking at a large
26 genus, because again, we've only got four positions when you do a

1 sequence --

2 JUDGE FREDMAN: Your sequence, though, right? Your 48, and
3 then the question is, why are we getting down to those four? You're saying
4 phosphorylatable, I'm saying I'm not sure that it's fair to take information
5 regarding a nuclear localization signal or amino acids near that and just
6 transfer them, 500 amino acids, and say well, the same things are going to
7 apply.

8 MR. WILSON: But again --

9 JUDGE FREDMAN: He doesn't have any evidence of anything at
10 the other distal end of the protein.

11 MR. WILSON: But Dr. Snowdy, again, in his thesis he talks about
12 the nuclear localization in the first two sections of his thesis. This is the
13 third section of his thesis where he has made these single amino acid
14 substitutions and is setting that apart. And he sets it apart in the introduction
15 as well where he says, you know, we also made these substitutions in order
16 to investigate nuclear localization, but actually found a result that we didn't
17 expect, and here's the result. And that result, then, leads and teaches a
18 POSA that taking these phosphorylatable amino acids and replacing them is
19 something that may increase transduction efficiency. And so, it's a separate
20 teaching in Snowdy that he separates out from his nuclear localization
21 experiments from the thesis itself.

22 JUDGE FREDMAN: The concern I have is that changes in a
23 protein and a viral surface protein of a virus that are distant have
24 significantly different effects. And I'm more familiar with adenovirus than
25 adeno-associated virus, but that's definitely the facts for other viruses, you
26 know? For HIV, for example, too. So -- okay, I hear what you're saying.

1 MR. WILSON: Okay. I'm looking at the clock on the wall, it says
2 13 minutes, I don't know if that was 13 minutes from 45, or if that's 13
3 minutes from --

4 JUDGE MITCHELL: No, that's at 45.

5 MR. WILSON: That's at 45 -- thank you.

6 JUDGE FREDMAN: You still have your 15 minutes.

7 MR. WILSON: Great, okay, very good. Okay.

8 Patent Owners also talk about off-target expression and the
9 concern about potential toxicity. And that argument is inconsistent with the
10 disclosure in the '772 Publication. First, the '772 Publication does not
11 identify liver tropism as something that should be avoided. It actually says
12 that a single vector with tropism in these three tissues, including liver, is
13 actually an intriguing, biologically significant thing. And so the '772
14 Publication also talks about liver tropism being difficult to get, and the
15 concern is actually then getting liver tropism, not dialing back. So based on
16 the just basic teachings of the '772 Publication, liver toxicity is not an issue
17 that a POSA would be concerned about for off-target expression.

18 To the extent that off-target expression is an issue, the '772
19 Publication also discloses many different ways to avoid or modulate off-
20 target expression, and I will put up Slide 20. This is paragraph 111 from the
21 '772 Publication, and what paragraph 111 of the '772 Publication says is that
22 if you are interested in focusing your expression, then a tissue-specific
23 promoter is one way to go. So if I'm interested in muscle expression then I
24 should use a muscle-specific promoter, and then that way I'll avoid off-target
25 issues. Slide 21 talks about -- is an excerpt from paragraph 150 and 242 of
26 the '772 Publication, and it talks about another way to avoid off-target

1 expression is to basically control your route of administration. So if you're
2 looking to maintain the vector in a certain area, inject it directly, so you can
3 inject it directly into muscle or another organ.

4 And then finally, 24, and this is an issue that's particularly
5 important and that the Patent Owners don't have a response to, but another
6 way to avoid or to mitigate off-target expression is, there is a difference --
7 and this is testimony from our expert, Dr. Schaffer. And what Dr. Schaffer
8 says is that there's a difference between biodistribution and infectivity. And
9 what he means by that is that you can increase transduction, you can ramp
10 up or dial up transduction efficiency, and you don't actually have to increase
11 the dosage of the virus. And in fact, if you dial up or you ramp up
12 transduction efficiency, you might be able to lower the dosage of the virus
13 and actually improve the safety overall.

14 So this is an important point, because Patent Owners assume that if
15 you're going to increase transduction, you have to increase the dose, and
16 that's not necessarily the case. You can actually improve transduction
17 efficiency, you'll get distribution of the virus in the same way, but you can
18 even lower the dose so that you don't get as much distribution to off-target
19 tissues as you would under the original dosage.

20 And finally, let me turn back to Slide 5. We've talked about the
21 '772 Publication and we've talked about Snowdy. I want to talk a little bit
22 about Fabb as well, because that's important for the combination. The final
23 reference, at the lower right-hand side, is Fabb, and Fabb teaches a micro-
24 dystrophin gene construct that can be packaged in an AAV. So the
25 dystrophin gene and the dystrophin cDNA for that matter is very long, it's
26 too large to be packaged, and so Fabb discloses a micro-dystrophin construct

1 that is small enough to be packaged within the AAV. Fabb also tested the
2 disclosed micro-dystrophin gene construct in an animal model and found
3 that the dystrophin construct was expressed and it restored function in
4 muscle.

5 And so Patent Owner has argued that the Petition doesn't talk about
6 targeting muscle, but muscle targeting is built into the references in Ground
7 6, it's built into the '772 Publication because it's talking about rh.10 having
8 excellent tropism in muscle, and it's built into Fabb which teaches you not
9 only how to get a dystrophin construct but also to package it in AAV and get
10 expression and actually a result in an in vivo animal model.

11 Patent Owner also argues that Claim 6 requires expression in
12 muscle, and this goes back to your earlier point, Your Honor, and your point,
13 the claim -- Ground 6 does talk, and it incorporates expression in muscle in
14 the references that we disclosed, but we don't need that for a finding that
15 Claim 8 is unpatentable. You know, again, Patent Owner mischaracterizes
16 the claim in their sur-reply when they talk about the Claim 8 requiring
17 expression in muscle. It does not. Slide 4 makes that completely clear. It
18 doesn't require expression in muscle, it doesn't require specific tropism. So
19 all Claim 8 requires is a construct that includes the AAV vector with the
20 particular sequence and a micro- or mini-dystrophin gene packaged within
21 that vector. All right?

22 Just to conclude, putting up Slide 5 again and looking at Ground 6,
23 Patent Owners never really address the combination of references that we're
24 talking about here. They don't address the actual teachings in the '772 Patent
25 and Snowdy as individual references, but more than that, they don't address
26 how the combination fits together. They make arguments about, Snowdy

1 doesn't disclose this or that, but we're not arguing that. We're arguing that
2 those elements are found in the '772 Publication. The '772 Publication has
3 the intriguing biological significance of rh.10. It would motivate a person of
4 skill in the art to look at rh.10 in comparison with AAV8 and to apply the
5 teaching of Snowdy to identify those four positions where rh.10 is
6 phosphorylatable, and the -- I'm sorry, yes, where rh.10 is phosphorylatable
7 and AAV is not.

8 So with that modified vector in hand, when the POSA has made
9 that vector, they would be motivated to use it in any of the three tissues:
10 muscle, liver, or lung. For a modified rh.10 vector which has been made and
11 has been designed to preserve excellent muscle tropism, a micro-dystrophin
12 gene construct is a straightforward choice. And for that reason, there is
13 motivation to make the construct, and Claim 8 is unpatentable.

14 JUDGE MITCHELL: Thank you.

15 MR. WILSON: Thank you, Your Honors.

16 MS. MORRISON: Your Honors, if we might -- I'm not sure how
17 we make the slides display for the benefit of the gallery? Oh, my apologies.
18 My apologies, Your Honors. Something so tricky as the power button.

19 JUDGE MITCHELL: Whenever you're ready.

20 MS. MORRISON: All right. Your Honors, Susan Morrison on
21 behalf of Patent Owners. I'd like to start -- much of what Petitioner's
22 Counsel said at the very beginning, we agree with. We did disclaim claims
23 to narrow, though I do dispute that we have conceded in any way that those
24 claims are unpatentable. We simply wanted to narrow the issues for this
25 proceeding. And so, Petitioner's counsel focused his arguments on Ground
26 6. I will focus my arguments there as well. And again, just for the Board,

1 Ground 6 argues that Claim 8 is obvious over the '772 Publication, Snowdy
2 and Fabb.

3 And so let me set the table a little bit by talking about the claims.

4 If we could go to Slide 3 and start with Claim 1. Claim 1, I've highlighted
5 three important pieces of Claim 1, and I'm going to talk about each of those
6 as I go along. But Claim 1 requires an AAV construct that has the sequence
7 of rh.46, where position 665 is the asparagine. That piece is talking about
8 the protein ball capsid that surrounds the virus. And then Claim 1 also
9 requires a heterologous gene to be encapsulated within that protein ball.

10 And if we go to the next slide, Slide 4, Claim 6 defines a number of potential
11 heterologous genes, and then if we go to the next slide, Slide 5. Slide 5
12 limits the heterologous gene -- or excuse me, Claim 8 on Slide 5 limits the
13 heterologous gene to a dystrophin gene product. And so that's the claim
14 we're focused on here today.

15 And so the question becomes what is the motivation? If a skilled
16 artisan is thinking, I need to deliver a dystrophin gene product, which is
17 what's required by Claim 8, what is that skilled artisan going to do? And if
18 we go to the next slide, this skilled artisan has -- we've got two paths laid out
19 here. The path on the right side of the slide is the path that the Petition says
20 a skilled artisan would follow. The path on the right is the path that we laid
21 out in our Patent Owner response and also in our surreply that a person of
22 skill in the art seeking to deliver a dystrophin gene product would follow.
23 And so --

24 JUDGE FREDMAN: I guess my problem with this argument for
25 you is, if we look at column 28 of your own patent, the '274 Patent, lines -
26 around 23 to 31, it talks about the composition of the invention may also be

1 used for the production of desired gene product in vitro. For in vitro
2 production, you can draw from the culture (INDISCERNIBLE) with a rAAV
3 containing the molecule for the desired product. So if we can express it in
4 any cell, right, HeLa cells, why do we care what the - sort of, your focus on
5 reversing the muscle is irrelevant, right? Why does it matter to me?

6 If I'm just doing it because I want to brew it in a big vat in a
7 laboratory to study the amount of dystrophin because I'm interested in that
8 protein, why do I care what the cell type is? Tropism doesn't matter, and
9 you're not claiming tropism matters, right? There's no recitation of tropism
10 in the claim, there's no requirement even for a muscle-specific promoter,
11 right?

12 MS. MORRISON: That's correct, there is no requirement of
13 tropism in the claim. The reason that tissue targeting or tropism becomes
14 relevant is because we're talking about delivering a dystrophin gene product,
15 which would go to muscle.

16 JUDGE FREDMAN: That could be delivered to any cell type.

17 MS. MORRISON: It could be delivered into any cell type, but if
18 you were --

19 JUDGE FREDMAN: And since you don't require a muscle-
20 specific promoter, I could just use a strong constitutive promoter and get it
21 expressed in HeLa cells or in CV-1s, or whatever.

22 MS. MORRISON: Well, I think the question is, would a person of
23 skill in the art be motivated to make changes to rh.10 or to any other vector
24 in order to increase tropism to, or targeting to a particular tissue type. That's
25 Petitioner's motivation, that you would be motivated to increase delivery to
26 the liver. If we could go to Slide 37? Mr. --

1 JUDGE FREDMAN: Their other motivation is improved
2 transduction, and so that would apply to every cell.

3 MS. MORRISON: But that's not in the Petition. Their motivation
4 to improve transduction is not in the Petition. That showed up in their reply.
5 And Mr. Wilson confirmed during his argument that the motivation to
6 improve tropism to the liver has always been their motivation. I just heard
7 him say that, because I wrote it down. And so improving transduction
8 generally is not the motivation; the motivation is to improve tropism to the
9 liver.

10 There's two problems with that. Number one is, Petitioner
11 misquotes the '772 Publication, and I have on Slide 37 a quote from
12 paragraph 250 of the '772 Publication, which is Exhibit 1007. And
13 Petitioner quotes this part, the second half of this sentence, that until now
14 gene transfer to the liver has been relatively disappointing. But that's not
15 what the '772 says. What the '772 says is that AAV8 provides an advantage
16 in terms of gene transfer to the liver, that until we had AAV8 was relatively
17 disappointing. And so it's not true that the '772 provides a motivation to
18 otherwise improve delivery to the liver, it says AAV8 meets that need. So
19 that's one problem with what they're saying.

20 The other issue with delivery to the liver, of course, is toxicity.
21 Petitioner's own expert says, at Slide --

22 JUDGE FREDMAN: I still just -- the underlying question here is,
23 so let's say they want to deliver to the liver. But they don't have to deliver to
24 an animal's liver; they can deliver to liver cells on a petri dish, right? And
25 those cells are not going to have the toxicity issue, because you can control
26 the amount of variant you can put on them. And you'll be having better

1 tropism because you'll be into those cells.

2 MS. MORRISON: But this claim is directed to -- thank you, Ms.
3 Kraning. So, this claim is directed to creating a gene therapy product using
4 AAV8.

5 JUDGE FREDMAN: Does your claim say gene therapy anywhere
6 in it?

7 MS. MORRISON: It does not, but it talks about delivering a
8 heterologous gene with expression --

9 JUDGE FREDMAN: Which is done for every single -- almost
10 every single vector delivers a heterologous gene for expression to create the
11 protein that you're interested in. That's -- when you go to the biotech
12 company on 270, all of them have big beer barrel-size vats where they're
13 growing cells that they're transfecting with heterologous genes to make
14 proteins that are usually antibodies in those cases, that are then being sold
15 for hundreds of millions of dollars. I mean, how is this different?

16 MS. MORRISON: Because the question here is what would a
17 skilled artisan be motivated to do in terms of delivering a dystrophin gene
18 product?

19 JUDGE FREDMAN: And so if we wanted to grow it in a muscle
20 cell, why couldn't we do that? I don't see why -- your argument is that it's
21 limited to gene therapy, and I think that the claim is not limited to gene
22 therapy. That's the problem with this argument.

23 MS. MORRISON: Well, let me --

24 JUDGE FREDMAN: I mean, you could have made a claim like
25 that, you provide the written descriptive support, but not because it requires
26 that.

1 MS MORRISON: Let me go back to Slide 6, because I want to
2 address the pieces of their Petition, including the question you're asking me,
3 Your Honor. Their Petition requires a series of choices, and one of the
4 choices that was focused on was the choice to change the phosphorylation
5 potential of certain --

6 JUDGE FREDMAN: That I'm interested in, yes.

7 MS. MORRISON: So let me go to that issue, which is as Slide 55
8 of my presentation, and this is from the Snowdy reference, which is Exhibit
9 1009. So there's a couple of issues with the Snowdy reference. Number
10 one, as Your Honor pointed out, Snowdy and the reference upon which it
11 relies, Jans & Jans, are both talking about nuclear localization signals, and
12 changing the phosphorylation potential of amino acids that are close in
13 proximity to a nuclear localization signal. Snowdy has nothing to do with
14 position 665 of the AAV capsid protein, which is as, I think you noted,
15 nearly 500 amino acids disparate from the amino acids that Snowdy is
16 talking about. So that's one issue, is that Snowdy's not teaching anything
17 about position 665.

18 Another -- if we could go to Slide 58, and this is -- the Slide 55
19 was Snowdy at page 126. On Slide 58, and this is Exhibit 1009 at pages 128
20 to 129, Snowdy specifically says in the second highlighted passage that I
21 have here on Slide 58, that it may be premature in the field's development to
22 assume that a given phosphorylation status would have the same effect on all
23 NLSs, as there is insufficient in the literature to support this assumption.
24 And the reason Snowdy is saying that is because he got the opposite result of
25 the reference that he relied on, Jans & Jans. If we could go back to Slide 57.

26 So what Snowdy found, and I have -- so, on Slide 57 I have an

1 excerpt from the Snowdy thesis on the left side, which is Exhibit 1009 at
2 page 126, and on the right side I have an excerpt from the Jans & Jans
3 reference, which is Exhibit 1017 at 2. So what Snowdy found is if I take a
4 phosphorylatable amino acid -- and to be clear, Snowdy never proved that
5 any of the three residues he looked at were actually phosphorylated, they just
6 had phosphorylation potential. If I take a phosphorylatable amino acid and I
7 turn it into an amino acid that cannot be phosphorylated, alanine, I get
8 transduction going way up. And if I change it to one that appears to be
9 constitutively phosphorylated, aspartic acid, phosphorylation goes way
10 down, right?

11 So if I remove phosphorylation potential, I get better transduction.
12 Jans & Jans found exactly the opposite, and that's on the right slide here of
13 Slide 57. Jans & Jans found that if he removed, or if they removed a
14 phosphorylatable serine, and they replaced it with something that was not
15 phosphorylatable, transduction went way down to four percent of wild-type.
16 Now these are, again, both related to nuclear localization, which has nothing
17 to do with position 665 of the AAV.

18 JUDGE FREDMAN: And Jans & Jans, that's -- is SV40, it looks
19 like? Large T-antigen, right?

20 MS. MORRISON: I'm sorry.

21 JUDGE FREDMAN: They were saying -- Jans & Jans is
22 essentially the SV40 large T-antigen? So (CROSSTALK) --

23 MS. MORRISON: It was for large T-antigen --

24 JUDGE FREDMAN: -- but it's not a adeno-associated virus
25 particle --

26 MS. MORRISON: It's not, but this is the reference that Snowdy

1 was relying on for his thesis.

2 JUDGE FREDMAN: I understand.

3 MS. MORRISON: So -- and Snowdy himself says, and I have
4 this on the next slide, Slide 58, which we looked at a moment ago, that Jans
5 & Jans -- that they expected, based on Jans & Jans, that they -- the serine to
6 alanine mutation would result in transduction efficiency going down, and in
7 fact they got it going up. So, Jans & Jans teaches, if I remove a
8 phosphorylation potential I get a huge drop in transduction efficiency,
9 Snowdy teaches it goes up. So a skilled artisan looking at these two
10 references is going, I don't know what's going to happen if I change the
11 phosphorylation potential next to an NLS, much less one that's 500 amino
12 acids away. It just simply doesn't teach that changing phosphorylation
13 potential is going to be relevant to changing the transduction efficiency of
14 the AAV capsid protein.

15 JUDGE FREDMAN: Or predictable, at least.

16 MS. MORRISON: And it's wholly unpredictable, what's going to
17 happen if you change that phosphorylation potential. And if you take that
18 piece of Petitioner's argument away, you're back to, there are 48 differences
19 between rh.10 and AAV8, which the panel said in its Institution Decision
20 and we think is absolutely right, is too many, and now in the world of *In re*
21 *Baird*, where you have many choices and many options.

22 Just another piece of this is that if you had, if the motivation was
23 simply to improve transduction potential generally of these -- and not
24 specific to liver cells, they need the liver-specific motivation in order to
25 choose AAV8, because the '772 Publication has, I believe it's 56 different
26 sequences of amino acids including rh.10 and AAV8. So unless you select

1 those two, you don't even get to -- and Ms. Kraning, if we could go back to
2 Slide 6.

3 Unless you select rh.10 and AAV8, you don't even get to that 48.
4 If the motivation is simply to improve transduction, and assuming you buy
5 the Snowdy argument about changing phosphorylation potential, you now
6 have 56 amino -- 56 sequences of 738 amino acids to choose from. And if
7 you're only looking at changing the phosphorylation potential, which again,
8 if you go with Snowdy, if you remove phosphorylation, transduction goes
9 up, Jans & Jans it goes down, but there are, according to Exhibit 1021,
10 which is a NetPhos program printout that Petitioner's expert put together,
11 there are 82 phosphorylatable amino acids in rh.10.

12 So unless you have that liver motivation to combine it with AAV8,
13 you're left with 82, and then the number of possible changes becomes
14 exponential. And the same is true if you have AAV rh.10 and AAV8, you
15 have 48. The number of potential changes is huge, and so without both of
16 those pieces, without both of those arguments, that you would modify to
17 improve liver targeting and you would believe what Snowdy says about
18 phosphorylation potential and disregard Jans & Jans, and that Snowdy said it
19 was premature to form such a belief, unless you believe all of those pieces,
20 you don't get to Claim 8. You don't get to the rh.46 sequence with the
21 asparagine locked in at position 665. Instead you have numerous changes
22 that you could potentially make, and that's in our Petition. We did some
23 calculations about just how many changes you start to run into.

24 One last point about Petitioner's argument on improving tropism to
25 the liver or improving targeting to the liver while maintaining it in muscle
26 and lung, one of the references that Petitioner cited in its reply brief for the

1 first time is a reference to Kern, which is Exhibit 1068. And Petitioner cites
2 this reference to show, I believe, hey, people were making single amino acid
3 mutations at this time. What Kern was doing was investigating what portion
4 of AAV2 was -- which is yet a different AAV that we haven't talked about
5 extensively today, but AAV2 at this time was the only AAV that had been
6 approved by FDA to go into human clinical trials. So there was a lot of
7 interest in AAV2.

8 And so what Kern was doing was investigating whether AAV2,
9 what portion of it was responsible for this heparin-binding function, which is
10 the heparin receptor allows AAV to bind, it's one of the major receptors for
11 AAV to bind, to enter cells. And what Kern found -- so Kern tested 33
12 different mutations. Some were single amino acid mutations, some were
13 multiple amino acids, and what Kern found, and this is the next slide, Slide
14 89, and this is from the abstract of Kern, this is Exhibit 1068 at 1, here on
15 Slide 89 of my presentation, that two single amino acid mutations -- so
16 AAV2 was known to go to both the liver and the heart, and Kern found that
17 two of these mutations increased transduction to the heart, but destroyed it,
18 all but destroyed it in liver. And so the idea that one could increase tissue
19 targeting to one tissue but maintain it, maintain this excellent tissue targeting
20 to other tissues, that's belied by Kern.

21 And if we go to the next slide, and this is Slide 90, which is from
22 the Kern reference, 1068 at 6 to 7, and this was for -- sorry, this was from a
23 two amino acid change, it was a double mutant. And Kern says that the
24 reporter gene activity of the double mutant was not detectable in the liver,
25 but it was surprisingly high in the heart. So Kern, by changing two amino
26 acids, was able to take a vector AAV2 that had previously gone to both liver

1 and heart, he changed two amino acids and suddenly it doesn't go to the liver
2 anymore. So a person of skill would know this and would be concerned that
3 making any changes at all could potentially send more of --

4 JUDGE FREDMAN: Does Kern explain what the change does?
5 In other words, does it -- that it no longer binds to heparin and binds to
6 something else?

7 MS. MORRISON: I believe that's right. Yes, it does. Your
8 Honor, it does explain that it no longer -- I believe they found that it does
9 not -- they ruined the heparin-binding motif with these changes and therefore
10 no longer bound very well to heparin.

11 JUDGE FREDMAN: Bound presumably to something else in the
12 heart?

13 MS. MORRISON: Presumably, I don't know that they identified
14 that.

15 JUDGE FREDMAN: Okay.

16 JUDGE MITCHELL: Wouldn't a POSA, though, wouldn't it be
17 equally plausible for a POSA looking at Kern to go okay, I'm going to do
18 single substitutions and follow that track? Instead of, okay, I won't do two
19 because that might have some sort of -- well, I mean, you don't know what's
20 going to happen, but I'll go one by one and sort of see what happens?

21 MS. MORRISON: So Kern is not a ground reference, and I don't
22 believe Kern teaches that. Kern made 33 different mutations, some of which
23 were singles, and some were multiples, and so I don't believe Kern teaches
24 that. And if you look to another reference -- so this was a reference that was
25 only cited in Petitioner's reply, it is not in the Petition, and so another
26 reference that Petitioner cited only in reply is the '126 provisional, which is a

1 provisional patent application that was filed in -- as one of the inventors was
2 our expert Dr. Samulski. And what Dr. Samulski and his team found -- so
3 first of all, Dr. Samulski testified that he and his team -- this was a team of
4 extraordinarily skilled artisans.

5 And so if we go to Slide 67. This is Dr. Samulski's testimony
6 when he's being asked about this at his deposition. He said that this idea of
7 making single amino acid changes -- so Kern was looking to define which
8 portions of the AAV capsid were responsible for heparin binding. Kern was
9 not trying to say, if I change these amino acids am I going to change the
10 targeting of the virus from one tissue to another? That was an incidental
11 result that they found, but Kern was looking to define the heparin-binding
12 region.

13 But Dr. Samulski testified, and there is no evidence in the Petition
14 of single amino acids changing the tissue targeting, but Kern -- sorry, Dr.
15 Samulski testified that he and his team were way out in front and they had a
16 four-year head start on doing these sorts of single amino acid changes.

17 And so, and again, Dr. Samulski and his team when they were
18 looking to deliver a dystrophin gene product, they used AAV8 as a negative
19 control, of changes you wouldn't want to make, you wouldn't want to be
20 more like AAV8, you would want to be more like the muscle tropic factors
21 of AAV1 and AAV7. But the only evidence in the record is that the only
22 group out there -- and this again, the '126 provisional, no one has argued that
23 it's prior art, and no one has shown that it's prior art, but it is near in time.
24 And so, but what Dr. Samulski and his team did was follow the path that we
25 have said a skilled artisan would follow if they were seeking to deliver a
26 dystrophin gene product.

1 And even within that path, Dr. Samulski and his team identified a
2 number of changes. So if we could go to Slide 73, Ms. Kraning. That there
3 were -- so they aligned the amino acids between AAV1 and AAV2, so
4 AAV2 was the vector they were trying to alter. AAV1 was a strong muscle
5 targeting vector. And so they aligned them, and they found 83 positions that
6 were different, and that's on the next slide, Slide 74.

7 This is from Exhibit 1059 at page 64; it's Figure 1A. These are the
8 83 different amino acids that they identified, and then they narrowed it by
9 seeing which ones were similar and which ones were different, and after
10 they did some narrowing, they then used the crystal structure to narrow it
11 down to 12.

12 And if we go to Slide 77, you can see on Slide 77, which is from
13 Exhibit 1059, which is the '126 provisional at page 65, it's Figure 1B, the
14 sites they selected, and yet again, none is within about 50 amino acids of
15 position 665. None of the candidates that they chose to test goes anywhere
16 near position 665. And instead, they used, like I said, AAV8 was used as a
17 negative control, and they wanted to move away from AAV8 and more
18 towards the muscle tropic vectors when they wanted to deliver dystrophin.

19 Okay, if we could go to Slide 27. We talked about, Your Honor
20 asked me earlier, Judge Fredman, why you would want to -- why you would
21 not be worried about targeting liver even in a cell culture system. And the
22 reason comes directly from Petitioner's expert. So if you're looking to
23 improve the targeting, if you were looking to change rh.10 at all, right,
24 because the '772 Publication -- let me jump back for just a moment. The
25 '772 Publication shows that rh.10, the vector that they say that you would
26 start with, that Petitioner says you would start with, rh.10 is already pretty

1 good in the liver, it's already pretty good in the muscle, and it's already
2 pretty good in lung.

3 So the question is why would you change it at all? And you can
4 see the data that shows that rh.10 is already pretty good in these tissues in
5 Table 8 of the '772 Patent, which I believe is at paragraph 253 of the '772
6 Patent. It's also on my Slide 39, among other places. It's several times in
7 our presentation, and it's also several times in our papers.

8 But you can see that rh.10 is already good in these tissues; we
9 agree with that. We agree that rh.10 is already good in all three tissues. And
10 so the question becomes why would you change it at all if you're looking to
11 deliver to the muscle? But why would you change it at all? And the reason
12 that you wouldn't want to do that is -- why you wouldn't want to improve
13 targeting to the liver is supplied by Petitioner's expert, and that's at Slide 27.
14 And it's because, for viruses that are administered systemically, the liver is
15 the default destination. And so if you've already got this virus, rh.10, that's
16 fairly good in three tissues increasing the targeting to the liver, you're going
17 to have a sink for your virus. And so it may not get to those other organs or
18 other tissues that are your intended target. And so Petitioner's own expert
19 explains why you wouldn't want to increase targeting to the liver.

20 JUDGE FREDMAN: Again, this is an intended use recitation.

21 MS. MORRISON: It is in part, but it's also, even if your intended
22 use was something else, even if it wasn't dystrophin for the muscle, this is
23 why you wouldn't want to increase targeting to the liver for rh.10 which is
24 already good in three tissues, because you've got --

25 JUDGE FREDMAN: This isn't like if you're using it as a gene
26 therapy, you wouldn't want to use it maybe, but it still doesn't -- if you were

1 using, again, CV-1 cells happen to be monkey kidney cells, would you use a
2 liver cell type? I unfortunately don't know one off hand. And you were
3 targeting those for expression, it doesn't seem to me that you would maybe
4 want to improve tropism for that, because you're expressing in that cell
5 culture a liver cell type, and that's a reason to do it, and cell culture is
6 perfectly legitimate here.

7 MS. MORRISON: If you were going to express a dystrophin
8 protein in liver cells in culture? Is that the question?

9 JUDGE FREDMAN: Right, yes, essentially. A cell type that you
10 happen to -- convenient in your lab or whatever, because they'll take cell
11 types because they have them, not necessarily because --

12 MS. MORRISON: So one problem with that, Your Honor, is that
13 there's no evidence in the record that anyone working with AAV was using
14 liver cells in culture. They were using HeLa cells in culture, and that's all of
15 the evidence in the record, that the cultured cells that were being used were
16 HeLa cells. And so I'm not aware of any evidence in the Petition or
17 anywhere else in the record that anyone was using a liver specific cell type
18 in culture to express --

19 JUDGE FREDMAN: It's fair to say there would be no reason to
20 particularly go for --

21 MS. MORRISON: Right, there would be no reason -- there would
22 be no motivation for a person of skill in the art to try to increase tropism to
23 the liver in a cultured cell --

24 JUDGE FREDMAN: Any more than in an -

25 MS. MORRISON: -- any more than any other kind of cell. And
26 their Petition, that sort of selection at the very beginning relies on a

1 motivation to increase targeting to the liver, and there simply would not be
2 that motivation for a cultured cell type. And indeed, our expert testified, and
3 I don't have the slide at my fingertips -- oh, 61, thank you to my team. Slide
4 61, our expert testified that cell culture can't define anything related to
5 tropism. And this is the only evidence on this point in the record.

6 JUDGE FREDMAN: That's little bit of an overstatement, but
7 yeah, okay.

8 MS. MORRISON: I'm sorry?

9 JUDGE FREDMAN: That's a little bit of an overstatement
10 actually, but yes.

11 MS. MORRISON: But nonetheless, it's the only evidence in the
12 record, and there is no evidence of anyone using a liver cell in culture. And
13 so the point is there would simply be no motivation to take rh.10, a vector
14 that's already pretty good in three cell types, and try to alter it to make it
15 better in the liver, if ultimately your goal is to deliver dystrophin. That's just
16 not something that a skilled artisan would do, and the only evidence in the
17 record about what a skilled artisan would do in that situation, thinking I'm
18 trying to deliver dystrophin and I want to change a vector to deliver
19 dystrophin, is in the '126 provisional, where Dr. Samulski and his team took
20 AAV2, they said we want to make it better to deliver dystrophin, so what do
21 we do? We compare AAV2 to AAV1 and 7, which are good in muscle, and
22 we use as a negative comparator something we don't want to do, AAV8, the
23 very vector that Petitioner is saying you would use as your comparison.

24 And so that goes back to that very first choice on Slide 6, where if
25 you've got rh.10, it's a good vector in three tissues, you've decided for some
26 reason you want to change it, why would you -- where would you change it?

1 What would be the motivation to do that? Our argument is if you are doing
2 anything related to dystrophin, you're going to look to the vectors that are
3 good in muscle because dystrophin is a protein that is ultimately expressed
4 in muscle cells, not in liver cells, and not elsewhere.

5 And so there would simply be no motivation to modify rh.10 to
6 improve liver targeting. And if that's where you are, if you're just at that
7 first step and you've got AAVrh.10, you're either not going to modify it at all
8 and you're going to be happy with this rh.10 vector that's fairly good in three
9 tissues, or if you're going to change it you're going to do what they did in the
10 '126 provisional and modify it to improve muscle targeting. And the reason
11 that Petitioner doesn't advocate that path is because AAV1 and AAV7 do not
12 have an asparagine at position 665. AAV1 has a serine, and AAV7 has a
13 threonine, both of which by the way are phosphorylatable residues at that
14 position.

15 And if you go to slide -- I have this shown on Slide 47, is the
16 sequence alignment. So this is a sequence alignment between AAV1 --
17 excuse me, AAVrh.10 on the top, with the serine position 665 and AAV7 on
18 the bottom, with the threonine at position 665. And you could see, if you
19 were going to make this choice, that there might be other residues that you
20 might consider modifying if you decided you wanted to make rh.10 more
21 like AAV7. But position 665, even if you chose that one, you would be
22 changing it to a threonine, which doesn't meet the claims. And the same
23 thing is true if you go to the next slide. This shows the comparison between
24 rh.10 and AAV1. Again, other positions you might change, but rh.10 and
25 AAV1 both have a serine at position 665.

26 And just one more, the next slide, Slide 49. And I'm sorry, these

1 are all -- these last three slides that we looked at are all from Exhibit 2032,
2 which was filed with our Patent Owner response, which is a series of
3 sequence alignments. Again, you can see on Slide 49, this is a sequence
4 alignment between AAV7, rh.10, and AAV8, 1, 2, and 3. And all of AAVs
5 1, 2, and 3, as well as rh.10 have a serine at that position, which again
6 further indicates that a post-translational modification is not going to
7 improve transduction, because if that were true all these AAVs wouldn't
8 have these phosphorylatable amino acids at this position. And so it's, again,
9 further evidence that modifying that residue, to take it from something that
10 can be phosphorylated to something that cannot be, is not going to improve
11 transduction generally because all these viruses have phosphorylatable
12 amino acids at that position.

13 And so if we could just go back to Slide 6 one last time. If the
14 motivation is just, as Your Honor suggested, Judge Fredman, to create a
15 vector with some sort of general scientific interest that you could use in
16 tissue culture, well now you have this rh.10 vector that's good in multiple
17 tissues, and if you want to change it, there's no reason to change it to make it
18 better in the liver. You might want to make it better in the liver or the
19 muscle or the lung, and now you have a bunch of different vectors to
20 compare it to across all of these 56 sequences that are in the '772
21 Publication, and you have even more changes that you could potentially
22 make, and now the number of changes is getting higher and higher and
23 higher.

24 And so unless Petitioner is correct that you'd specifically want to
25 modify it to improve liver targeting, as opposed to muscle or lung or some
26 other tissue that rh.10 is not already good in, perhaps you'd want to improve

1 rh.10, it's already good in liver and muscle and lung, why not try to make it
2 good in the brain or in the eye, or some other tissue in the body, to make it
3 an even better vector? But if that's your choice, then you're not choosing
4 AAV8, you're choosing some other vector to modify it with, again, assuming
5 you want to modify it at all.

6 And so if you're looking to make a vector that is just good for
7 scientific study, for general scientific interest, you're not going to choose
8 AAV8, you're going to choose something else. Or perhaps you'd choose
9 AAV8 and ten other vectors and start running comparisons and figuring out
10 where to make changes, but now we're not at 48 changes, we're at tens or
11 hundreds of thousands or numbers I don't even know how to say, millions,
12 tens of millions, billions of changes that you could potentially make to try to
13 improve those vectors. And that is certainly well outside the realm of what's
14 obvious.

15 So just to conclude, I see I have some time left, I'm happy to
16 address any additional questions, but the slide that I have on the screen here,
17 Slide 6, Petitioner has to have shown that each of these choices on the right
18 side of the slide, just leaving the left side alone for a moment, that a person
19 of skill in the art would have been motivated to make each of these choices
20 to get to the asserted claim. And they simply have failed. The Petition has
21 failed to show that a person of skill in the art would make each of these
22 choices. And if you find that a person of skill in the art would not have
23 made any one of these choices, the Petition fails. And we would submit that
24 a person of skill in the art, even having chosen, I'll give them the first choice,
25 having chosen rh.10, would not have been motivated to modify it to improve
26 liver targeting over any other issue, would not have chosen AAV8, would

1 not have modified phosphorylatable amino acids to ones that were not
2 capable of being phosphorylated, and if a person of skill in the art would not
3 have made any one of those choices, the Petition fails, and they have not
4 proven that the claim is unpatentable. So unless there's any further
5 questions, I'll --

6 JUDGE MITCHELL: I'm fine, thank you.

7 MS. MORRISON: All right, thank you.

8 JUDGE FREDMAN: Thank you.

9 JUDGE MITCHELL: Just so you know, for both of you I've
10 added in whatever was left over into your rebuttals.

11 MR. WILSON: Thank you, Your Honor.

12 JUDGE MITCHELL: And whenever you're ready.

13 MR. WILSON: So, Your Honors, I'd like to start by addressing
14 some of the arguments that have been made about Snowdy and the nuclear
15 localization issue. Snowdy says specifically in the section where he's
16 substituting phosphorylatable amino acids with non- phosphorylatable amino
17 acids, he analyzes those results and he says that's not -- he's not looking, he
18 does not expect and he is not looking at a nuclear localization issue, because
19 he got the opposite result that he expected based on what he would have
20 predicted from a nuclear localization reference, Jans & Jans. And that is
21 cited in Exhibit 1005, and that's paragraph 275. And it's also cited then in
22 the declaration at Exhibit 1009, pages 128 to 129.

23 And what Snowdy says in his thesis is that he's looking, it appears
24 that he's looking at a surface phosphorylation phenomenon when he's
25 looking at position 181, and when he makes that serine to alanine
26 substitution, that that is a -- he believes or he understands that that's a

1 phosphorylation issue when he obtains the increased transduction efficiency.
2 So, and that is Exhibit 1009 at pages 135 to 136, and it's cited in the
3 declaration at 1005, page 108, note 8. So he believes he's looking at a
4 surface phenomenon, and to your point, Judge Fredman, you know, then
5 how does that translate to something that's at position 665? Well, position
6 665 is on the surface, it is a surface amino acid.

7 And so a POSA would understand -- let me just put for the record
8 that the discussion of 665 being on the surface is at Exhibit 1005, pages 115
9 to 116, note 8. And so as a surface amino acid, the result that Snowdy is
10 getting, and in talking about the phosphorylation of the position 181, which
11 is on the surface of the capsid, a POSA would understand that that would
12 translate to other surface amino acids and position 665 is one of those
13 surface amino acids.

14 Patent Owner also talked about Jans & Jans as showing
15 unpredictability, and if I have the result in Jans & Jans and Snowdy, I
16 wouldn't know which way to go. Well, the results in Jans & Jans would not
17 discourage a POSA from making the modifications to AAVrh.10, because a
18 POSA has the results in Snowdy. Snowdy is relating to AAVs, and as you
19 pointed out, Your Honor, Jans & Jans is talking about SB40 large T-antigen.

20 And so the fact that the results in Snowdy would not have been
21 predicted by Jans & Jans, it actually supports the motivation, because
22 Snowdy got an unexpected result for AAVs. And Snowdy makes that point
23 in his thesis, this is an interesting result that's specific to the AAV capsid.
24 And what Patent Owner is trying to do is give Jans & Jans equal weight, but
25 a POSA studying AAVs is not going to do that. They're going to be focused
26 on the results in Snowdy. Jans & Jans didn't even deal with transduction, it

1 wasn't looking at a virus at all. And so a POSA is not going to --

2 JUDGE FREDMAN: SV40 is a virus.

3 MR. WILSON: I'm sorry?

4 JUDGE FREDMAN: SV40 is a virus.

5 MR. WILSON: Yes, but the study that they're doing is not focused
6 on the virus. What they're doing is they're injecting the protein directly into
7 the cells, and they're looking at nuclear localization effects. So they're not
8 looking at transduction from a virus into a cell. Snowdy does, and Snowdy
9 is specifically looking at transduction in AAV.

10 Patent Owner also talks about Snowdy showing the
11 unpredictability in the art, and Snowdy actually proves the opposite.
12 Snowdy demonstrates that phosphorylation matters for AAV transduction.
13 He substituted three amino acids, and he found function in one out of the
14 three. And he's creating function. It's important to note here, he's not just
15 destroying function or eliminating function, but he's created a function of
16 increasing transduction efficiency, which is a very hard thing to do. But he
17 does that in one of the three positions, one out of three positions, which is a
18 pretty extraordinary track record. So on the contrary, instead of showing
19 unpredictability, Snowdy proves that the phosphorylation really does matter
20 for purposes of AAV transduction.

21 Again, when Patent Owner argues that a POSA would not be able
22 to follow Snowdy, Snowdy provides a roadmap for which amino acids to
23 select, which ones to potentially look at. It's not unpredictable. Taking the
24 guidance in Snowdy and the result that Snowdy gets, a POSA would be able
25 to apply that teaching to other comparisons of sequences, such as the rh.10
26 and AAV8. It doesn't take a genius, it doesn't take extraordinary skill to do

1 that. It would be well within the capabilities of a POSA.

2 JUDGE FREDMAN: So how do you address why AAV8 would
3 be the selecting comparison, not one of the other AAVs, like 1 or 7?

4 MR. WILSON: Yes, that's because, Your Honor, the AAV8 is
5 selected because what Patent Owner disregards is the additional teaching in
6 the '772. And basically it says, liver tropism's been hard to get, and yes, you
7 may have this new AAV8 vector that has the best liver transduction, but
8 that's the motivation then to say, '772 Publication says rh.10 has multiple
9 tropisms in different tissues, is it possible to confer some of that extra good
10 tropism from AAV8 onto rh.10? So it's that additional teaching in '772 --

11 JUDGE FREDMAN: But again, I still think the argument that she
12 makes has some power, which is why liver? In other words, you're saying
13 you want to do liver, but do you have even a cell culture model where liver
14 was desirable or something?

15 MR. WILSON: Well, we do, but --

16 JUDGE FREDMAN: Can you point to that?

17 MR. WILSON: Yes. As an initial response though, Your Honor,
18 the '772 Publication tells you, liver is hard to get. So that's the motivation
19 for liver itself, it's difficult to obtain, so a POSA would be motivated by that.

20 JUDGE FREDMAN: Because the '772 is interested in actual gene
21 therapy, which I think is really more of the focus. Dystrophin is not
22 necessarily desirably delivered to the liver --

23 MR. WILSON: Right.

24 JUDGE FREDMAN: -- so that doesn't really work. So you have
25 to have it for delivery for a different reason.

26 MR. WILSON: Sure, and so you asked also if there was evidence

1 in the record about delivery in cell culture in liver cells. And there is
2 evidence, and in fact it's from their own expert. So the Wu publication from
3 2006 is a study in hepatocytes in vitro, this is Exhibit 1072 at paragraph 227.

4 And in Wu, they use hepatocytes, liver cells, in culture to study
5 tropism, and then similarly in Wu at paragraph 40 in Exhibit 1072, it talks
6 about cells in culture can provide insights into tropism, and in particular
7 using the hepatocyte example. So Wu really covers a couple of points that
8 Patent Owners made. One, cell culture is informative of tropism in tissues,
9 and Wu is specifically looking at liver cells, hepatocytes, and looking at
10 whether or not certain vectors can infect those types of cells. There's also
11 Exhibit 2011, this is a reference that was cited in the POPR, so this is one of
12 Patent Owner's references to Blake. It's also looking at dystrophin
13 expression in liver cells.

14 Patent Owners also argued that Snowdy doesn't teach how to target
15 new cell types, and that that teaching doesn't apply to obtaining new tropism,
16 and that it's very difficult to obtain new tropism. Well, we're not arguing
17 that Snowdy has to do that, because we're not looking for new tropism, we're
18 looking for an existing tropism and to see if we can increase the transduction
19 efficiency. And that's exactly what Snowdy did. So we're not looking to
20 target new cell types, all a POSA is looking to do is to increase the
21 transduction in an existing cell type.

22 Right, and so also to go back to the point about why would a
23 POSA be interested in potentially transducing liver cells when you're talking
24 about a dystrophin construct, the Blake reference, which is Exhibit 2011,
25 says that at least one isoform of dystrophin is expressed in the liver. And in
26 fact, the --

1 JUDGE FREDMAN: Can you tell me what page number that is,
2 in that reference?

3 MR. WILSON: Yes. We will look that up for you.

4 JUDGE FREDMAN: Okay, whenever you get there.

5 MR. WILSON: Yes, so that's page 4 of the reference, and it's
6 under, that's Exhibit 2011, Blake page 4, and it talks about the dystrophin
7 protein. It's right above the header, and it says that dystrophin, Dp71, which
8 is an isoform of dystrophin, is detected in most non-muscle tissues,
9 including brain, kidney, liver, and lung. And Dr. Schaffer, our expert has
10 also opined, so there may be, because the dystrophin is expressed in multiple
11 tissues in the body, there may be a benefit to a vector just like rh.10, which
12 has multiple tissue tropisms, and that even though you may be wanting to
13 target muscle cells, because that is one of the tissues in which dystrophin is
14 expressed, there may be benefits to having a vector that also transduces in
15 other cell types, because those other tissues are also potentially places where
16 different dystrophin isoforms are expressed.

17 Okay, and Patent Owner also referred to Dr. Samulski's '126
18 provisional. The '126 provisional is interesting, because Dr. Samulski
19 applied the teachings of Snowdy in that application, and actually used
20 phosphorylation as a benchmark for identifying individual amino acid
21 substitutions, where substitutions could be made to improve transduction
22 efficiency. And specifically what Dr. Samulski did is he found that he was
23 able to confer some of the muscle tropism from AAV1 onto AAV2 by
24 replacing the threonine in AAV2, which is phosphorylatable, with an
25 asparagine, which was found at AAV1 in the corresponding position. And
26 he actually found an enhancement at two positions that were tested,

1 positions 450 and 716.

2 So if anything, the '126 provisional is exactly what we're talking
3 about a POSA would do with Snowdy and the primary reference of the '772
4 Publication. It's something that's shown in the '126 provisional as a strategy
5 for identifying how to increase tropism in an AAV vector by doing just what
6 Dr. Snowdy did, comparing the sequences, in that case AAV1 and AAV2,
7 and looking for positions where the amino acid in AAV2 is
8 phosphorylatable, and the amino acid in AAV1 was not. And again, he
9 found enhancement at two positions tested, which is a remarkable track
10 record. And again, I think, if anything, confirms the predictability of this
11 approach rather than any unpredictability.

12 Also, let me put up Slide 28, and I also wanted to mention, and this
13 goes back to our discussion about dystrophin being expressed in other
14 tissues, this is Exhibit 1062, this is the Bowles reference, and this is a
15 reference from Dr. Samulski's laboratory. And their own expert, Dr.
16 Samulski, has also published -- this is at page 1 of this exhibit, has also
17 published that dystrophin is expressed in different tissues, different types of
18 muscle, brain, and retina, in different isoforms. So again, a multi-tropic
19 vector would be potentially useful and have benefits even in the dystrophin
20 application, where you're looking for muscle tropism but also potentially
21 tropism to other tissues.

22 And then Patent Owners also talk about why would you change
23 rh.10 at all? And why wouldn't -- I mean again, this is sort of the same
24 argument that they're making as far as naturally occurring variants. You
25 know, they say, oh, a POSA would just use a naturally occurring variant, and
26 then they're arguing oh, why would you change rh.10 at all? Well, the '772

1 Publication teaches you that making modifications to these types of vectors
2 is an interesting thing and it's something that a person of ordinary skill
3 potentially would want to do.

4 And here then the question is, well why would you try to increase
5 the liver transduction? That goes back to the motivation in the '772
6 Publication. '772 Publication identifies rh.10 as being particularly
7 interesting because it's got tropism in all three tissues. It says this has
8 unique biological significance. So a POSA looking at the '772 is thinking, is
9 it possible to make rh.10 even better? Is there any way that I can even take
10 this really significant, important vector, and make it a super vector, make it
11 an even better transducer?

12 And that goes back to the teaching in the '772 Publication that
13 says, you know, liver has been difficult in the past. It has been something
14 that's been difficult to get, and it's hard to do. And the '772 teaches, but we
15 have this AAV8 that has really exceptional liver tropism. Rh.10 is almost as
16 close to AAV8 in liver, but not quite. And so that would be the motivation.
17 A POSA would say geez, I have this really amazing highlighted vector in
18 rh.10 that's excellent in all three tissues, but not quite as good as AAV8 in
19 liver, and liver's been hard to get. So that's the motivation for combining
20 those two and taking a look at then is there something about AAV8 that I
21 can change to confer the exceptional liver tropism onto rh.10.

22 JUDGE FREDMAN: I will say that the --

23 MR. WILSON: Yes, Your Honor.

24 JUDGE FREDMAN: -- Bowles reference does mention that de-
25 targeting liver, actually. That's one of their goals, essentially.

26 MR. WILSON: I'm sorry, Your Honor, it talks about targeting in

1 muscle -- or it talks about expression in muscle and brain.

2 JUDGE FREDMAN: It talks about it, but it talks about de-
3 targeting liver, actually, during the goals.

4 MR. WILSON: Right. And again, other references, including the
5 Blake reference, which is at Exhibit 2011, that's a reference from Patent
6 Owners that talks about expression in all the different tissues.

7 JUDGE FREDMAN: But simply because there is expression
8 doesn't mean you necessarily want to drive it there.

9 MR. WILSON: Well actually, there's another reference that Patent
10 Owner cites, this is Exhibit 2018 by Uchino, U-C-H-I-N-O, and it actually
11 does talk about multiple roles for dystrophin. And it says that dystrophin
12 was found in neuronal cells in particular, and that in --

13 JUDGE FREDMAN: Different references speak to different
14 things, some of them are talking about splice variants, and different splice
15 variants have different roles. It doesn't seem like --

16 MR. WILSON: That's right, that's right.

17 JUDGE FREDMAN: So the main dystrophin would be a
18 particular splice variant, it doesn't necessarily mean that it's the same thing.

19 MR. WILSON: It would --

20 JUDGE FREDMAN: And actually express -- the thing expressed
21 in muscle may not be the same thing expressed in brain.

22 MR. WILSON: That's right, the references definitely talk about
23 different isoforms and that different isoforms are potentially located in
24 different cells, but Uchino talks about how in the CNS, at least one isoform
25 is expressed in CNS, and it talks about DMD patients who have the
26 muscular dystrophy and are not expressing dystrophin, that they have no

1 expression of that dystrophin isoform in their neuronal cells, and that that
2 may have, you know, that that suggests multiple roles for dystrophin and
3 that there may be a need or a benefit to having micro-dystrophin expressed
4 in multiple types of cells.

5 And so I see my time is nearly up, and I just wanted to really
6 conclude by looping back to the discussion on Snowdy and how the Snowdy
7 thesis talks about the phosphorylation phenomenon that he's seeing as not
8 being related to nuclear localization, he doesn't attribute it to that. He does
9 focus on the concept that the 181 amino acid is on the surface, so it appears
10 to be a phosphorylation issue, and that amino acid 665 is also on the surface,
11 the evidence shows that. And so a POSA would understand that looking at
12 those amino acids on the surface and phosphorylation on the surface, those
13 would be the locations that potential modifications would improve
14 transduction efficiency. Thank you.

15 JUDGE MITCHELL: Thank you.

16 MS. MORRISON: So, I first want to start by noting that I heard a
17 number of new arguments just now that are not in the Petition, and, frankly,
18 I hadn't heard them before today. So, I want to address several of those
19 arguments.

20 First, I heard a new argument that a person of skill in the art would
21 credit Snowdy over Jans & Jans, because Jans & Jans wasn't relevant to
22 AAV. That's not in Petition, it wasn't in the Reply, but I also think it's belied
23 by Snowdy itself, which Snowdy himself cites Jans & Jans and talks
24 extensively about how his results are different than Jans & Jans, and so
25 concedes, nearly, himself that (CROSSTALK) --

26 JUDGE FREDMAN: I mean, I think if you're looking for AAV

1 changes, you'd look at an AAV reference rather than an SB40 reference. I
2 mean, that's just common sense.

3 MS. MORRISON: But you'd look to the reference that the AAV
4 reference cites.

5 JUDGE FREDMAN: You may look at it, but I think you'd look at
6 the reference that they -- yeah. Okay, I see your point. Move on, please.

7 MS. MORRISON: And another issue with that is Snowdy never
8 proved that any of the sites that he was looking at were indeed
9 phosphorylatable, or that any of the changes that he made had anything to do
10 with phosphorylation as opposed to something else.

11 And so Jans & Jans, by contrast, did do that study, and that's at
12 slide -- well, I won't go into it in detail, but we've cited that portion of Jans
13 & Jans, and that's at Slide 63. It's Exhibit 1017 at 6, Figure 5. Jans & Jans
14 actually looked at, if we make these changes, is it relevant to -- is it because
15 of phosphorylation or something else? Jans & Jans did that study and
16 showed changes in phosphorylation -- if not phosphorylation, potential
17 phosphorylation.

18 Snowdy didn't do that study on AAV2 on any of the sites he
19 looked at. And certainly there's no evidence in the record, related to position
20 665, whether that serine is phosphorylatable, because not all serines and
21 threonines are indeed -- and tyrosines, I believe, too -- are indeed
22 phosphorylatable, much less phosphorylated, or undergo any post-
23 translational modification.

24 So, without that study, without a study like the one Jans & Jans
25 did, Snowdy can't teach that changing the phosphorylation potential of that
26 particular residue was what changed it, as opposed to some other binding

1 site, or something else. Snowdy can't teach that it's about phosphorylation.
2 Certainly, no one has taught that with respect to position 665 specifically.
3 So that was a new argument.

4 I also heard Petitioner talk about the Wu 2006 reference, which is
5 Exhibit 1060. So, Wu 2006, as the name that the parties have given it
6 shows, is not prior art. It's after the priority date. It's not in the Petition.
7 And it's comparing AAV1 and AAV6, two different AAVs than what we've
8 been talking about today. And so it's not about any other relevant vector.

9 Moreover, Figure 3 of Exhibit 1060, which I don't have on a slide,
10 but does show that in Wu 2006 they were using a liver-specific promoter,
11 which would have skewed the results in favor of liver tropism. And so Wu
12 2006 can't teach anything about liver expression of any protein, which – and,
13 again, this Wu 2006 reference, it's not in the Petition, it's not prior art, it's not
14 a ground reference, and it doesn't teach anything about expression or
15 changes to rh.10 based on AAV8, AAV7, or any other vector. It's just not
16 about that.

17 I next heard some evidence about -- and, again, this was a new
18 argument -- that an exhibit that Patent Owner cited in our POPR showed that
19 dystrophin was expressed in the liver. So, I don't believe that's anywhere in
20 the Petition, or anywhere else in Petitioner's documents, or indeed in any
21 relevant document to the record today, because I believe it was only cited in
22 the POPR. And their Petitioner's expert -- I believe it's on Slide 23. Ms.
23 Kraning -- I'm sorry, I've got the wrong slide. Yes. I apologize; you do
24 have the right slide. She's ahead of me, as usual.

25 Dr. Schaffer, Petitioner's expert -- so this is from Petitioner's
26 expert's declaration at Exhibit 1005 -- testified in his declaration that when

1 you are looking to improve transduction, people of skill in the art understood
2 that there was a need to improve transduction to multiple cell types. He says
3 liver cells for the treatment of hemophilia and so on, to lung cells for the
4 treatment of cystic fibrosis, and to muscle cells for the treatment of muscular
5 dystrophies. And so, again, a skilled artisan, focused on the problem to be
6 solved by Claim 8, delivering of dystrophin protein, would be focused on the
7 muscle cells. This is from Dr. Schaffer, Petitioner's expert's own
8 declaration.

9 So back to -- I heard reference to Exhibit 2011. That's not in the
10 record. The document that Petitioner's expert cited is the Bowles reference,
11 which is Exhibit 1062 at page 1, but the Bowles reference does not say that
12 dystrophin was expressed in the liver. It notes that it's expressed in various
13 types of muscle, in the retina, and in the brain, but not liver.

14 And I also heard reference to Exhibit 2018, which I think is the
15 Uchino reference, again cited in the POPR. That's not a reference that
16 Petitioner cited at all, anywhere.

17 I also heard an argument that a skilled artisan would want to take
18 rh.10 and turn it into a super-vector. That's also not an argument that's in the
19 Petition. The motivation that's in the Petition is to take rh.10 and to improve
20 the tropism to the liver. Making it into a super-vector that has tropism to
21 many tissues is not an argument that was in the Petition. And again, rh.10,
22 as shown in the '772 Publication, already has good tropism for multiple
23 tissues. And so there's no motivation described anywhere in any of the
24 papers in this proceeding to create rh.10 into a super-vector.

25 I heard an argument on the '126 provisional that Dr. Samulski and
26 his team used the teachings of Snowdy to make the changes. That's simply

1 not true. Dr. Samulski -- that's Petitioner's interpretation, but when Dr.
2 Samulski was asked this question at his deposition -- and this is cited in our
3 surreply at page 24, in footnote 8, and it's Exhibit 1063, which is Dr.
4 Samulski, Patent Owner's expert's deposition, Exhibit 1063 at page 195.
5 Dr. Samulski unequivocally testified that they were not using Dr. Snowdy's
6 work in doing the work in the '126 provisional. And so Petitioner would like
7 to interpret that work that way, but there's simply no evidence that that's the
8 case.

9 I'd also like to note that all of these arguments that are not in the
10 Petition -- as I'm sure Your Honors know quite well, the Petition is the
11 master of the IPR. Allowing arguments that are not in the Petition violates
12 SAS and the regulations under the Administrative Procedures Act. And so
13 allowing Petitioners to inject new arguments at this stage of the proceedings
14 is simply -- it's unfair, and it violates the rules and the case law that we're all
15 subject to.

16 Ms. Kraning, could you go back to Slide 6 just one last time?
17 Again, in closing, the Petition here relies upon the idea that a skilled artisan
18 would start with the '772 Publication and would make a series of choices.
19 And if the Board finds that a person of skill in the art would not make any
20 one of these choices, if they would not modify AAVrh.10 to improve liver
21 targeting, if they would not choose AAV8 but would choose either another
22 vector or multiple other vectors, if they would not believe that Snowdy
23 teaches that you would limit the positions based on phosphorylation
24 potential, you simply don't get to the patented claims, and the Petition has
25 failed to show that the claims are unpatentable.

26 If I may just have one moment, Your Honors?

1 JUDGE MITCHELL: Sure.

2 JUDGE FREDMAN: Sure.

3 MS. MORRISON: Unless Your Honors have any questions, I
4 have nothing further.

5 JUDGE MITCHELL: Thank you very much.

6 MS. MORRISON: Thank you.

7 JUDGE JENKS: I don't have additional questions. Thank you.

8 JUDGE MITCHELL: Thank you both. This has been extremely
9 helpful. Y'all both did an excellent presentation, so we really appreciate it.
10 If you don't mind sticking around a couple of minutes just to make sure the
11 court reporter can ask you any questions. We were trying to anticipate what
12 she might hear beforehand, but if you all would stick around, that would be
13 great. So, thank you so much, and we will take this case under advisement,
14 and we're adjourned.
15 (Whereupon, the above-entitled matter went off the record at 3:02
16 p.m.)

IPR2024-00580
Patent 11,680,274 B2

PETITIONER:

Robert B. Wilson
Anne S. Toker
James M. Glass
QUINN EMANUEL URQUHART & SULLIVAN LLP
robertwilson@quinnemanuel.com
annetoker@quinnemanuel.com
jimglass@quinnemanuel.com

PATENT OWNER:

Susan E. Morrison
FISH & RICHARDSON P.C.
morrison@fr.com

Dion M. Bregman
Julie S. Goldemberg
Guylaine Hache
MORGAN, LEWIS & BOCKIUS LLP
dion.bregman@morganlewis.com
julie.goldemberg@morganlewis.com
guylaine.hache@morganlewis.com