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UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAREPTA THERAPEUTICS, INC.,)
 Petitioner,)
 v.)
)
 THE TRUSTEES OF THE UNIVERSITY OF) Case IPR2024-00580
 PENNSYLVANIA,) Patent 11,680, 274
)
 Patent Owner,)
 and)
 REGENXBIO INC.)
 Exclusive Licensee.)
)

Deposition of DR. DAVID V. SCHAFFER
 Berkeley, California
 Friday, November 1, 2024

Reported Stenographically by
 Michael P. Hensley, RDR, CSR No. 14114

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1 Deposition of DR. DAVID V. SCHAFFER, commencing at
 2 the hour of 9:09 A.M. and concluding at the hour of
 3 5:43 P.M. on Friday, November 1, 2024, at the location
 4 of 41 Tunnel Road, Berkeley, California 94705, before
 5 Michael Hensley, Registered Diplomat Reporter,
 6 Certified Shorthand Reporter No. 14114, in and for the
 7 State of California.

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Page 5 1 INDEX 2 3 EXAMINATIONS 4 WITNESS: DR. DAVID V. SCHAFER Page 5 BY ATTORNEY MORRISON 6 6 7 EXHIBITS 8 No. Description Page 9 2023 "Enhancing the clinical potential of 169 10 AAV vectors by capsid engineering to 11 evade pre-existing immunity" 12 2024 "Library Selection and Directed 180 13 Evolution Approaches to Engineering 14 Targeted Viral Vectors" 15 2025 "AAV shuffles to the liver: 237 16 Commentary on Lisowski et al." 17 2026 "Adeno-Associated Virus Vectors and 249 18 Neurological Gene Therapy" 19 20 21 22	Page 6 1 Via Videoconference 2 Friday, November 1, 2024 3 9:09 A.M. - 5:43 P.M. 4 -o0o- 5 THE COURT REPORTER: Good morning. My name is 6 Mike Hensley. I am a California Certified Shorthand 7 Reporter, CSR #14114. Today's proceedings are being 8 captured by stenographic means. 9 DR. DAVID V. SCHAFER, 10 having been first duly sworn, was examined and testified 11 as follows: 12 EXAMINATION 13 BY ATTORNEY MORRISON: 14 Q. Good morning, Dr. Schaffer. 15 A. Good morning. 16 Q. We just met off the record. My name is Susan 17 Morrison. I represent REGENXBIO in these proceedings, 18 and I'll be asking you some questions today. 19 A. Thank you. Very good to meet you. 20 Q. Nice to meet you as well. 21 Can you please state your name and residential 22 address for the record.
Page 7 1 A. Sure. David Schaffer. 2 Lincolnshire Drive, 2 Oakland, California 94618. 3 Q. Dr. Schaffer, have you ever been deposed 4 before? 5 A. This is my first deposition. 6 Q. All right. Do you understand that today I 7 will ask questions, and you will answer them as best you 8 can? 9 A. Yes, I understand. 10 Q. And you understand that you are under oath. 11 The court reporter just swore you in, and so you've 12 sworn to tell the truth; right? 13 A. I acknowledge I'm under oath, and I will tell 14 the truth. 15 Q. And that is just like you're in a court of 16 law. 17 Do you understand that? 18 A. Yes, understood. 19 Q. And you understand that the testimony you give 20 today can be used in these proceedings. 21 Do you understand? 22 A. Yes, understood.	Page 8 1 Q. And so you need to provide honest and truthful 2 answers, and you'll do that; right? 3 A. I looked forward to doing so. 4 Q. Now, your attorney, Mr. Wilson, may make some 5 objections, but you understand you're obligated to 6 answer my questions unless he instructs you not to 7 answer. 8 A. I understand, yes. 9 Q. Now, you can ask me to clarify one of my 10 questions if it's unclear. But if you answer it, I'll 11 take it as an indication that you understood it. 12 Is that fair? 13 A. Yes. 14 Q. Please also let me finish my questions before 15 you respond, and I'll do the same for you. Okay? 16 A. Look forward to being courteous, yes. 17 Q. Okay. And Mike will, I'm sure, appreciate 18 that if we both do that. 19 I'll try to take a break every hour. 20 A. Mm-hmm. 21 Q. But if you need a break sooner than that, just 22 let me know, and I'd be happy to take one at any time.

Page 9 1 Okay? 2 A. Okay. Thank you. 3 Q. The only exception to that is if I have a 4 question pending, I'll ask that you answer it before we 5 take a break. 6 A. Okay. Complete the -- sure. 7 Q. Complete the question and answer and then we 8 can take a break. 9 Is that okay? 10 A. Sounds good. 11 Q. All right. Is there any reason, medical or 12 otherwise today, that you can't give complete, truthful, 13 and accurate testimony? 14 A. There is no reason, medical or otherwise, that 15 I can't be truthful -- 16 Q. Okay. 17 A. -- in the responses, yes. 18 Q. Okay. Great. 19 I see that you have two very large binders in 20 front of you. What is in those binders? 21 We don't have to go through every document at 22 this point, but if you could give me a description of	Page 10 1 what's in those binders. 2 A. Sure. The first binder contains my 3 declaration at the top. And the declaration itself, as 4 you likely noticed and I'm sure you've seen it, contains 5 a number of exhibits or references; so the remainder of 6 both of the binders is the -- in order, what those 7 references are. 8 Q. I see. 9 So is it all of the exhibits that were filed 10 to your declaration? 11 A. I believe it's all the exhibits. In some 12 cases, like Albert's text, it's not the entire textbook. 13 Q. Sure. 14 A. It's the sections that were referred to. 15 Q. Okay. And would you mind if I -- 16 A. Certainly. 17 Q. I don't know the easiest way to do this, but 18 if I just took a look and see what's in these binders. 19 I see. 20 Okay. So for the record, Dr. Schaffer has 21 brought two binders with him. They contain a copy of 22 his declaration it appears, as well as Exhibits 10 --
Page 11 1 excuse me -- 1001 through 1004 to these proceeding, as 2 well as 1006 through -- let's see, it looks like 1006 3 through 1023, as well as 1026, 1029 through 1054, and 4 1056, all of which are already of record in these 5 proceedings. 6 A. Thank you. 7 Q. I'll give those back to you. 8 And I also have copies of many of those 9 documents that we'll look at today. I'm happy to have 10 you use the copy you brought, or I have separate stapled 11 copies. Whatever you're comfortable with is fine with 12 me. 13 A. Thank you. 14 (Discussion off the record.) 15 /// 16 BY ATTORNEY MORRISON: 17 Q. All right. Dr. Schaffer, when were you first 18 retained by Sarepta in these proceedings? 19 A. Yeah. I can't recall the exact date. It's 20 approximately between one and one and a half years ago 21 or so. 22 Q. So somewhere between approximately May and	Page 12 1 November of 2023? 2 Does that sound about right? 3 A. It sounds about right, yeah. Approximately a 4 year or so ago. If I -- I didn't bring my laptop. If I 5 had my hard drive, I could look that up, but my 6 apologies. 7 Q. Sure. 8 And who was it that reached out to you on 9 behalf of Sarepta? What person? 10 A. It was Robert here. 11 Q. And had you ever known or worked with 12 Mr. Wilson before? 13 A. We were just meeting for the first time then. 14 Q. And do you know how Mr. Wilson got your name 15 or how you were -- became on his radar to work as an 16 expert in this case? 17 A. He didn't -- 18 ATTORNEY WILSON: I'm just going to caution 19 you -- 20 THE WITNESS: Okay. Sure. 21 ATTORNEY WILSON: -- as to any communications. 22 Don't reveal any attorney-client privileged or work

Page 13 1 product information. 2 But otherwise, you can answer. 3 THE WITNESS: Okay. 4 I do not know how he became acquainted with 5 me. 6 BY ATTORNEY MORRISON: 7 Q. Okay. And have you ever worked with -- I 8 don't think -- have you ever been retained as an expert 9 before? 10 I know you said you've never testified. 11 Have you ever been retained in a case before? 12 A. Not in a case. I've done consulting 13 beforehand, but I've not actually been involved in a 14 case beforehand. Lots of consulting for companies 15 but -- 16 Q. Have you ever done litigation consulting 17 before? 18 A. I was involved in the beginning of a case to 19 provide scientific information, but it settled 20 relatively early; so it never proceeded all the way to 21 deposition and certainly, not to trial. 22 Q. Okay. And did you -- and in that case, did	Page 14 1 you provide an expert report or declaration like the one 2 you did here? 3 A. I didn't. It didn't proceed that far. 4 Q. Okay. And generally, what was the subject 5 matter of that case? 6 A. It was a case in which stem cells were being 7 harvested from a patient and readministered, and very 8 unfortunately, the patient passed away. 9 Q. Okay. 10 A. And so the case was resolving around whether 11 or not that was due to some ill doings by the company 12 that provided the stem cells. 13 Q. Okay. So it was not a patent litigation; fair 14 to say? 15 A. That's correct. 16 Q. Okay. And are you aware that, in addition to 17 this -- these IPR proceedings in which you have provided 18 a declaration, that there's also a litigation going on 19 in the district court in the District of Delaware? 20 A. I have read some -- you know, news comes out 21 about some of these and -- because it affects the field 22 as a whole.
Page 15 1 Q. Sure. 2 A. So I have in personal knowledge. I've read 3 some press releases. 4 Q. And have you been retained for the district 5 court proceeding as well? 6 A. I have not. 7 Q. Okay. Now, you said earlier that you've 8 never -- you've never been deposed before; is that 9 right? 10 A. That's correct. 11 Q. And you've only -- this is the second time 12 you've ever been retained as an expert witness in a 13 legal proceeding; is that right? 14 A. That's correct. 15 Q. Have you ever testified in any proceeding? 16 A. No, I have not. 17 Q. Okay. Have you ever consulted -- you said 18 you've consulted with industry. Have you ever consulted 19 for Sarepta? 20 A. I've not consulted for Sarepta. 21 Q. Okay. Do you consult for any -- and I'm not 22 asking which ones at this moment, but do you consult for	Page 16 1 other companies in the gene therapy space? 2 A. I do consult for other companies in gene 3 therapy, yes. 4 Q. Have you ever consulted with for REGENXBIO? 5 A. I've never consulted for REGENEX. 6 Q. And to the extent you can tell me without 7 revealing confidential information -- I'm not seeking 8 anything confidential -- are there any companies with 9 whom you're -- you can tell me you are consulting in the 10 gene therapy space today? 11 ATTORNEY WILSON: Right. Just to reiterate 12 the -- the caution there that was built into the 13 question, if you have any third-party confidential 14 obligations and, of course, don't reveal that 15 information but if you can otherwise testify, you may. 16 THE WITNESS: Yes, you know, when one signs a 17 consulting agreement, there's sometimes a paragraph 18 saying that you're not able to reveal that, you know, 19 this relationship publicly. 20 BY ATTORNEY MORRISON: 21 Q. Sure. 22 A. To be, I mean, it's several companies in gene

4 (Pages 13 to 16)

Page 17 1 therapy that I'm consulting with. I honestly can't 2 remember whether or not that paragraph is present within 3 those consulting agreements so I should probably, you 4 know, defer to those companies. 5 Q. Fair enough. Okay, if you can -- I can either 6 hand you a copy or if you want to open your binder? 7 A. Sure. 8 Q. I have a copy of -- it's Exhibit 1001. It's 9 the '274 patent. Would you like a copy or you want to 10 use the one in your binder? Here? 11 A. You have a copy here. There we go. 12 (Procedural admonition by the Court Reporter.) 13 ATTORNEY MORRISON: Mr. Wilson, would you like 14 a copy? 15 ATTORNEY WILSON: Sure. Thank you. 16 BY ATTORNEY MORRISON: 17 Q. And I just -- if you just take a look at the 18 '274 patent, which I think is maybe the exhibit before. 19 It's Exhibit 1001 to these proceedings. 20 A. Thank you. 21 Q. And I just want to confirm that this is 22 U.S. Patent 11,680,274, and this is the patent about	Page 18 1 which you have provided opinions in this matter; is that 2 right? 3 A. That's confirmed. Yes. We've been referring 4 it as the '274 patent. 5 Q. And this is the patent that you analyzed and 6 have provided opinions about in your declaration? 7 A. That's correct. 8 ATTORNEY MORRISON: Okay. I'm also going to 9 introduce previously-marked Exhibit 1005 which is your 10 declaration. 11 I believe it's in the front of your binder. 12 ATTORNEY WILSON: Sure. Thank you. 13 ATTORNEY MORRISON: Exhibit 1005 is the 14 declaration that you signed in these IPR proceedings, 15 and I'll read the number for the record, 2024-00580. 16 BY ATTORNEY MORRISON: 17 Q. Right? 18 A. That's correct. 19 Q. And if you go to page 119, the very last page 20 or your declaration, that's your signature? 21 A. I can confirm that's my signature, yes. 22 Q. And you signed this on February 21st of this
Page 19 1 year; correct? 2 A. That's correct. 3 Q. About how much time did you spend preparing 4 this declaration, Exhibit 1005? 5 A. Probably a couple dozen hours. 6 Q. Okay. And can you tell me about the process 7 of preparing the declaration. How did you go about 8 doing that? 9 A. It was the result of a series of iterative 10 Zoom meetings between myself and counsel where I 11 supervised the collection of information, you know, made 12 appropriate references to references that I felt were 13 relevant, you know, many of which became exhibits, and 14 the iterative process of revising and refining and 15 finalizing that document. 16 Q. Okay. And so let me -- let me drill down on 17 that a little bit. 18 You said you "supervised the collection of 19 information." What do you mean by that? The collection 20 of the references or something else? 21 A. Collection of the references. 22 Q. Was there other information that you were	Page 20 1 collecting as part of the process of preparing your 2 declaration? 3 A. I was providing scientific material to be able 4 to shape my opinions about the claims of the '274 patent 5 and in addition referring those materials to counsel 6 because I felt they were relevant for -- for the 7 declaration. 8 Q. What sort of scientific information were you 9 providing in addition to the references that are 10 exhibits to your declaration? 11 A. It's really the references. 12 Q. Okay. Was there any other information that 13 you provided other than your thoughts and opinions, but 14 scientific information that you provided for counsel -- 15 to counsel other than what's in the references that are 16 attached to your declaration? 17 A. Yeah, I have no recollection of any materials 18 that didn't end up finally getting entered as an 19 exhibit. 20 Q. Okay. 21 All right. And in those iterative Zoom 22 meetings, you were discussing those references with

Page 21 1 counsel and the preparation of your declaration? 2 A. That is correct. 3 Q. Who wrote the first draft of the declaration? 4 A. Counsel wrote the initial draft, which I then 5 edited and refined and ended up being, you know, 6 somewhat lengthy iterative process to be able to arrive 7 at the final document. 8 Q. Okay. And do you know who -- what person 9 wrote the initial draft or what people? 10 A. It was people within the law firm so, to my 11 knowledge, the people I've interacted with the most are 12 counsel here, Robert Wilson, and counsel Anne Toker. 13 Q. Okay. Is there anyone else at Quinn Emanuel 14 that you've interacted with that you recall? 15 A. Not to my knowledge, no. 16 Q. Okay. And do you know if Mr. Wilson and 17 Ms. Toker wrote that initial draft or were there others 18 that were helping testimony? 19 A. I believe they wrote the initial draft. 20 Q. Okay. Who was on those Zoom meetings that you 21 had with counsel? Was it Mr. Wilson and Ms. Toker? 22 A. That's correct.	Page 22 1 Q. Okay. Was there anyone else on those Zoom 2 meetings? 3 A. No. 4 Q. Did you ever speak to anyone at Sarepta, the 5 company -- within the company -- when you were preparing 6 this declaration? 7 A. No. 8 Q. Did you speak to anyone else in the field when 9 you were preparing this declaration? 10 A. No. 11 Q. Did you speak to anyone about the declaration 12 besides Mr. Wilson and Ms. Toker? 13 A. No. 14 Q. Would you go to paragraph 17 of your 15 declaration, which is on page 4. When I refer to the 16 page numbers, I'm going to refer to the page numbers at 17 the middle of the bottom of the page. 18 A. The bottom middle. 19 Q. Not the page numbers on the exhibit, because 20 they are different. 21 A. Yeah, thank you. 22 Q. And I'll try to be clear if that changes
Page 23 1 throughout the day. 2 A. I appreciate it. 3 Q. All right. So in paragraph 17 you state that, 4 in forming your opinions, you considered all of the 5 references cited including the following documents, and 6 then you have a long list of documents as well as a 7 table of documents. 8 Do you see that? 9 A. I see that, yes. 10 Q. And those documents include the '274 patent 11 which is Exhibit 1001; right? 12 A. Correct. 13 Q. As well as, what, 55 other exhibits which are 14 numbered Exhibits 1002 through 1056; is that right? 15 A. That's correct. 16 Q. All right. What do you mean by you 17 "considered each of these references"? What does that 18 mean? 19 A. Considered in the sense that if I took a look 20 at some of the claims of '274 and I was asked to be able 21 to provide scientific opinions related to those claims, 22 I felt that these references provided scientific	Page 24 1 information that was materially relevant to -- to my 2 analysis, my scientific analysis, of the claims. 3 Q. Did you read each of these documents in their 4 entirety? 5 A. I didn't read each of the documents in their 6 entirety. For example, Alberts, which is probably a 7 thousand pages. 8 Q. Mm-hmm. Did -- are there any that you read in 9 their entirety? 10 A. Certainly there were some I did read in their 11 entirety, yes. 12 Q. Which ones do you recall reading entirely? 13 A. The '274 patent, my CV, the -- certainly the 14 declaration. 15 Q. Mm-hmm. 16 A. '772 patent. 17 Q. And that's Exhibit 1007 for the record. 18 A. Yes. Exhibit 1008 I've probably read 10 times 19 since it was originally published. 1009 I scanned in 20 its entirety. 1010 read it in its entirety. 1011, 21 1012, 1013 read in their entirety. 22 1017, 1018, 1019, 1020.

Page 25 1 Q. Mm-hmm. 2 A. 1021, 1022, 1023. 1029 and 1030, I authored. 3 1031, 1032, I've certainly read in their entirety. Read 4 sections of 1033, 1034, '35, '36, '37, '38, '39. 1040, 5 probably read in its entirety when I took the course way 6 back when but not -- not recently. Only referred to 7 sections of it. 8 And then all of those fact sheets certainly 9 easy to read in their entirety. 1048, 1049, 1050, '51, 10 '52, '53, '54 read sections of that were relevant, and 11 then 1056 is another version of Alberts -- 12 Q. Okay. 13 A. -- that I read excerpts of. 14 Q. Okay. You said that -- with respect to 15 Exhibit 1009, which is the SS.SNODI reference -- 16 A. Mm-hmm. 17 Q. -- that you scanned that in its entirety. 18 Are there portions that you read more closely 19 than others? 20 What did you mean when you said you scanned 21 it? 22 A. Scanned in the sense that there were two	Page 26 1 versions of that. You know, there was one that was 2 available in the public archive, the database, and then 3 there was also one that was obtained from the library at 4 UNC Chapel Hill; so I read through and compared the two 5 in real time on two different screens to confirm it was 6 same document. So I used the word "scanned" for that, 7 but what I meant is I read those two versions 8 simultaneously, side by side to confirm their identity. 9 Q. Okay. About how much time would you say you 10 spent reading all of these documents? 11 A. That was probably the majority of the, you 12 know, several dozen hours that I spent, and then the 13 balance of that was reading versions or reading 14 iterations of 1005, my declaration, as well as providing 15 feedback to counsel in Zoom meetings. 16 Q. Okay. And so I think you said earlier that 17 you spent a couple of dozen hours, and that would 18 include all the time you spent reading. 19 A. That's correct. 20 Q. Okay. Are there any other documents that you 21 read and considered in forming your declaration that are 22 not included in this list?
Page 27 1 A. This is a pretty exhaustive list; so this 2 includes the scientific information that I took into 3 consideration aside from, you know, common knowledge of 4 what an amino acid looks like. 5 Q. Have you read the patent owner's preliminary 6 response that was filed by University of Pennsylvania 7 and REGENXBIO in May of 2024? 8 A. I did read that, yes. 9 Q. And when did you read that? 10 A. I read it within two weeks of it being 11 released. It was forwarded to me by counsel; so I sat 12 down and read it. 13 Q. And have you read it more recently than that? 14 A. Read it, perhaps, two weeks ago. 15 Q. Okay. So you've read it, you would say, two 16 times? 17 A. Yes. 18 Q. Okay. And have you read the institution 19 decision entered by the Patent Trial and Appeal Board 20 that was issued on -- in September of this year? 21 A. Yes. I read that. Counsel forwarded it to 22 me; so yeah.	Page 28 1 THE WITNESS: Sorry. 2 ATTORNEY WILSON: Just a caution -- 3 THE WITNESS: Okay. 4 ATTORNEY WILSON: -- not to reveal -- 5 THE WITNESS: Sounds great. 6 ATTORNEY WILSON: -- any communication between 7 us. 8 But you can answer the questions. 9 THE WITNESS: Okay. Thank you. 10 BY ATTORNEY MORRISON: 11 Q. And when did you read that decision? 12 A. I read it within a couple of weeks of it being 13 publicly released. 14 Q. Okay. And have you read it another time since 15 then? 16 A. I scanned it a couple of weeks ago. 17 Q. Okay. What did you do to prepare for your 18 deposition today? 19 A. I read a lot of materials including, of 20 course, my declaration, as well as a lot of the exhibits 21 that are cited here and had, you know, discussions with 22 counsel.

Page 29 1 Q. When did you have discussions with counsel? 2 A. Over the past two to three weeks. 3 Q. Were those in person, by Zoom, some of both? 4 A. By Zoom until yesterday, which was in person. 5 Q. Okay. How many times did you meet with 6 counsel over the last couple of weeks to prepare for 7 your deposition? 8 A. Approximately five times. 9 Q. And approximately how long were each of those 10 five times? 11 A. Yesterday was longer, but the other meetings 12 were on the order of two hours. 13 Q. Okay. So you had approximately four Zoom 14 sessions that lasted approximately two hours each, and 15 then an in-person meeting yesterday? 16 A. That's correct. 17 Q. And how long was the in-person meeting? 18 A. It was seven hours -- well, plus a lunch 19 break. 20 Q. Seven hours including lunch or -- 21 A. Not including lunch. 22 Q. Okay. Where did you have that meeting?	Page 30 1 A. It was here at the Claremont Hotel. 2 Q. And who was present on those Zoom meetings? 3 A. In the Zoom meetings, it was counsel -- 4 counsels Toker and Wilson. 5 Q. Mm-hmm. And what about yesterday? 6 A. Yesterday, Counsel Wilson was present in 7 person and Counsel Toker by Zoom. 8 Q. Okay. And during those Zoom or in-person 9 meetings that you had with counsel, did you review any 10 materials that are not part of your declaration? 11 A. We didn't review materials that are not part 12 of the declaration. 13 Q. Okay. So everything that you went over with 14 counsel is in these binders that are sitting in front of 15 you. Is that fair? 16 A. That's fair. 17 Q. On the second page of your declaration, page 2 18 in paragraph 8, you talk about some of your experience. 19 A. Yes. 20 Q. And you talk about your work, including: 21 [As Read] Molecular evolution and 22 engineering of viral gene delivery vehicles.
Page 31 1 Do you see that? 2 A. I see that phrase, yes. 3 Q. Can you give a bit more detail on what you 4 mean by that. 5 What does your work include with respect to 6 this clause I just read, in particular? 7 A. Sure. I have an academic lab that's about two 8 miles from here at the University of California at 9 Berkeley where I'm a faculty; so this work has been 10 conducted in my lab for approximately 25 years or so. 11 So we've been doing work on engineering, the AAV capsid 12 to be able to get enhanced gene delivery. 13 Q. And you mention viral gene delivery vehicles, 14 plural, in paragraph 8. 15 Are there other gene delivery vehicles that 16 you work on that are not AAV? 17 A. We do, yes. 18 Q. And what are those? 19 A. We have worked on lentiviral vectors, 20 adenoviral vectors. We currently also work on vaccinia 21 viral vectors. Most of the work has been AAV. 22 Q. And I apologize. You said "lentiviral," and I	Page 32 1 missed the second one. 2 A. Adenoviral. 3 Q. Adenoviral, thank you. 4 And are those -- AAV plus the other three 5 vectors you mentioned, are those all for gene therapy 6 applications? 7 A. That's correct. 8 Q. And aside from engineering of viral gene 9 delivery vehicles, what other areas does your research 10 focus not outside of that? 11 A. Mm-hmm. Our work focuses on gene therapy and 12 cell therapy; so we have an effort within the lab to be 13 able to engineer stem cells as therapeutics to be able 14 to treat disease. That's a smaller component of our lab 15 at the moment. 16 The majority of the work is focused on viral 17 vectors and gene therapy. 18 Q. Okay. What percentage of your lab's work 19 would you say is focused on AAV gene therapy? 20 A. Approximately half, currently. 21 (Procedural admonition by the Court Reporter.) 22 BY ATTORNEY MORRISON:

Page 33 1 Q. Okay. As part of your declaration, you've 2 given a definition of the person of ordinary skill in 3 the art. 4 Do you recall that? 5 A. I recall that. 6 Q. It's in paragraph 115. 7 A. Thank you. 8 Q. I don't have the page number written down, my 9 apologies. It's page 44. 10 A. I am at that page. Thank you. 11 Q. Okay. And do you see your definition of a 12 person of ordinary skill in the art in paragraph 115? 13 A. I see the definition, yes. 14 Q. And you say that: 15 [As Read] A person of ordinary skill in 16 the art in the field of the '274 patent would 17 have had at least a PhD in biochemistry, 18 molecular biochemistry, or related field and 19 between 1 and 4 years of post-doctoral 20 experience in the field of gene therapy. 21 Right? 22 A. That's correct.	Page 34 1 Q. How did you come up with that definition? 2 A. It's a definition of a person that -- a 3 profile of a person that I often have, or graduate from 4 my lab, at the time that I feel that these people are 5 qualified to be able to work in the field. 6 Q. Did you come up with this definition on your 7 own? 8 A. It was a definition that was initially 9 suggested by counsel, and it's something that I fully 10 agree with. I have no concerns about definition. 11 Q. Do you know Dr. Mark Kay? 12 A. I do know Dr. Kay. 13 Q. Do you know that Dr. Kay provided an expert 14 report in a different litigation between REGENXBIO and 15 the University of Pennsylvania on one side and Sarepta 16 on the other? 17 A. I read some material written by an expert 18 witness Leone that made references to Mr. Kay -- or I 19 can't recall if it was Dr. Kay or Mr. Kay. I assumed 20 that that was Mark Kay. I didn't actually know for 21 sure. 22 Q. Okay. And so fair to say you didn't review
Page 35 1 Dr. Kay's report from the other litigation between the 2 parties? 3 A. I didn't. 4 Q. You did review some of the plaintiff's reports 5 from that other litigation, Dr. Leone's and 6 Dr. Metzger's reports; is that right? 7 A. There's some materials. I believe they're 8 exhibits here within the binders. They're excerpted 9 materials, I believe, not the entire declarations of 10 these -- of these expert witnesses; so it's the 11 material. To my knowledge, it became publicly 12 available; so that's the material I was able to read. 13 Q. Okay. And you said that this definition 14 that's in paragraph 115 was suggested by counsel? 15 A. That's correct. 16 ATTORNEY WILSON: Object to form. 17 BY ATTORNEY MORRISON: 18 Q. And are you aware that the definition is 19 nearly identical to the definition that Dr. Kay provided 20 in the litigation? 21 A. I'm not aware of that. 22 Q. Okay. Now, your PhD, Dr. Schaffer, is in	Page 36 1 chemical engineering; is that right? 2 A. Chemical and biomolecular engineering, yes. 3 Q. Okay. Is there a reason you didn't include a 4 PhD in chemical or biomedical engineer -- excuse me -- 5 A. Biomolecular. 6 Q. -- biomolecular engineering as part of your 7 definition of person of skill in the art? 8 ATTORNEY WILSON: Object to form. Sorry. 9 THE WITNESS: I consider it to be a related 10 field. 11 BY ATTORNEY MORRISON: 12 Q. Okay. And so you -- but you didn't enumerate 13 it specifically in paragraph 115? 14 A. I didn't enumerate it. 15 Q. Okay. 16 A. Enumerating would include, you know, cell 17 biology and virology and bio-engineering, et cetera; so 18 I -- those are lumped into related field. 19 Q. Okay. And so you didn't alter the definition 20 that was suggested to you by the lawyers. Is that fair? 21 ATTORNEY WILSON: Object to form. 22 THE WITNESS: I felt that it's a strong

Page 37 1 definition that I agreed with. 2 BY ATTORNEY MORRISON: 3 Q. Okay. But you didn't make any changes to it; 4 is that correct? 5 A. I did not feel the need to revise this -- this 6 language. 7 Q. Okay. So -- and so you didn't revise the 8 language; is that right? 9 ATTORNEY WILSON: Object to form. 10 THE WITNESS: I didn't feel the need. I feel 11 this is an accurate definition. 12 BY ATTORNEY MORRISON: 13 Q. Okay. And so, again, my question is you said 14 you didn't feel the need to revise it and so I just want 15 to make sure that you in fact did not revise the 16 definition that was provided to you by the lawyers; is 17 that right? 18 ATTORNEY WILSON: Object to form. 19 THE WITNESS: Yeah, the definition is a fully 20 accurate definition that represents my opinion of what a 21 POSA would be within the field. 22 BY ATTORNEY MORRISON:	Page 38 1 Q. Okay. So Dr. Schaffer, the definition was 2 provided to you by -- or suggested to you by the 3 lawyers; is that right? 4 ATTORNEY WILSON: Object to form. 5 THE WITNESS: This is -- as I mentioned, you 6 know, the initial draft was prepared by counsel and I 7 iterated through it, you know, multiple times so the 8 final document represents my opinion. 9 BY ATTORNEY MORRISON: 10 Q. Right. And I understand that, and what I'm 11 asking is did you make any alterations to the definition 12 of person of ordinary skill in the art that appears in 13 paragraph 115? 14 ATTORNEY WILSON: Object to form. 15 THE WITNESS: Yeah, I feel it's an accurate 16 representation of my view of what a POSA is, you know, 17 in the same sense of if I look up a word in Webster, I 18 wouldn't change that definition. It gives us an 19 accurate definition; represents my opinion. 20 BY ATTORNEY MORRISON: 21 Q. Sure. I understand that, and so my question 22 is really simple; and I'm sorry if I'm being unclear,
Page 39 1 but my question is just did you -- yes or no. 2 Did you change the definition that was 3 provided to you by the lawyers? I understand you feel 4 it is accurate, but did you make any alterations to it? 5 ATTORNEY WILSON: Object to form. 6 THE WITNESS: Yeah, the entire document 7 represents my opinions; so I -- as I signed it on the 8 last page; so this is an accurate representation of my 9 view. 10 BY ATTORNEY MORRISON: 11 Q. Is there something that's confusing about my 12 question, sir? Like, did you alter it or not? 13 ATTORNEY WILSON: Object to form. 14 THE WITNESS: I'm simply saying that this 15 document, in its entirety, represents my opinions; so 16 whether or not particular sections underwent a lot of 17 iteration, the entire final document is an accurate 18 representation of my opinion. 19 BY ATTORNEY MORRISON: 20 Q. I understand. But, again, the lawyers 21 suggested to you the definition in paragraph 115; right? 22 ATTORNEY WILSON: Object to form.	Page 40 1 THE WITNESS: The document -- the initial 2 draft, as I had indicated, was prepared by counsel and 3 went through extensive iteration. The final product 4 is -- is my work. 5 BY ATTORNEY MORRISON: 6 Q. Right. 7 A. This represents my opinion. 8 Q. Can we focus on paragraph 115. You're open to 9 that page, right, sir? 10 A. I'm open to that page, yes. 11 Q. Okay. And so focusing just on that paragraph, 12 are you -- you with me so far? 13 A. Yes. 14 Q. Okay. Did you make any edits to paragraph 115 15 from the draft that the lawyers provided you, or did you 16 feel that their definition was accurate and therefore 17 that you did not need to make edits? 18 ATTORNEY WILSON: Object to form. 19 THE WITNESS: I feel this definition is 20 accurate. 21 BY ATTORNEY MORRISON: 22 Q. And so you did not need to make edits to the

Page 41 1 definition the lawyer provided you. Is that correct? 2 ATTORNEY WILSON: Object to form. 3 THE WITNESS: Yeah, I actually don't recall 4 whether or not I made, you know, redline edits to it. I 5 feel that this is an accurate representation of my 6 opinion. 7 Q. Okay. So you don't recall whether you edited 8 the definition that the lawyers provided you; is that 9 right? 10 ATTORNEY WILSON: Object to form. 11 THE WITNESS: I -- all I can say is that the 12 final product is my opinion. 13 BY ATTORNEY MORRISON: 14 Q. Okay. But you didn't add chemical engineering 15 as a field? 16 A. I didn't add chemical engineering as a field. 17 Q. And you didn't add biomolecular engineering as 18 a field? 19 ATTORNEY WILSON: Object to form. 20 THE WITNESS: I didn't add any other words 21 simply because, you know, "related field" is a catch-all 22 phrase that catches a lot.	Page 42 1 BY ATTORNEY MORRISON: 2 Q. Okay. 3 A. So one could continue to add many different 4 things like structural biology or virology or molecular 5 virology or medical virology. The list would probably 6 be, you know, fairly long; so I didn't feel there's a 7 need to be able to, you know, add every single field 8 that's present where somebody would have relevant 9 expertise; so I feel that "a related field" is a 10 catch-all phrase that -- that captured those accurately. 11 Q. And so you didn't feel the need to add those? 12 A. I didn't feel the need to add something beyond 13 "related field." 14 Q. Okay. Do you know Dr. Paola Leone? 15 A. I do not know her personally. 16 Q. And do you know Dr. Mike Metzger? 17 A. I don't know him personally. 18 Q. Do you know of either of them? 19 A. I didn't know of either of them. I read -- 20 Leone's bio is one of the exhibits; so I'm -- I'm 21 familiar with her background, that she works in New 22 Jersey; but otherwise I don't know her personally.
Page 43 1 Q. Okay. Do you know Dr. Gabor Rubanyi? 2 A. I don't. 3 Q. And do you know Dr. Jude Samulski? 4 A. I do know Dr. Samulski. 5 Q. How do you know Dr. Samulski? 6 A. Through professional contacts over the past 7 couple of decades. We both work in the AAV field. 8 Q. And you've, in fact, written papers with 9 Dr. Samulski; right? 10 A. Have I written -- there's a review article 11 that I co-authored with him, yes. 12 Q. Okay. And you would say Dr. Samulski is well 13 known and well respected in the field? 14 A. I would agree with that, yes. 15 Q. All right. And would you say Dr. Samulski is 16 a expert in the field of AAV gene therapy? 17 A. I would agree with that, yes. 18 Q. All right. If you go to -- we're going to go 19 back in your declaration, which is Exhibit 1005, to 20 paragraph 18, which is on page 9. 21 A. I'm on page 9. 22 Q. Okay. And you say, in paragraph 18 on page 9,	Page 44 1 that you are, in this section, describing your 2 understanding of certain legal standards relating to the 3 issue of "obviousness" and then you go on. Do you see 4 that? 5 A. That's correct. The legal standard of 6 "obviousness" was explained to me, and this is 7 summarizing my understanding of the concept. 8 Q. And who explained the legal standard of 9 "obviousness" to you? 10 A. Counsel explained it. 11 Q. And that was counsel from Quinn Emmanuel, 12 Mr. Wilson and Ms. Toker? 13 A. That's correct. 14 Q. And do you recall when they provided this 15 explanation to you? 16 A. I don't recall which meeting. 17 Q. Okay. And did they provide that explanation 18 verbally or was it as part of the draft document? How 19 was that provided to you? 20 A. It was a combination. 21 Q. Okay. Did you draft this section, that's 22 Section 3 of Exhibit 1005, based on that verbal

Page 45 1 explanation or did they provide the first draft of the 2 and you wrote -- you looked at it? 3 A. As with the entire document the first draft 4 was prepared, and then I supervised the irritative 5 process of refining it till it arrived in the final 6 form. 7 Q. And you said "the entire document was first 8 prepared," you mean by counsel? 9 A. That's correct. 10 Q. Okay. 11 A. Based upon discussions, extensive discussions, 12 that we had had. 13 Q. Sure. 14 You say in paragraph 23, which is in the same 15 section but on the next page -- or excuse me, two pages 16 later on page 11. 17 Do you see where I am? 18 A. I am at paragraph 23. Yes. 19 Q. Okay. You say in the first sentence: 20 [As Read] I understand that it is 21 impermissible to evaluate obviousness from a 22 hindsight perspective using the teachings of	Page 46 1 the patent as a guide. 2 Do you see that? 3 A. Yes. One moment. I'm going read the -- the 4 paragraph. 5 Q. Yeah. Go right ahead. 6 A. Thank you. Yes. 7 Q. And that sentence I just read, what does that 8 mean to you, and how did it impact your analysis? 9 A. "Hindsight," as I understand it, the principle 10 is that if there are multiple elements that are present 11 within a given subject matter that combining those 12 elements had to have been obvious to a POSA and could 13 not have been guided by the final subject matter that's 14 being considered. 15 Q. What do you mean "could not have been guided 16 by the final subject matter that's being considered"? 17 A. Yeah, forgive me. This is a scientific, you 18 know, interpretation rather a legal one; so I'm sure 19 it's not up to the standard of other people within this 20 room but if a -- you know, if a -- an invention involves 21 element A and the element B and it's, you know, the 22 combination of those two elements that is at the heart
Page 47 1 of the invention, then one can't just use that subject 2 matter of, you know, A plus B within claim language to 3 be able to say that -- look backwards in hindsight and 4 see something was obvious. It had to have been obvious 5 to a POSA prior to the -- the filing of that subject 6 matter that it was obvious to put together A and B. 7 Q. Okay. 8 All right. I want to talk about some 9 technical background, some more in the scientific area 10 than the legal one. And you have a long section 11 beginning on page 12 of your declaration that talks 12 about technical background in your declaration; right? 13 A. Yes. 14 Q. If you could go to paragraph 61, which is on 15 page 27. 16 A. Yes. I see paragraph 61. 17 Q. And the first sentence in that paragraph says: 18 [As Read] The ability to deliver genes 19 with high efficiency and specificity is 20 important for gene therapy. 21 A. That's what the first sentence says, yes. 22 Q. And so I want to ask about two pieces of that	Page 48 1 sentence. 2 A. Mm-hmm. 3 Q. When you say "deliver genes with high 4 efficiency," what do you mean by that? 5 A. It means that if the DNA is the cargo of a 6 delivery vehicle, you would like enough DNA to be able 7 to arrive at the intended target to be able to have an 8 effect, ideally, a therapeutic effect for a patient. 9 Q. Okay. 10 And when you say "at the intended target," are 11 you referring to a specific -- you want it to arrive at 12 a specific tissue or at a specific place in the cell? 13 both of those things? more things than that? 14 What do you mean by "intended target"? 15 ATTORNEY WILSON: Object to form. 16 THE WITNESS: So I would say -- if I could, 17 perhaps, maybe this is answering your question. Please 18 let me know if it doesn't. You know, I would define 19 "efficiency" as how much material arrives in the nucleus 20 of a cell. Like, how good are you at being able to 21 transfer your genetic material, your DNA medicine to the 22 site where it has the potential to have activity?

Page 49 1 And then I would say specificity is which 2 places is it mediating delivery to, and for a gene 3 therapy, you want to have an effect. You want it to be 4 able to benefit a patient. So by the word 5 "specificity," I mean it has to at least arrive at the 6 target tissue, at the intended tissue where it could 7 have a beneficial effect for a disease. 8 BY ATTORNEY MORRISON: 9 Q. So the -- when you -- in that sentence when 10 you use the word "specificity," you're talking about the 11 target tissue that the gene therapy is being delivered 12 to to give the intended effect, and efficiency is about 13 the arrival at the nucleus of the -- of the DNA into the 14 nucleus of the cell. 15 Do I have that right? 16 A. That's correct. 17 Q. Okay. And in general, gene therapies need to 18 target a particular tissue type, depending on the 19 disease state being treated. 20 Is that fair as a general matter? 21 ATTORNEY WILSON: Object to form. 22 THE WITNESS: I would say that if you're	Page 50 1 considering a target, it depends upon the disease; so in 2 some situations, the target might be very specific, like 3 a photoreceptor neuron to be able to treat an ocular 4 disease. In some cases, it's the entire body. You 5 know, lysosomal storage diseases are an interesting 6 example there, where it affects every cell in the body. 7 So "target" is really a relative word that 8 depends upon the disease that's being treated. 9 BY ATTORNEY MORRISON: 10 Q. And so is it fair to say that what the target 11 tissue is or target tissues, perhaps, is dependent upon 12 the disease being treated? 13 A. That's a fair statement, yes. In some cases, 14 one would want -- like, to have very broad specificity 15 if multiple tissues are affected. In some cases, for 16 some specific situations, like I mentioned for a 17 retinitis pigmentosa in the eye, the target is quite 18 specific. It's a given cell type. 19 Q. And you mention in paragraph 65, which is on 20 page 28 of your declaration, Exhibit 1005, you talk 21 about AAV efficiently infecting: 22 [As Read] Both dividing and nondividing
Page 51 1 cells in a variety of tissues. 2 And then you list a series of tissues. 3 Do you see that? 4 A. I see that paragraph, yes. 5 Q. And are there -- this is perhaps -- you can 6 tell me if this is too broad of a question, but are 7 there other tissues that you might want to target with 8 AAV gene therapy beyond those listed here? 9 A. Yeah. I'll mention first just to clarify, I'm 10 considering AAV as a class of entities in this case; so 11 this is a -- AAVs, in general, have the capacity to be 12 able to infect the dividing and nondividing cells. And 13 in addition, if one wants to target tissues, you know, 14 to be able to mediate delivery at least to those tissues 15 this is an initial list that, you know, covers a lot of 16 therapeutic ground, but there are other diseases where 17 one would want to infect other cell types that are not 18 present in this list. 19 (Clarification inquiry by The Court Reporter.) 20 THE WITNESS: One would want to deliver DNA to 21 other cell types that are not present within this list. 22 BY ATTORNEY MORRISON:	Page 52 1 Q. Can you give me an example of one that's not 2 in this list. 3 A. One example is vasculature. You know, in some 4 cases, vasculature can play a role in hypertension. 5 Q. Are there others? 6 A. Synovial. So joint, you know, arthritis 7 affects the joint. That's an interesting target, 8 important target. 9 Q. I see you have "brain" listed. 10 What about the central nervous system, more 11 generally? Is that a target for AAV gene therapy? 12 A. Yes. The central nervous system refers to the 13 brain, plus the spinal cord, plus the retina; so brain 14 and retina are listed here. In some cases, spinal cord 15 is an interesting -- a really important target. 16 Q. Is spinal cord for a target separate from 17 brain and retina? 18 Can each of those be their own target, or are 19 they always targeted together? 20 A. There are some situations where the spinal 21 cord is the primary site of disease. And so in that 22 case, one would want to deliver at least to the spinal

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1 cord.

2 **Q. Okay. What about the bladder?**

3 A. It has not been a widespread, you know, focus
4 or topic for gene delivery. I have heard about people
5 talking about delivering to bladder cancers. And then
6 in addition, there's some situations where the bladder
7 lining loses integrity, which causes problems for the
8 function of the tissue.

9 **Q. What about the kidney?**

10 A. The kidney, there are diseases, such as
11 polycystic kidney, that do affect kidney. There are
12 investigators in the field, especially most recently,
13 very recently who have been considering delivery to the
14 kidney.

15 **Q. And what about the mesenteric lymph nodes?**

16 A. Lymph nodes are possibly interesting. Either
17 for, in some cases, vaccine applications, if one would
18 like to expose the immune system to an antigen. My
19 personal opinion is I don't think AAV is very good as a
20 vaccine vector, but there are some people who have been
21 talking about using AAV delivery to expose the immune
22 system to antigen.

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1 **Q. Okay. What about for -- are there gene**
2 **therapies that target the lymph nodes outside the**
3 **vaccine context?**

4 A. Not to my knowledge.

5 **Q. Okay. Now, different AAV vectors can have**
6 **different affinities for different tissues.**

7 **Is that fair or --**

8 A. That's right. The word that the field would
9 use is "tropism." "Tropism" refers to the collection of
10 cells that a given AAV is capable of infecting.

11 **Q. And so you would want to choose an AAV vector**
12 **with the tropism to the tissue you're trying to target**
13 **as a general matter.**

14 **Is that fair?**

15 ATTORNEY WILSON: Object to form.

16 THE WITNESS: Yeah. I might say that a little
17 bit differently.

18 BY ATTORNEY MORRISON:

19 **Q. Sure.**

20 A. That if one wants to be able to treat a
21 condition that affects a particular disease -- sorry --
22 a particular tissue or a collection of cells, you would

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1 want to choose an AAV that can at least make it to those
2 cell types.

3 **Q. What do you mean, "can at least make it to**
4 **those cell types"?**

5 A. In some cases, AAV's affectivities go beyond a
6 single cell type or a given tissue type; so I don't view
7 that as a negative. So the requirement of the bar is
8 that it at least gets to the cell type that's affected
9 by a disease.

10 **Q. Okay. And so if you wanted to target the --**
11 **let's see, the liver, for example, you would want to**
12 **choose an AAV that would at least have tropism for the**
13 **liver; is that right?**

14 ATTORNEY WILSON: Object to form.

15 THE WITNESS: I would want to choose an AAV
16 that's capable of efficient delivery to liver at least.
17 If it happens to go elsewhere, I don't view that as, you
18 know, necessarily problematic, but one would want to
19 choose something that at least goes to liver.

20 BY ATTORNEY MORRISON:

21 **Q. And so if you -- but you wouldn't want to**
22 **choose -- strike that. Let me start overt.**

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1 **If your desire is to target the lung, you**
2 **wouldn't want to choose an AAV that preferentially**
3 **affects -- infects the spinal cord, for example.**

4 **Is that fair?**

5 ATTORNEY WILSON: Object to form.

6 THE WITNESS: I think it's a relative
7 consideration. You know, "preferentially" is a relative
8 word. So what I would say is that -- and, you know, we
9 often do this within the field. You define what's
10 called a "target product profile." It's, like, what are
11 the properties of my therapeutic or my delivery vehicle
12 that I need to have as a requirement to be able to treat
13 a condition.

14 So you typically say that with a given dosage,
15 I would like to have a certain efficiency for the target
16 cells, and that's then sufficient.

17 If it -- if it happens to go elsewhere even,
18 you know, quote/unquote preferentially, that's not too
19 much of a concern to me as long as I hit the criteria
20 for what's necessary to be able to treat a given
21 condition.

22 BY ATTORNEY MORRISON:

14 (Pages 53 to 56)

Page 57 1 Q. Do you -- when designing an AAV gene therapy, 2 do you select a vector based on the tropism of that 3 vector? 4 ATTORNEY WILSON: Object to form. 5 THE WITNESS: I would select a vector that's 6 capable of mediating, you know, what I mentioned as the 7 target product profile by which I mean it has to hit 8 some threshold of efficiency for a given target tissue 9 to be able to benefit a patient suffering from a 10 condition within that tissue. 11 BY ATTORNEY MORRISON: 12 Q. I want to make sure I understand and let me 13 give you a specific example. 14 So if I want to target a disease that's in the 15 vasculature, for example, I would want to choose an AAV 16 that has at least tropism for the vasculature. Is that 17 fair? 18 ATTORNEY WILSON: Object to form. 19 THE WITNESS: I think it's fair that if one 20 wanted to target vasculature you would choose a vector 21 that within its tropism, within its capabilities of 22 realm, it has the capacity to be able to make it to	Page 58 1 vasculature. 2 BY ATTORNEY MORRISON: 3 Q. Mm-hmm. 4 A. But if I -- oh, sorry. If I could respond 5 with an example. There's an interesting FDA-approved 6 gene therapy Zolgensma. You might be familiar, and this 7 is by Novartis. They are trying to get delivery to the 8 spinal cord, and they're doing intravenous 9 administration of AV9. AV9 goes lots of places, it goes 10 to liver, it goes to skeletal muscle. In fact only a 11 minority of it goes to the spinal cord, however it's -- 12 it's a life-saving gene therapy. 13 BY ATTORNEY MORRISON: 14 Q. But AAV9 does have tropism for the spinal cord 15 in addition; right? 16 A. It does have some capacity to reach the spinal 17 cord. 18 Q. And so if you're choosing your AAV, you would 19 want to choose -- strike that. Let me start over again. 20 If you are choosing -- let's use my 21 vasculature example. If you are targeting a disease 22 that impacts vasculature, the AAV you choose, you would
Page 59 1 want to choose one that has tropism for vasculature; 2 correct? 3 A. Yes. I would want to choose one that at least 4 has tropism for vasculature. 5 Q. And certain -- certain tissues, certain target 6 tissues are more difficult to hit. Is that fair? 7 ATTORNEY WILSON: Object to form. 8 THE WITNESS: I think that, you know, amongst 9 the natural AAVs that had been considered, they have 10 tropism, you know, preferentially for some tissues 11 versus others. You know, the -- the hope is that one 12 can find an AAV that's sufficiently good at one or more 13 tissues that it could be the basis of a gene therapy. 14 BY ATTORNEY MORRISON: 15 Q. So but certain tissues like the central 16 nervous system were traditionally difficult to target. 17 Is that fair? 18 ATTORNEY WILSON: Object to form. 19 THE WITNESS: That is a technical question. 20 If I could provide a technical response. 21 BY ATTORNEY MORRISON: 22 Q. Sure.	Page 60 1 A. There are multiple routes of administration. 2 There are multiple ways to do delivery and inject in the 3 nervous system, and there are multiple serotypes; so it 4 is possible to find a combination of those things, 5 especially the delivery method that's capable of 6 effective delivery to the nervous system. 7 Q. Let me -- let me take you back to the time of 8 the invention; so in 2000 and -- the 2004, 2005 time 9 frame. 10 At that time there are certain tissues that 11 were more difficult to target like the central nervous 12 system. Is that fair? 13 A. The central nervous system has always been 14 viewed as a tough target because of the blood brain 15 barrier yet the very first AAV gene therapy was in the 16 central nervous system. 17 Q. And when was Zolgensma approved? 18 ATTORNEY WILSON: Object to form. 19 BY ATTORNEY MORRISON: 20 Q. Approximately? 21 A. Zolgensma was approved in 2019. 22 Q. So 14 years after the approximate priority

Page 61 1 date of the '274 patent; is that right? 2 A. The -- that is correct. 3 Q. Okay. If you could turn to the Snowdy 4 reference, which I believe is Exhibit -- 5 A. 1009 it looks like. 6 Q. Yes. 7 A. I just happened to find it in the tab. 8 (Clarification inquiry by the Court Reporter.) 9 ATTORNEY MORRISON: Yes, it's S-n-o-w-d-y. 10 If you go to page 15 -- 11 ATTORNEY WILSON: Susan, do you happen to have 12 a copy? 13 ATTORNEY MORRISON: I do. I'm sorry. 14 ATTORNEY WILSON: No worries. Thank you. 15 ATTORNEY MORRISON: Mm-hmm. 16 THE WITNESS: And this is in the bottom middle 17 pagination. 18 BY ATTORNEY MORRISON: 19 Q. Let me make sure. 20 No, I'm sorry. This is in the -- in the 21 pagination of the exhibit; so it's actually page 1 of 22 the thesis.	Page 62 1 A. Thank you. 2 Q. Page 15 of the document as a whole. 3 A. I'm at page 15, Sarepta Exhibit 1009. 4 Q. Okay. And Snowdy talks about, in the second 5 full paragraph, that there is a lack of method for 6 providing efficient delivery of genes to the nervous 7 system; is that right? 8 A. Let me read the paragraph, thank you. 9 Q. Sure. 10 A. Yes. The paragraph start with: 11 [As Read] Progress-limiting aspect of 12 gene therapy in the brain is the lack of 13 methods providing efficient gene delivery. 14 Q. Of genes to the nervous system; right? 15 A. Delivery of genes to the nervous system, yes. 16 Q. And you would agree that at the time this 17 thesis was written in 2004 -- or, sorry, 2003 was the 18 writing of the thesis -- that was true? 19 Is that fair? 20 A. It's a -- "efficient" is a relative word; so a 21 number of us were already using AAV for gene delivery to 22 the nervous system. It was efficient enough for some
Page 63 1 applications; not efficient enough for others, but, yes, 2 it certainly wasn't capable of solving every disease 3 condition in the nervous system at that time. 4 Q. Okay. Are there other tissue types that, at 5 the time of the invention, were particularly 6 delivered -- difficult to deliver AAV to? 7 ATTORNEY WILSON: Object to form. 8 THE WITNESS: I believe what you're saying 9 what are other tissue targets that might be of interest 10 for AAV gene therapy where the properties of the virus 11 might need to be improved? 12 BY ATTORNEY MORRISON: 13 Q. Yes. That's exactly right. 14 A. All right. The heart is an interesting 15 target, a compelling target with unmet medical need and 16 a difficult gene therapy target. 17 Q. And there's different AAV serotypes that are 18 known to be better at targeting specific tissues in 19 general. Is that fair? 20 ATTORNEY WILSON: Object to form. 21 THE WITNESS: If you consider a, you know, 22 several natural versions of AAV and analyze where they	Page 64 1 happen to mediate efficient gene delivery, some are 2 better than others at particular tissue types. 3 BY ATTORNEY MORRISON: 4 Q. For example, AAV1 was known to deliver 5 tissue -- excuse me, deliver efficiently to muscle. Is 6 that fair? 7 ATTORNEY WILSON: Object to form. 8 THE WITNESS: Yeah, AAV1 was considered to be 9 an effective gene delivery for muscle early in the 10 field. 11 BY ATTORNEY MORRISON: 12 Q. And AAV7 was also known to be an effective 13 gene-delivery vehicle for muscle early in -- early in 14 the field. Is that fair? 15 ATTORNEY WILSON: Object to form. 16 THE WITNESS: Yes, let me look at -- 17 To my knowledge, AAV7 wasn't really reported 18 until the -- the inventors of this patent started 19 generating data. Oh, should I have kept a -- 20 BY ATTORNEY MORRISON: 21 Q. No. 22 A. Okay.

Page 65 1 So there are AAV7 data that are recorded in 2 the '772 patent publication. That's the first time, or 3 to my knowledge, that's the first instance of 7 -- of 4 AAV7 being reported within the field and there are some 5 muscle gene delivery data reported in there. 6 Q. Okay. We'll look at that in detail later. 7 And AAV9 was reported to be good to the -- at 8 delivering gene therapies to the heart. Is that fair? 9 ATTORNEY WILSON: Object to form. 10 THE WITNESS: AAV9 has pretty broad 11 biodistribution. AAV9 biodistributes to, well, clearly 12 the -- the spinal cord at least within neonates -- 13 within newborns -- because it's the basis for Zolgensma. 14 It biodistributes to the liver, skeletal muscle, and 15 somewhat -- I can't recall the biodistribution to the 16 heart, but I would say that it's much more efficient at 17 liver than heart. 18 BY ATTORNEY MORRISON: 19 Q. Okay. 20 All right. I think -- I think we've been 21 going about an hour. 22 A. Okay.	Page 66 1 Q. Do you want to take a break or do you want to 2 keep going? 3 A. Short break wouldn't -- wouldn't hurt. 4 Q. Okay. 5 A. Thank you. 6 ATTORNEY MORRISON: Let's do that. 7 (A break was taken.) 8 BY ATTORNEY MORRISON: 9 Q. Okay. Welcome back, Dr. Schaffer. 10 A. Thank you. 11 Q. Did you talk to Mr. Wilson at the break about 12 the substance of the deposition? 13 A. No. We talked about flights home. 14 Q. Okay. And so back to the sort of technology, 15 underlying technology, AAV capsid is formed of three 16 different proteins in a 60-unit capsid; is that right? 17 A. That's correct. 18 Q. And those three proteins are called VP1, VP2, 19 and VP3? 20 A. That's correct. VP stand for "viral protein." 21 Q. And the same string of DNA encodes all three 22 of those proteins; right?
Page 67 1 A. That's correct. The same gene inside -- AAV 2 genome encodes all three of those. AAV genome. 3 Q. And VP1 is the longest of the three proteins; 4 is that right? 5 A. That's correct. 6 Q. And then VP2 is shorter than VP1, but a subset 7 of the amino acids that are in VP1; is that right? 8 A. That's correct, yeah. VP2 is 137 amino acids, 9 typically, shorter than VP1. 10 Q. And it's the end terminus of VP1 that is not 11 present in VP2; is that right? 12 A. If you take VP2 and add 137 amino acids onto 13 the end terminus, you know; so add that VP1 unique 14 region then you end up with VP1, yes. 15 Q. And so -- and then VP3 is shorter still than 16 VP2; correct? 17 A. That's correct. If you take VP3 and add 202 18 amino acids onto the end terminus including the 137 from 19 VP1 -- sorry, if you add from 138 amino acids to 202 20 amino acids onto the end terminus of VP3, you get VP2. 21 Q. Okay. And those three proteins form -- come 22 together to form a viral capsid; right?	Page 68 1 A. That's correct. VP1, '2, and '3 combine 2 together to create the viral capsid in a ratio of around 3 1 to 1 to 10. 4 Q. You said in a ratio of 1 to 10 to 10; is that 5 right? 6 A. That's right. As you mentioned a moment ago, 7 60 copies of the viral proteins assemble to form the 8 capsid, and so it would be five copies roughly of VP1, 9 five of VP2, and then 50 of VP3. 10 Q. Okay. And different regions of the capsid 11 protein have different functions in terms of the capsid; 12 is that right? 13 ATTORNEY WILSON: Object to form. 14 THE WITNESS: Different surface regions on the 15 virus have different functions, have different 16 properties or different ways of interacting with cells 17 and tissues. 18 BY ATTORNEY MORRISON: 19 Q. For example, the -- well, let me ask you this: 20 What's a nuclear localization signal? 21 A. A nuclear localization signal is a -- 22 typically, a peptide present as part of a larger protein

Page 69 1 that interacts with components inside the cell that 2 mediate its entry or import into the nucleus. 3 Q. So from the cytoplasm of the cell into the 4 nucleus. 5 Is that fair? 6 A. That's correct, from the cytosol into the 7 nuclear limit. 8 Q. And the nuclear localization signals are 9 typically located in VP1 or sometimes in VP2; is that 10 right? 11 ATTORNEY WILSON: Object to form. 12 THE WITNESS: The field has been studying 13 nuclear localization signals trying to -- well, taking a 14 step back. 15 AAV has the capacity to move through the 16 nuclear pore. As we discussed earlier, it can infect 17 nondividing cells, which means it has to be able to make 18 it through the nuclear pore. So the field has been 19 trying to discover where the nuclear localization 20 activity of AAV resides. You know, where within AAV is 21 responsible for nuclear localization. 22 BY ATTORNEY MORRISON:	Page 70 1 Q. In 2005, at the time of the invention, it was 2 believed that the nuclear localization signals were in 3 VP1; is that right? 4 ATTORNEY WILSON: Object to form. 5 THE WITNESS: I cannot recall the exact date. 6 Dr. Samulski, whom you referred to earlier, was one of 7 the leaders in investigating the location of these 8 nuclear localization signals; so he suggested several 9 putative nuclear localization sequences within the VP1 10 and VP2 unique region. I can't recall the timing where 11 that was published, though. 12 BY ATTORNEY MORRISON: 13 Q. Okay. And Dr. Samulski's work did not suggest 14 any nuclear localization signals in VP3; is that right? 15 ATTORNEY WILSON: Object to form. 16 THE WITNESS: To my recollection, Dr. Samulski 17 has not suggested nuclear localization signals within 18 VP3. 19 BY ATTORNEY MORRISON: 20 Q. And tropism is generally controlled by the VP3 21 portion of the capsid protein; right? 22 ATTORNEY WILSON: Object to form.
Page 71 1 THE WITNESS: I would say the entire capsid -- 2 you know, the VP1, VP2, and VP3 unique region, you know, 3 which all form the capsid, it's the entire -- the capsid 4 in its entirety that determines the infectious 5 properties of the virus and, as a result, the tropism. 6 BY ATTORNEY MORRISON: 7 Q. The capsid -- I just want to make sure I 8 understand. The capsid protein in its entirety, or the 9 capsid in its entirety controls tropism, in your view? 10 A. I meant those two to be synonymous -- 11 Q. Okay. 12 A. -- you know, meaning the collection of the 13 proteins that make up the capsid control the tropism of 14 the virus. 15 BY ATTORNEY MORRISON: 16 Q. And I just want to make sure I understand. 17 You mean the collection of the capsid, that 60 -- the 18 collection of 60 capsid proteins that come together to 19 form the capsid, that collectively controls tropism, in 20 your view? 21 That's what you mean? 22 A. That's correct. The collection of the 60	Page 72 1 subunits that self-assemble to form the capsid, that 2 determines the tropism in the infectious properties of 3 the virus. 4 Q. Okay. 5 And we already talked about the viral capsid 6 has a particular structure when those 60 units come 7 together. 8 Is that fair? 9 A. That's correct. When the 60 subunits come 10 together, the field refers to it as an icosahedron, 11 which is this 20-sided structure. 12 I refer to it as a hollow soccer ball. 13 Q. And the -- that capsid protein -- or excuse 14 me -- the capsid may change confirmation when it binds 15 to a particular site inside or outside the cell. Is 16 that fair? 17 ATTORNEY WILSON: Object to form. 18 THE WITNESS: There have been studies -- I 19 can't recall the dates; I can recall the research 20 groups -- that have analyzed the structure of the 21 capsid, either in isolation or in complex with the 22 receptor, where a receptor is the initial site or some

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1 of the sites on the cell's surface that virus docks with
 2 that have indicated that the confirmation of the viral
 3 surface can change upon binding to a receptor.
 4 BY ATTORNEY MORRISON:
 5 **Q. And so it may be the case that residues that**
 6 **are not on the surface when the capsid is not docked to**
 7 **a particular receptor site may be on the surface when**
 8 **receptor -- when the capsid does dock. Is that fair?**
 9 ATTORNEY WILSON: Object to form.
 10 THE WITNESS: There is a lot of change in the
 11 confirmation of the virus upon binding to the receptor.
 12 There's also change in the confirmation of the virus
 13 triggered by other events. So, you know, the -- if you
 14 could repeat your question. I can't recall the first
 15 phrase that you mentioned. That would be helpful.
 16 BY ATTORNEY MORRISON:
 17 **Q. Sure. So maybe let me ask a better question.**
 18 **I think you just said that there are**
 19 **conformational changes that are triggered by the various**
 20 **under difference conditions. Is that fair?**
 21 A. That's a fair --
 22 ATTORNEY WILSON: Object to form.

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1 That's okay.
 2 THE WITNESS: Yes. There are conformational
 3 changes that are -- conformational alterations or
 4 changes or evolution in the structure of the virus that
 5 are triggered by various events.
 6 BY ATTORNEY MORRISON:
 7 **Q. And those conformational changes could result**
 8 **in amino acid residues that are not on the surface in**
 9 **one confirmation being on the surface as a result of one**
 10 **of those conformational changes. Is that fair?**
 11 ATTORNEY WILSON: Object to form.
 12 THE WITNESS: There are certain triggers that
 13 result, yes, in exposure of new amino acid sites to the
 14 exterior of the virus.
 15 BY ATTORNEY MORRISON:
 16 **Q. Okay.**
 17 **When -- and, again, this is, sort of, stepping**
 18 **back to basics of AAV and infection. That's where I**
 19 **want to go.**
 20 **There are a number of steps that the virus has**
 21 **to take to go from the extracellular space all the way**
 22 **to the nucleus. Is that fair?**

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1 **It's got to move through some different**
 2 **things?**
 3 A. That's right. The virus has to traverse
 4 through various steps to be able to make it from outside
 5 the cell to inside the nucleus.
 6 **Q. And so a first test to bind to a receptor on**
 7 **the outside of a cell. Is that fair?**
 8 ATTORNEY WILSON: Object to form.
 9 THE WITNESS: That's correct. People refer to
 10 the term "primary receptor," which simply means what is
 11 the first entity, first molecule on the surface of the
 12 cell that the virus docks with and binds to to initiate
 13 that process of being able to -- being able to enter
 14 into the cell.
 15 BY ATTORNEY MORRISON:
 16 **Q. And different AAVs are going to have -- sorry.**
 17 **Let me start over again.**
 18 **Different AAV serotypes are going to have**
 19 **different receptors on the outside of the cell that they**
 20 **bind to; is that right?**
 21 ATTORNEY WILSON: Object to form.
 22 THE WITNESS: Different AAV serotypes do dock

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1 with different primary receptors.
 2 BY ATTORNEY MORRISON:
 3 **Q. And that's a component of tropism; right?**
 4 A. It is believed to be a component of tropism.
 5 Tropism is a complicated word that is really the sum, I
 6 think, or the result of all of those steps that the
 7 virus has to traverse to be able to make it from the
 8 outside of the cell to the inside of the nucleus.
 9 **Q. Okay. So once --**
 10 A. Oh, sorry. I did not mean to interrupt you.
 11 **Q. No. Go ahead.**
 12 A. I incompletely answered the prior question.
 13 I would say also tropism is determined by, you
 14 know, the success of the virus being able to make it
 15 from the injection site into a patient, all the way to a
 16 given tissue or cell; so we described the steps it has
 17 to go once it arrives at the surface of the cell to get
 18 to the nucleus. There are also preceding steps that
 19 would lead to it even successfully getting to the
 20 surface of a cell that are determined in certain
 21 contributors to tropism.
 22 **Q. Okay. And what are those preceding steps that**

19 (Pages 73 to 76)

Page 77 1 you're referring to? 2 A. It depends upon the route of the 3 administration. I could give a couple of examples if 4 that would be useful. 5 Q. Sure. 6 A. So with an injection into the vascular system 7 into blood, AAV would have to go through circulation, be 8 able to go through vasculature to make it to the inside 9 of a given tissue, whether it be, you know, skeletal 10 muscle or liver, and then safely arrive at the surface 11 of a given cell type within those tissues prior to 12 initiating that step that you mentioned, you know, 13 docking with the primary receptor and then eventually 14 making its way into the nucleus. 15 If you consider a -- you know, a very 16 different route of administration, if I were doing gene 17 delivery to the eye, I wouldn't inject into the 18 vasculature. I would inject straight into the eye. But 19 still, the virus has to be able to make it through the 20 liquid in the inside of the eye, the so-called vitreous 21 humor, and then be able to say if you're trying to 22 deliver to a photoreceptor, an example we used earlier,	Page 78 1 has to be able to make it through a lot of dense tissue 2 to be able to reach the photoreceptor neuron and then 3 that step that you just mentioned, docking with the 4 primary receptor, initiates. 5 Q. Okay. So I want to step back and make sure we 6 have all the steps. 7 So from the injection site, whatever that is, 8 the AAV has to make it through the various portions of 9 the body to get to its target tissue before it can then 10 dock and enter a cell. Fair? 11 A. That's correct. It has to make it through a 12 number of tissue barriers to be able to make it to a 13 given tissue or to a given cell type. 14 Q. And then it has to dock on that primary 15 surface receptor; correct? 16 A. That is correct. 17 Q. Once it's docked on that primary surface 18 receptor, it then has to be internalized into the cell; 19 correct? 20 A. That's correct. 21 Q. And then it has to be trafficked through the 22 cytoplasm of the cell to the nucleus -- to the nuclear
Page 79 1 pore; right? 2 A. That's correct, yes. It has to be able to 3 make it outside of that endosome and into the cytosol 4 and then has go from the cytosol into the nucleus. 5 Q. So you introduced a new word. I just want to 6 make sure -- clear for the record what that is? 7 A. Sure. 8 Q. When the AAV enters the cell through the cell 9 membrane it does that through an -- through an endosome? 10 A. That's right. A portion of the cell membrane 11 buds off to create a sphere of membrane known as a 12 vesicle, or in this case an endosome. 13 Q. And then the AAV has to escape that endosome 14 and traffic through the cytosol through -- to the 15 nuclear pore; correct? 16 A. That's correct. 17 Q. And then it has to transport across the 18 nuclear pore into the nucleus; correct? 19 A. That is correct. It has to traverse the 20 nuclear pore. 21 Q. And then it has to go through a process of 22 viral uncoating?	Page 80 1 A. That's right. The capsid proteins have to 2 disassemble to be able to liberate the DNA on the 3 inside. 4 Q. And then after all of that the AAV can 5 replicate and do its work in gene therapy or in a viral 6 infection to further infect; right? 7 A. There's one -- or a couple final steps. 8 It's -- at that stage the AAV genome, the DNA inside 9 that capsid is a single strand of DNA; so it has to be 10 able to convert into double-stranded DNA, and then that 11 ends up forming the, you know, what you might consider 12 to be the active drug product of a gene therapy. 13 Q. Okay. And I think we already said this, but 14 the targeting of the correct cell type happens 15 extracellularly through the body; correct? 16 ATTORNEY WILSON: Object to form. 17 THE WITNESS: It's the entire delivery process 18 that's determined into tropism. 19 (Clarification inquiry by The Court Reporter.) 20 THE WITNESS: The entire delivery process is a 21 determinant of tropism. 22 ///

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1 BY ATTORNEY MORRISON:
 2 **Q. And I apologize. I didn't say tropism, but I**
 3 **mean the targeting of the particular primary receptor,**
 4 **that happens extracellularly?**
 5 ATTORNEY WILSON: Object to form.
 6 THE WITNESS: The virus docks with the primary
 7 receptor extracellularly and as we discussed, the -- the
 8 extracellular receptor is one determinant to tropism as
 9 are other steps in the delivery step -- in the delivery
 10 process.
 11 BY ATTORNEY MORRISON:
 12 **Q. Right. And I apologize. I'm not talking**
 13 **about tropism specifically right now.**
 14 A. Mm-hmm.
 15 **Q. I'm just asking that that targeting is**
 16 **happening -- the targeting that leads to the docking**
 17 **outside the cell, that all is happening extracellularly;**
 18 **right?**
 19 ATTORNEY WILSON: Object to form.
 20 THE WITNESS: Well, I -- the word "targeting"
 21 I would refer to as, you know, all the steps that have
 22 to happen in order for AAV to at least infect, you know,

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1 a given cell type or infect a given target cell.
 2 BY ATTORNEY MORRISON:
 3 **Q. Okay.**
 4 A. The binding to the primary receptor is one of
 5 those steps, but I would not say that receptor binding
 6 equals targeting.
 7 **Q. I see. Let me choose a different word, then.**
 8 **I was not trying to be tricky.**
 9 **The movement of the AAV through the body until**
 10 **it targets a primary receptor -- until it binds to a**
 11 **primary receptor -- that's all happening**
 12 **extracellularly?**
 13 A. That's correct.
 14 **Q. Okay.**
 15 A. You know, when AAV traverses from the needle
 16 tip all the way to the surface of the cell, that's all
 17 outside the cell. Extracellular.
 18 **Q. Okay. And then after that binding to the**
 19 **primary receptor, the remainder of the trafficking is**
 20 **happening intracellularly. Is that fair?**
 21 ATTORNEY WILSON: Object to form.
 22 THE WITNESS: Yes. Once AAV binds to a

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1 primary receptor and then initiates that process of
 2 endocytosis, there's more nuance there that's not fully
 3 understood, you know, AAV has to bind to additional
 4 receptors in order to get endocytosed, but that's not
 5 fully understood within the field.
 6 ///
 7 (Clarification inquiry by The Court Reporter.)
 8 THE WITNESS: So once it gets internalized
 9 from that point forward, getting all the way to the
 10 nucleus is, by definition, inside the cell.
 11 BY ATTORNEY MORRISON:
 12 **Q. There's discussion in your declaration of**
 13 **phosphorylation of particular amino acids; right?**
 14 ATTORNEY WILSON: Object to form.
 15 THE WITNESS: It's -- yes, it would be great
 16 if we could be on the same page and can refer to the
 17 location.
 18 BY ATTORNEY MORRISON:
 19 **Q. Sure. Yeah, I'm actually not asking about any**
 20 **specific place.**
 21 A. Okay.
 22 **Q. I have a general question about where**

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1 **phosphorylation is happening. That's what I'm going**
 2 **just to -- so let me just ask it.**
 3 **The phosphorylation of amino acid residues**
 4 **would happen inside the cell, not extracellularly;**
 5 **right?**
 6 ATTORNEY WILSON: Object to form.
 7 THE WITNESS: There's -- I mean that's a
 8 general term what you're saying; so, I mean, I have a
 9 section here, you know, Snowdy teaches that removal of
 10 phosphorylation sites in AAV capsid proteins to improve
 11 transduction efficiency; so I do describe
 12 phosphorylation in that particular location, yes.
 13 BY ATTORNEY MORRISON:
 14 **Q. Right, and I'm asking a much more general**
 15 **question. The enzymes that do that phosphorylation,**
 16 **those are inside the cell; right? They're not in the**
 17 **bloodstream?**
 18 ATTORNEY WILSON: Object to form.
 19 THE WITNESS: There's a -- you know, I can't
 20 recall what fraction of the human genome encodes enzymes
 21 that mediate phosphorylation. Kinases. So I can't say
 22 actually as to whether or not their extracellular

21 (Pages 81 to 84)

Page 85 1 kinases. They're extracellular phosphatases certainly. 2 (Clarification inquiry by The Court Reporter.) 3 THE WITNESS: I'm not aware of whether or not 4 all such enzymes are inside the cell. 5 BY ATTORNEY MORRISON: 6 Q. You do know -- I think you mentioned this -- 7 there are phosphatases in the bloodstream; right? 8 A. I recall reading, you know, I would have to 9 refer back to it. It's not my field. 10 Q. Okay. 11 A. But there are phosphatases on the outside of 12 the cell. 13 Q. Okay. And a phosphatase, just so the record 14 is clear, is something that would remove a phosphate ion 15 from a -- 16 A. That's right. A phosphatase is an enzyme that 17 cleaves a phosphate from a -- from a protein or from 18 another substrate. 19 Q. Yeah. So let just make sure you and I are on 20 the same page and that the record is clear. 21 Phosphorylation is the addition of a phosphate 22 ion to, in this case, an amino acid; is that right?	Page 86 1 A. That's right. Phosphorylation involves the 2 addition of that phosphate ion to a -- you know, I would 3 say phosphorylation adds phosphate residues, or 4 molecules, onto proteins. There are certainly lots of 5 other molecules where phosphates get added on to in 6 biology. Not all of them are proteins. 7 Q. Right, but for purposes of what we're talking 8 about today, we're talking about phosphorylation of 9 amino acids; right? 10 A. For the purposes of today, yes, we're talking 11 about phosphorylation of amino acids and proteins. 12 Q. And that's done by enzymes called kinases? 13 A. That is correct. Kinases use ATP to add 14 phosphates onto a substrate. 15 Q. And phosphatases remove phosphate ions from a 16 substrate? 17 A. That's correct. 18 Q. Okay. And so we agree that there are 19 phosphatases in the bloodstream generally; right? 20 A. I -- I'm not an expert in that area. 21 Q. Okay. That's fine. 22 And you -- you aren't -- I think you said you
Page 87 1 aren't aware of whether there are kinases that could 2 achieve phosphorylation in the blood stream; is that 3 right? 4 A. I'm not aware. 5 ATTORNEY WILSON: Object to form. 6 THE WITNESS: Yeah, I do know whether -- I 7 don't know the distribution of kinases on the inside 8 versus the outside of the cell. 9 BY ATTORNEY MORRISON: 10 Q. Okay. But you do know that there are kinases 11 on the inside of the cell? 12 A. There are certainly kinases on the inside of 13 the cell. 14 Q. Okay. Okay. So I want to talk just for a few 15 minutes for the '274 patent which is Exhibit 1001. 16 A. I paged to the '274 patent. 17 Q. And I think -- okay. 18 And Mr. Wilson already has a copy -- 19 ATTORNEY WILSON: I do, thank you. 20 ATTORNEY MORRISON: -- of that. All right. 21 BY ATTORNEY MORRISON: 22 Q. Do you know Dr. James Wilson is one of the	Page 88 1 inventors of the '274 patent? 2 A. I see James Wilson listed here as an inventor. 3 Q. And do you know Dr. Wilson? 4 A. Not well, but we're in the same field, have 5 been in the same field for a number of years; so I would 6 say we're acquaintances. 7 Q. And Dr. Wilson, would you consider him an 8 expert in the field of gene therapy? 9 A. Dr. Wilson has done a lot of work in gene 10 therapy for the last couple of decades so I think that 11 would qualify him as an expert. 12 Q. Okay. And what about Dr. Gao? Do you know 13 Dr. Gao? 14 A. I do know Dr. Gao, yes. 15 Q. And how do you know of Dr. Gao? 16 A. Similar that we go to a lot of the same 17 conferences and so we've bumped into each other over the 18 years, are familiar with each other's work. 19 Q. Okay. And what about Dr. -- and I'm sorry, 20 would you consider Dr. Gao an expert in the field of 21 gene therapy, AAV gene therapy? 22 A. Dr. Gao has been publishing in that field for

Page 89 1 20 to 25 years; so I would consider him to be an expert. 2 Q. And then what about the last inventor, Dr. Luk 3 Vandenberghe? 4 A. Yes. I'm acquainted with Dr. Vandenberghe as 5 well. 6 Q. And how do you know Dr. Vandenberghe? 7 A. Similar to Drs. Gao and Wilson. Same field, 8 and so we're familiar with each other's work and bump 9 into each other at conferences. 10 Q. Would you consider Dr. Vandenberghe an expert 11 in the field of gene therapy? 12 A. He's published extensively in gene therapy; so 13 I would consider him to be an expert. 14 Q. Okay. We can go to the specific places in the 15 patent if it's helpful, but would you agree with me that 16 the '274 patent discloses two sets of inventions: One 17 is using singleton mutations to improve the function of 18 AAV vector, and other is it discloses several new AAV 19 capsids separate from that? 20 ATTORNEY WILSON: Object to form. 21 THE WITNESS: It would be great if we could go 22 to those locations. It has been some time since I've	Page 90 1 read this patent; so it would be helpful to refresh my 2 memory. 3 BY ATTORNEY MORRISON: 4 Q. Yeah, of course. 5 So if you can go to -- in the '274 patent, 6 which is Exhibit 1001 -- to column 2 of the patent, 7 which is on page -- it's on the page that's marked at 8 the bottom, it's page 26. 9 A. I'm at column 2 of page 26. 10 Q. And if you go all the way to the bottom of 11 column 2, it talks about in that -- and I'll let you -- 12 I'm not going to read the whole thing into the record, 13 but I'll let you read that paragraph, and then I'll ask 14 you a question. 15 A. And what -- how does the paragraph start? 16 Q. It starts with, "The present invention 17 provides a method for improving." 18 Do you see where I am? 19 All the way at the bottom of column 2, under 20 "Detailed Description of the Invention." 21 A. Great. Thank you. 22 I've read through that paragraph, thanks.
Page 91 1 Q. And in this paragraph, it talks about 2 improving the function of AAV vectors which contain one 3 or more singletons; right? 4 A. That's what the language says, yes. 5 Q. Okay. And so there's a method discussed in 6 this patent for improving the function of vectors by 7 changing what the patent refers to as singleton 8 mutations? 9 ATTORNEY WILSON: Object to form. 10 THE WITNESS: Let me refresh my definition of 11 a -- or my memory of the definition of "singleton." 12 BY ATTORNEY MORRISON: 13 Q. Sure. I believe it's there in column 3 at 14 line 10. 15 A. I've read two paragraphs starting, you know, 16 with "As used herein, the term 'singleton' refers to," 17 and that does describe, you know -- if you could go back 18 to your question, that would be helpful. 19 Q. And sure. 20 My question was just there's a method 21 discussed in the '274 patent for improving the function 22 of AAV vectors by changing singleton mutations.	Page 92 1 ATTORNEY WILSON: Object to form. 2 THE WITNESS: Yeah. Those paragraphs refer to 3 a, you know, AAV vector having a modified capsid; so 4 those two in particular don't talk about improving a 5 capsid, but if there's another location, I'd be happy to 6 discuss that. 7 BY ATTORNEY MORRISON: 8 Q. If you go to the first paragraph I asked you 9 to read at the bottom of column 2 -- 10 A. Yes. 11 Q. -- it says: 12 [As Read] The present invention provides 13 a method for improving the function of an AAV 14 vector. 15 Do you see that? 16 A. I do, yes. 17 Q. And so the first piece of this invention is 18 talking about improving the function of an AAV vector by 19 modifying singletons; right? 20 ATTORNEY WILSON: Object to form. 21 THE WITNESS: The first paragraph does talk 22 about using singletons to change sequences and also

Page 93 1 talks about ways to improve, you know, packaging yield 2 or transduction efficiency. 3 BY ATTORNEY MORRISON: 4 Q. And then if you go over to column 8 of the 5 patent, which is on page 29 of Exhibit 1001? 6 A. I'm at column 8. 7 Q. And look at -- do you see the line numbers in 8 the middle? 9 A. I do, yes. 10 Q. Go to line 32 in column 8, where it starts, 11 "In a further embodiment"? 12 A. I'll take a moment to read that paragraph. 13 Q. Yes. Thank you. 14 A. I've read the paragraph. Thank you. 15 Q. And so in this paragraph, it talks about an 16 additional embodiment of the invention, a further 17 embodiment "provides AAV having novel capsid," and then 18 it lists a series of novel capsids; right? 19 A. That's right. It lists several novel capsids. 20 Q. And the novel capsid that's at issue in the 21 claims of the '274 patent is the one called rh.46; 22 right?	Page 94 1 A. That's correct. 2 Q. Okay. 3 And so the claims -- and if you'd like to look 4 at them, they're on the last page of the patent -- 5 A. Sure. 6 Q. -- on page 122 of Exhibit 1001. But the 7 claims of the '274 patent are directed to that novel AAV 8 sequence rh.46; right? 9 ATTORNEY WILSON: Object to form. 10 THE WITNESS: Reading the claims right now to 11 refresh my memory of claim 1; so it's a -- it refers to, 12 you know, sequence ID 4, or at least the first romanette 13 refers to the sequence ID 4 and says that -- you know, 14 it's claiming the sequence of that rh.46, known as ID 4. 15 BY ATTORNEY MORRISON: 16 Q. And I think you're referring to claim 1 of 17 the -- 18 A. The first romanette refers either to the exact 19 sequence or to an amino acid sequence of at least 20 95 percent identity to that exact sequence with a -- an 21 asparagine in position 665. 22 (Clarification inquiry by The Court Reporter.)
Page 95 1 THE WITNESS: With an asparagine in position 2 665. 3 BY ATTORNEY MORRISON: 4 Q. And claim 1 that we were just looking at 5 doesn't talk about singleton mutations; right? 6 ATTORNEY WILSON: Object to form. 7 THE WITNESS: If you read through claim 1, it 8 doesn't appear to have the word "singleton" in it. 9 BY ATTORNEY MORRISON: 10 Q. Okay. And I think you already mentioned this, 11 but claim 1 requires a particular sequence, and it also 12 requires that the amino acid at position 665 is an 13 asparagine; right? 14 ATTORNEY WILSON: Object to form. 15 THE WITNESS: I believe it's an "or"; so it 16 says the exact sequence or a sequence that's at least 17 95 percent identical to that SEQ ID 4, and has the 18 asparagine at position 665. 19 BY ATTORNEY MORRISON: 20 Q. And the exact SEQ ID number 4 also has an 21 asparagine at 665; right? 22 ATTORNEY WILSON: Object to form.	Page 96 1 THE WITNESS: I believe it has -- I believe 2 SEQ ID 4 rh.46 has an asparagine at position 665. 3 ATTORNEY MORRISON: Okay. And I wanted to 4 note for the record that we had an additional 5 participant join the deposition. Dr. Jude Samulski is 6 now on the Zoom as well. 7 DR. SAMULSKI: Hey, guys. Hi, David. 8 THE WITNESS: Hello. 9 BY ATTORNEY MORRISON: 10 Q. Okay. So talking now -- we can go back to 11 your declaration. 12 You have particular grounds in your 13 declaration that you rely on for your invalidity 14 analysis; is that right? 15 A. I have several grounds where I have, you know, 16 provided material which I believe indicates that some of 17 these claims or all of these claims are obvious. 18 Q. Okay. And you have four references that you 19 rely on in total across those six grounds; is that 20 right? 21 A. I don't recall the number off the top of my 22 head. I'd be surprised if it were only four, since

Page 97 1 there are a number of references. But if you could take 2 me through those, I'd be happy to go through them. 3 Q. Sure. I'd be happy to. 4 So ground 1, which starts at page 74 of your 5 declaration, asserts that claims 1 and 3 through 6 are 6 obvious over the '772 publication; right? 7 A. That's correct. 8 Q. And there's no other references in ground 1; 9 is that right? 10 ATTORNEY WILSON: Object to form. 11 THE WITNESS: Well, I make a number of 12 references, you know, for example, you know, "See 13 Exhibit 107.0037." So there are a number of references. 14 I -- perhaps you can clarify what you mean by 15 "reference." 16 BY ATTORNEY MORRISON: 17 Q. Sure. 18 Where are you looking, Dr. Schaffer? Page -- 19 what page are you on? 20 A. Claim 1, paragraph 1 -- or paragraph 195 that 21 talks about references to exhibits. 22 Q. Well, Exhibit 1007 --	Page 98 1 A. That's the '772 publication. 2 Q. -- is the '772 publication; right? 3 A. That's correct. 4 Q. And so if you look at paragraph 194 on 5 page 74, it's your opinion that: 6 [As Read] Claims 1 and 3 through 6 of the 7 '274 patent are obvious over the 8 '772 publication. 9 Right? 10 A. That is my opinion in ground 1, yes. 11 Q. Okay. And that's your opinion in ground 1? 12 A. That's right. 13 Q. Okay. And in ground 2, you say that those 14 same claims, claims 1 and 3 through 6, of the '274 15 patent are obvious over the '772 publication in 16 combination with the Xie paper. 17 And it's on page 97 if that's helpful. 18 A. Thank you. 19 I'm at ground 2 right now that describes, yes: 20 Claims 1 and 3 through 6 are obvious over the '772 21 publication in combination with Xie -- G. 22 Q. And then ground 3 is -- which starts on
Page 99 1 page 104, is that claims 1 and 3 through 6 are obvious 2 over the '772 publication in combination with Snowdy; 3 right? 4 A. That's correct. That's a reading of the 5 statement, the top statement, for ground 3. 6 Q. Okay. And then grounds 4, 5, and 6 address 7 claim 8 of the '274 patent; right? And those are on 8 pages 112, 115, and 117, respectively, if that's 9 helpful? 10 A. That's right. Ground 4 is on 112. Ground 5 11 is on 115 and ground 6 is on -- yes, on page 117. 12 Q. And each of those grounds addresses claim 8 of 13 the '274 patent; right? 14 A. Grounds 4, 5, and 6 address claim 8. 15 Q. Okay. And in ground 4 you assert that claim 8 16 is obvious over the '772 publication and the reference 17 by Fabb; is that right? 18 A. That's correct. 19 Q. And in ground 5 you assert claim 8 is obvious 20 over the '772 publication in combination with Xie, in 21 further combination with Fabb; right? 22 A. That's correct.	Page 100 1 Q. And then finally in ground 6 you assert that 2 claim 8 is obvious over the '772 publication in 3 combination with Snowdy and in further combination with 4 Fabb; right? 5 A. That's an accurate statement of the ground, 6 yes. 7 Q. Okay. So the four references that you rely on 8 across your six grounds are the '772 publication, the 9 Xie reference, the Snowdy reference and the Fabb 10 reference; is that right? 11 A. That's correct. 12 Q. Okay. Who chose those references to be 13 included in your grounds? 14 ATTORNEY WILSON: Object to form. 15 And also caution you as to any attorney-client 16 or work product communications. Any communications you 17 had with counsel. 18 ATTORNEY MORRISON: And I'll just note for the 19 record there's no attorney-client privilege between an 20 expert and a lawyer, but you can go ahead and answer. 21 ATTORNEY WILSON: There's certainly a 22 privilege and a work product immunity.

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1 THE WITNESS: So these four references I feel
 2 to be, you know, very relevant to the analysis within
 3 these grounds.
 4 BY ATTORNEY MORRISON:
 5 **Q. So did you do -- well, let me ask you this:**
 6 **Did you do any searching through the literature to find**
 7 **references for this declaration?**
 8 A. There -- so, for example, Fabb, it was
 9 well-known at the time that micro-dystrophins did exist.
 10 You know, being somebody within the field, I was very
 11 familiar with those.
 12 In addition, Dr. Samulski had been talking
 13 about nuclear localization sequences within the AAV
 14 capsid, and I was familiar with that work at the time.
 15 **Q. Right. So that wasn't my question, my**
 16 **question was whether you ran any literature searches --**
 17 **you, yourself, Dr. Schaffer, did you run any literature**
 18 **searches to look for references for this declaration?**
 19 A. I would say that it was not that difficult to
 20 search because I was already familiar with that work.
 21 **Q. Okay. Did you run any literature searches?**
 22 ATTORNEY WILSON: Object to form.

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1 THE WITNESS: So as I mentioned, I was
 2 familiar with the work; so it didn't take that much
 3 searching to be able to find it.
 4 BY ATTORNEY MORRISON:
 5 **Q. So you drew on references that you were**
 6 **already familiar with. Is that fair?**
 7 A. I was already familiar with the work of Fabb
 8 and with the work of Samulski -- or Snowdy -- here since
 9 Snowdy was working in Samulski's lab.
 10 **Q. So what about the '772 publication? Were you**
 11 **familiar with that before this case?**
 12 A. I wasn't familiar with it. I tend to read the
 13 scientific literature more than the patent literature.
 14 I was certainly familiar with the work that was coming
 15 out of Dr. Wilson's lab related total novel AAV
 16 variants.
 17 **Q. Okay. And so were you familiar with Dr.**
 18 **Wilson's patents before you started work on this case?**
 19 A. I was familiar with the data presence within
 20 the patents. I had not read the patents cover to cover.
 21 I tend to focus on scientific literature.
 22 **Q. Had you ever read any of Dr. Wilson's patents**

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1 **before you started working on this case?**
 2 ATTORNEY WILSON: Object to form.
 3 THE WITNESS: So I certainly read a lot of the
 4 specification. In cases, specifications find their way
 5 no publications verbatim; so in that sense I would have
 6 read sections of the specification present within the
 7 patents including all the relevant data.
 8 BY ATTORNEY MORRISON:
 9 **Q. So that wasn't my question. My question was**
 10 **had you ever read any of Dr. Wilson's patents before you**
 11 **began working on the case?**
 12 ATTORNEY WILSON: Object to form.
 13 THE WITNESS: I've read material presence
 14 within the patent because it was known in the scientific
 15 literature.
 16 ///
 17 BY ATTORNEY MORRISON:
 18 **Q. So you read scientific literature coming out**
 19 **of Dr. Wilson's lab that may overlap with the patents.**
 20 **Is that fair?**
 21 A. That is -- yes I read scientific literature
 22 that contained data present within these patent

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1 applications.
 2 **Q. But you hadn't read the patent applications**
 3 **themselves?**
 4 ATTORNEY WILSON: Object to form.
 5 THE WITNESS: I have not spent time reading
 6 the patent applications.
 7 BY ATTORNEY MORRISON:
 8 **Q. Okay. So how did you choose the '772**
 9 **publication as a reference to include -- and that**
 10 **reference is in all your grounds; right? All six?**
 11 A. That is correct.
 12 **Q. And how did you choose the '772 publication as**
 13 **a reference to include in all six grounds?**
 14 A. Because I was very familiar with the
 15 scientific state of the field at that time; a POSA would
 16 have been. A lot of that work was presented publicly
 17 within conferences.
 18 **Q. Is there a reason you chose the '772**
 19 **publication as opposed to a piece of scientific**
 20 **literature that you were already familiar with?**
 21 A. I certainly patent myself. Patents do have a
 22 lot of information about the state of the art at the

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1 time; so the '772 publication contains a lot of
2 information about novel AAV capsids, as does the
3 scientific literature.

4 **Q. And so why did you choose to use the '772**
5 **publication as opposed to the scientific literature?**

6 ATTORNEY WILSON: Object to form.

7 THE WITNESS: The '772 publication contains a
8 lot of information about the state of the field at the
9 time.

10 BY ATTORNEY MORRISON:

11 **Q. So why did you choose that instead of the**
12 **scientific literature?**

13 ATTORNEY WILSON: Same objection. Object to
14 form.

15 THE WITNESS: Yeah, the '772 publication
16 contains a lot of relevant information about the state
17 of the field at the time.

18 BY ATTORNEY MORRISON:

19 **Q. Was the '772 publication provided to you by**
20 **counsel?**

21 ATTORNEY WILSON: Object to form. Also, I'll
22 caution you as to any communications with counsel --

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1 THE WITNESS: Yes.

2 ATTORNEY WILSON: -- based on privilege and
3 work product.

4 THE WITNESS: So I'll defer to my counsel in
5 saying that we shouldn't share work product.

6 BY ATTORNEY MORRISON:

7 **Q. So are you refusing to answer the question of**
8 **whether counsel provided you with the '772 publication?**

9 ATTORNEY WILSON: Again, I'll caution you as
10 to specific communications, and you can answer the
11 question yes or no.

12 THE WITNESS: Yes.

13 BY ATTORNEY MORRISON:

14 **Q. And so that's "yes," counsel for Sarepta**
15 **provided you with the '772 publication?**

16 ATTORNEY WILSON: Object to form.

17 THE WITNESS: Yes.

18 BY ATTORNEY MORRISON:

19 **Q. What about the Xie reference? Did counsel for**
20 **Sarepta provide you with the Xie reference?**

21 A. The Xie reference was extremely well known.

22 You know, from the moment that it published. I actually

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1 don't recall whether I provided it to them first or they
2 provided it to me first. We certainly discussed it.

3 **Q. What about the Snowdy thesis? Did counsel for**
4 **Sarepta provide the Snowdy thesis to you?**

5 A. I -- I can't recall whether I provided it to
6 them or they provided it to me. I certainly did discuss
7 the work that was taking place in Dr. Samulski's lab
8 since that was well known at the time by a POSA or by
9 myself.

10 **Q. Were you familiar with the Snowdy thesis**
11 **before -- that specific document -- before your work on**
12 **this case?**

13 A. I was familiar with the work that had been
14 presented from Dr. Samulski's lab about nuclear
15 localization signals. That work was coming out at the
16 time in the early 2000s.

17 **Q. So had you ever read Dr. Snowdy's thesis, or**
18 **reviewed it, or seen it, before your work on this case?**

19 ATTORNEY WILSON: Object to form.

20 THE WITNESS: I recall seeing talks out of the
21 Samulski lab, out of the Dr. Samulski's lab, describing
22 nuclear localization signals and phosphorylations

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1 thereof. So I was familiar with that work prior to
2 2005.

3 BY ATTORNEY MORRISON:

4 **Q. I understand you were familiar with the work.**
5 **I'm asking whether specifically you were familiar with**
6 **Dr. Snowdy's thesis before your work on this case?**

7 ATTORNEY WILSON: Object to form.

8 THE WITNESS: No.

9 BY ATTORNEY MORRISON:

10 **Q. Okay. And then finally the Fabb reference,**
11 **were you familiar with the Fabb reference before your**
12 **work on this case?**

13 ATTORNEY WILSON: Object to form.

14 THE WITNESS: Yeah, the Fabb reference
15 describes micro-dystrophins which had been presented
16 within the field; so I was familiar with the Fabb
17 reference.

18 BY ATTORNEY MORRISON:

19 **Q. Okay. And so had you read the Fabb reference**
20 **before your work on this matter?**

21 A. I read a lot of materials. I wouldn't say

22 necessarily cover to cover, but I was familiar with

Page 109 1 that. 2 Q. Okay. How did you decide to use the '772 3 publication in all of the grounds of your declaration? 4 A. '772 teaches a lot of really interesting 5 information about the knowledge of the field and AAV 6 serotypes within the field at that time. I find it to 7 be, you know, pretty comprehensive description of the 8 state of the field at that time. 9 Q. And we can look at it, but what is the really 10 interesting information about the knowledge of the field 11 that you think the '772 publication teaches? 12 And it's Exhibit 1007 if you'd like to look at 13 that. 14 ATTORNEY WILSON: Do you have a copy, Susan? 15 Thank you. 16 THE WITNESS: Yeah, I can page to it really 17 quick. 18 So the state of the field was that a number of 19 AAVs had been isolated typically as contaminants within 20 adenoviral stocks, you know, hence adeno-associated 21 virus, the name of AAV. 22 There was one AAV that had been isolated from	Page 110 1 human tissue, AAV5, but at that time, or up until this 2 time, it was really AAV6 that had been described and 3 discussed within the field. 4 So Dr. Wilson began to pursue what you might 5 call a metagenomic approach these days; began to search 6 for additional AAV genomes within natural tissues and 7 began to describe these AAVs and this is a publication 8 that really, you know, in my opinion raised a number of 9 new AAV variants that had been isolated beyond AAV1 10 through 6. 11 BY ATTORNEY MORRISON: 12 Q. And so how did you choose to use this 13 publication as opposed to something else as the 14 ground -- or as the reference that ran through all your 15 grounds? What was it about the '772? 16 ATTORNEY WILSON: Object to form. 17 THE WITNESS: Yes. '772 provides a lot of, 18 you know, data about several novel AAV serotypes and 19 summarizes, you know, the state of knowledge at the time 20 that this was submitted about those interesting 21 serotypes. 22 BY ATTORNEY MORRISON:
Page 111 1 Q. Okay. And I think I asked you about 2 Drs. Wilson and Gao already. 3 Do you know Mr. Mauricio Oliveira? 4 A. I don't know Dr. Oliveira. 5 Q. Okay. All right. You would agree with me 6 that none of the sequences disclosed in the '772 7 publication has a sequence that is both 95 percent 8 identical to rh.46 and also has an asparagine at 9 position 665; right? 10 ATTORNEY WILSON: Object to form. 11 THE WITNESS: Yeah. The patent publication, 12 the '772, teaches a sequence that has 95 percent or 13 greater sequence identity to rh.46 and has an asparagine 14 at 665. 15 /// 16 BY ATTORNEY MORRISON: 17 Q. The '772 publication lists a number of 18 sequences; right? 19 A. A number of sequences are listed yes. 20 Q. It lists, I think, 56 sequences in -- amino 21 acid sequences in Figure 2; is that right? 22 ATTORNEY WILSON: Object to form.	Page 112 1 THE WITNESS: I haven't counted them, but I -- 2 if it is -- if you say it's 56 I'll -- 3 BY ATTORNEY MORRISON: 4 Q. And if you'd like to look at it, you turn to 5 Figure 2. Figure 2 is on page 98 of Exhibit 1007. 6 A. I'm at Figure 2. 7 Q. And so Figure 2 lists -- you're welcome to 8 count them if you'd like, but I'll represent to you that 9 there are 56 sequences listed in Figure 2. 10 Does that seem about right, looking at the 11 page? 12 A. Roughly. I'll trust you on that number. 13 Q. Okay. And these 56 sequences include ones 14 that were known prior to Dr. Wilson's work; right? 15 A. For example, it appears AAV6 is in here. I'm 16 seeing AAV5; so those were known prior to this work. 17 Q. And prior to this work you'd agree with me 18 AAVs 1 through 6 were known; right? 19 A. That's correct. Prior to this work, AAV1 20 through 6 were known. 21 Q. And if you'd like to look, you certainly can, 22 but AAVs 1 through 6 are all listed in figure 2 in

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1 various places.

2 A. It appears they are listed here in various
3 places. I'm missing perhaps a couple. I'm not seeing
4 AAV2 off the top of my head or AAV3.

5 **Q. AAVs 2 and 3 are 11 and 12 down, if that's**
6 **helpful.**

7 A. Thank you. The notation, or the indentation,
8 is a little bit different here. For AAV6, it says AAV6
9 VP1 but it says AAV2 and AAV3 without the VP1; so the
10 indentation led to me missing them.

11 **Q. Okay. And of the sequences that are listed**
12 **here, just these 56 sequences, none of these 56 is both**
13 **95 percent identical to rh.46 and also has an asparagine**
14 **at position 665?**

15 ATTORNEY WILSON: Object to form.

16 THE WITNESS: Yeah, for this particular
17 figure, none of the variants listed have those
18 properties, but the rest of the patent teaches a
19 sequence of that nature.

20 BY ATTORNEY MORRISON:

21 **Q. I understand that's your opinion. That's not**
22 **my question at this moment. My question at this moment**

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1 **is that the sequences listed in this figure, none of**
2 **them are both 95 percent identical to rh.46 and have an**
3 **asparagine at position 665; right?**

4 ATTORNEY WILSON: Object to form.

5 THE WITNESS: Yes. Within this early figure
6 in the patent invention, no individual sequence has the
7 properties you mentioned, which is greater than
8 95 percent of sequence identity to, I believe, rh.46,
9 you mentioned, plus an asparagine at that position, but
10 the rest of the patent, you know, the subsequent patent
11 does teach a sequence of that nature.

12 BY ATTORNEY MORRISON:

13 **Q. And so is your opinion that the patent teaches**
14 **more sequences than are just the one that's listed here?**
15 **Is that fair?**

16 ATTORNEY WILSON: Object to form.

17 THE WITNESS: I think it's the opinion of the
18 inventors, because they describe more sequences than
19 exist just here.

20 BY ATTORNEY MORRISON:

21 **Q. And what's the basis for what you just said?**
22 **Where in the patent are you pointing?**

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1 A. There are multiple places. They use the word
2 "artificial capsid" or "artificial sequence" at least a
3 dozen times, and they describe throughout the
4 specification of the patent the existence of such
5 artificial sequences.

6 **Q. And so it's your opinion that the '772**
7 **publication teaches that you could modify these**
8 **sequences based on other information in the patent?**

9 A. I think it's the opinion of the inventors. It
10 doesn't really have to be my opinion. It's actually in
11 the text of the patent specification.

12 **Q. Okay. So -- but your opinion is that the '772**
13 **patent teaches more sequences than are just listed in**
14 **figure 2. Is that a fair statement?**

15 A. We could go to the text that actually says
16 that. You know, one doesn't really need to rely on my
17 opinion for that. It's actually in the specification of
18 the patent itself.

19 **Q. Okay.**

20 A. There we go. I just happened to land on a
21 page. It talks about -- you know, I'm at paragraph 91.

22 **Q. Okay. Thank you.**

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1 A. Would you like me to read or --

2 ATTORNEY WILSON: No. Wait for a pending
3 question.

4 ATTORNEY MORRISON: Yeah.

5 THE WITNESS: Okay.

6 BY ATTORNEY MORRISON:

7 **Q. And what specific -- is there -- you don't**
8 **have to read the whole sentence but if there is a place**
9 **in paragraph 91 that you're relying on, if you could**
10 **just point me to the beginning of the sentence?**

11 A. "For example."

12 **Q. "For example, it may be desirable to modify,"**
13 **is that --**

14 A. That's right, yes. From there to the end of
15 the paragraph is one of these examples of their
16 description of novel sequences that can be generated.

17 **Q. And so the inventors of the '772 patent taught**
18 **that you could modify the sequences that they had**
19 **discovered and make additional sequences that were**
20 **within the scope of their invention. Is that fair?**

21 A. Paragraph 91 is one example of that kind of
22 language or that kind of teaching.

29 (Pages 113 to 116)

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1 **Q. And are there -- in your recollection are**
 2 **there other teachings like that in the '772 patent**
 3 **publication?**
 4 A. Yes. The word "artificial sequence" is
 5 reported throughout the entire specification.
 6 **Q. Going back to -- well, you can look at**
 7 **whatever you want, but looking at Figure 2, how did you**
 8 **choose rh.10 to start your analysis of obviousness?**
 9 A. The -- again the specification is very
 10 insightful or interesting. The inventors of this patent
 11 chose rh.10.
 12 **Q. And what do you mean "The inventors of this**
 13 **patent chose rh.10"?**
 14 A. As one moves further into the patent and the
 15 gets into the examples, rh.10 is repeatedly mentioned as
 16 a compelling vector with useful properties.
 17 **Q. And you did, in this matter, a series of**
 18 **alignments which appear I think in Exhibits 1018, '19,**
 19 **and '20?**
 20 A. Let's see. If you could give me a moment that
 21 would be really helpful.
 22 **Q. Yeah. Take your time.**

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1 A. Just so I can refresh my memory about the
 2 numbers.
 3 ATTORNEY MORRISON: And, Mr. Wilson, if you'd
 4 like a copy, I have those.
 5 ATTORNEY WILSON: Yeah, that would be great if
 6 we're going to go into it. Thank you.
 7 THE WITNESS: I'm at Exhibits 1018 through
 8 1020, yes.
 9 ATTORNEY MORRISON: And these have all been
 10 previously marked.
 11 ATTORNEY WILSON: Thank you.
 12 BY ATTORNEY MORRISON:
 13 **Q. All right. And these are the only alignments**
 14 **that you did of sequences in the '772 publication;**
 15 **right?**
 16 A. These are the only alignments that I did.
 17 That's correct. Beyond analyzing figures.
 18 **Q. Sure. Now, Dr. Schaffer, did -- who**
 19 **physically did these alignments?**
 20 A. They were done -- with my supervision, done by
 21 counsel, to my knowledge.
 22 **Q. Okay. And so did you do any alignments**

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1 **yourself in the lab?**
 2 ATTORNEY WILSON: Object to form.
 3 THE WITNESS: Did you say in my lab?
 4 BY ATTORNEY MORRISON:
 5 **Q. In your -- I'm sorry in your laboratory.**
 6 A. Oh, laboratory. So the alignments were done
 7 with my supervision. They -- the alignments, after they
 8 were completed, I took a look at them and they meet
 9 my -- you know, what I would consider to be my standards
 10 for a good alignment.
 11 **Q. And you said they were done with your**
 12 **supervision?**
 13 A. That's correct.
 14 **Q. Do you know the person that did the**
 15 **alignments?**
 16 A. I believe it was done by one of the two
 17 counsels.
 18 **Q. Okay. Do you know whether Mr. Wilson or**
 19 **Ms. Toker did the alignments?**
 20 A. I believe it was Ms. Toker.
 21 **Q. Okay. And do you know -- well, strike that.**
 22 **Do you ever do alignments yourself,**

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1 **Dr. Schaffer?**
 2 A. I do alignments myself.
 3 **Q. And how often do you do that?**
 4 A. I would say, you know, quite a few times a
 5 year.
 6 **Q. Mm-hmm. What programs do you use?**
 7 A. I use BLAST. I use Benchling. I use Clustal.
 8 **Q. Have you ever used Clustal -- start over.**
 9 **Have you ever used Clustal Omega before?**
 10 A. I've used Clustal. There are a number of
 11 versions of Clustal. I'll have to confess that I can't
 12 recall which version I used. It's whatever.
 13 **Q. When's the last time you did an alignment that**
 14 **you recall? You yourself.**
 15 A. The last time I did an alignment was two weeks
 16 ago.
 17 **Q. And there a reason you had counsel at Quinn do**
 18 **these alignments instead of doing them yourself?**
 19 ATTORNEY WILSON: Object to form.
 20 THE WITNESS: Yes. The work product here is
 21 something that I stand by, and I made the recommendation
 22 to be able to do this alignment. It's nice that, in

30 (Pages 117 to 120)

Page 121 1 this case, somebody was opening to doing it. 2 BY ATTORNEY MORRISON: 3 Q. All right. Back to Figure 2. 4 A. Figure 2 within -- 5 Q. I'm sorry. Figure 2 of the '772 6 publication -- 7 A. Great. Thank you. 8 Q. -- which is Exhibit 1007 to the declaration. 9 A. Let me turn to that. 10 I'm at Figure 2 of the '772 publication. 11 Q. And I believe we agreed before that there are 12 -- and, again, if you'd like to count, you certainly are 13 welcome to, but there are 56 sequences disclosed here? 14 ATTORNEY WILSON: Object to form. 15 THE WITNESS: If you indicate there are 56 16 sequences -- which appears to be a combination of new 17 sequences as well as existing serotypes, then if it's 18 56, I believe you. 19 BY ATTORNEY MORRISON: 20 Q. Did you look at whether any of these other 21 sequences would be a valid starting point for your 22 analysis other than rh.10?	Page 122 1 ATTORNEY WILSON: Object to form. 2 THE WITNESS: Yes. Rh.10 was called out 3 multiple times in the patent as a pretty special 4 important serotype; so that's where we started. 5 BY ATTORNEY MORRISON: 6 Q. Why was it special or important according to 7 the patent? 8 A. There are a number of data that it reported 9 within the patent involving delivery to several tissues 10 that were of interest to the inventors in the field and 11 the, you know, the rh.10 had extremely interesting 12 properties and compelling properties in those data to 13 the point that the inventors repeatedly highlighted the 14 superior performance of rh.10. 15 Q. All right. We're going to go through that 16 data in a minute; so I won't make you do it right now. 17 Did you consider whether any of these other 18 serotypes would be a starting point for your analysis? 19 A. I didn't consider the other serotypes given 20 that rh.10 was highlighted as such an important vector 21 to consider. 22 Q. Okay. And did you consider whether any -- any
Page 123 1 of these other serotypes that are disclosed in figure 2 2 were within 95 percent identity of rh.46? 3 A. I didn't do such analysis. Rh.10 was really 4 highlighted by the inventors as a pretty extraordinary 5 vector; so that's where my analysis started. 6 Q. And you do know, though, that there are other 7 capsids that are in Figure 2, other capsid proteins, 8 that are within 95 percent of rh.46; right? 9 ATTORNEY WILSON: Object to form. 10 THE WITNESS: I didn't do that analysis. 11 BY ATTORNEY MORRISON: 12 Q. Okay. 13 A. So if you could show such analysis then I 14 would follow your guidance, but I didn't do such 15 analysis myself. 16 Q. Sure. You said you did review the POPR 17 submitted by patent owners here; right? 18 ATTORNEY WILSON: Object to form. 19 THE WITNESS: The POPR? Could you please -- 20 BY ATTORNEY MORRISON: 21 Q. Yes, I'm sorry. The Patent Owner Preliminary 22 Response that REGENXBIO and University of Pennsylvania	Page 124 1 submitted. You did review that; right? 2 A. I did review the preliminary response. 3 Q. And in that preliminary response the patent 4 owners laid out that there were 13 other capsids in 5 Figure 2 that are within 95 percent of rh.46? 6 ATTORNEY WILSON: Object to form. 7 THE WITNESS: Yes. I was unaware until 8 reading that preliminary report that there were 9 apparently other sequences that have 95 percent or 10 greater identity. I'll, you know, I would want to see 11 the analysis before agreeing with it. 12 BY ATTORNEY MORRISON: 13 Q. Sure. You didn't do any alignments yourself 14 to see whether any of the other capsid proteins listed 15 in Figure 2 of the '772 publication were 95 percent 16 identical to rh.46; right? 17 A. I didn't do any alignments of other sequences 18 within figure 2 given that rh.10 was really highlighted 19 repeatedly by the inventors as a very important and 20 superior vector. 21 Q. So you chose not to do any other alignments 22 because of what the inventors said about rh.10; is that

Page 125 1 right? 2 A. Yes. The inventors really highlighted the 3 importance and the extraordinary properties of several 4 vectors; so that's why my analysis started. 5 Q. Were there other vectors that the inventors 6 highlighted other than rh.10? 7 ATTORNEY WILSON: Object to form. 8 THE WITNESS: Yes. Perhaps you could consider 9 some language within the patent if that would be 10 helpful. 11 BY ATTORNEY MORRISON: 12 Q. Sure. We can. I want to walk through that in 13 some detail; so I don't want to make you do it twice, 14 and before we get into that why don't we take a short 15 break and then we can walk through all that together in 16 detail. Does that sound okay? 17 A. Sounds good thanks. 18 (A break was taken.) 19 BY ATTORNEY MORRISON: 20 Q. Welcome back, Dr. Schaffer. 21 A. Thank you. 22 Q. Did you talk to your counsel about the	Page 126 1 substance of your deposition during the break? 2 A. No, we didn't. 3 Q. Okay. You've mentioned a couple of times -- 4 we talked about rh.10; so let's look at where you talk 5 about that in your declaration, and we'll look at that 6 with the '772 publication. 7 A. Thank you. 8 Q. And if it's helpful, I can provide you a 9 separate copy of the '772 so you don't have to flip back 10 and forth. 11 A. It would be helpful. I'll page to my 12 declaration. It would be terrific to have a separate 13 copy of '772 in that case. They're in the same binder. 14 Q. Yes. So here, I'm providing you with a extra 15 copy of Exhibit 1007 which is the '772 publication. 16 A. Thank you. 17 Q. Okay. So if you go to your declaration at 18 page 79, which is in your section on -- 19 Looking for -- we're on Zoom? 20 (Discussion off the record.) 21 BY ATTORNEY MORRISON: 22 Q. Okay. So, Dr. Schaffer, we've turned to
Page 127 1 paragraph 207 of your declaration, which is in your 2 section on the '772 publication. 3 A. Yeah. So my paragraph 207 of my declaration. 4 Q. Okay. And in paragraph 207 you talk about 5 what you've already said on the record today that the 6 '772 publication singles out AAV rh.10, and you go on 7 from there; is that right? 8 A. That's right. The '772 talks about the superb 9 tropism of rh.10. 10 Q. Okay. So in paragraph 208, the next 11 paragraph, which is on page 79 of Exhibit 1005, you note 12 that the '772 publication suggests -- this is the last 13 sentence -- that this novel AAV has some intriguing 14 biological significance. 15 ATTORNEY WILSON: Object to form. 16 THE WITNESS: That's a quotation from the '772 17 publication; so the inventors refer to rh.10 as having 18 intriguing biological significance. 19 BY ATTORNEY MORRISON: 20 Q. And do you agree that rh.10 has intriguing 21 biological significance? 22 A. I agree with the assessment of the inventors.	Page 128 1 Yes, it has intriguing biological significance to me as 2 well. 3 Q. If rh.10 has intriguing biological 4 significance, then why would you modify it? 5 ATTORNEY WILSON: Object to form. 6 THE WITNESS: Rh.10 has interesting properties 7 in multiple tissues. I'd be happy to dive into the data 8 as well, but here, this is a summary. The inventors 9 summary of the data that indicates that rh.10 is, you 10 know, outstanding in liver and muscle or very strong in 11 liver and muscle also outstanding in -- compared to AAV8 12 in liver and outstanding compared to AAV1 within muscle. 13 So in addition, you know, they indicate as you 14 summarized in that last sentence that led them to 15 conclude it had intriguing biological significance. So 16 some rh.10 is very strong in muscle very strong in lung 17 and second only to AAV8 in liver, but there's room for 18 improvement within the liver. So that would motivate a 19 POSA, or motivate me, to try to take rh.10 and modify it 20 to improve its properties within that third tissue while 21 preserving the properties in the lung and the muscle. 22 BY ATTORNEY MORRISON:

Page 129 1 Q. And you say in paragraph 2009 -- sorry, 209, 2 that gene transfer in the liver, up till now, has been 3 "relatively disappointing." 4 A. That phrase is a quote from the patent 5 inventors or from the '772 publication, or 6 specifications, yes. Efficiency of gene transfer to 7 liver that, until now, has been relatively 8 disappointing. 9 Q. So let's look at the paragraph you cite which 10 is paragraph 250 of the '772 publication. It's on 11 page 132 of the '772 publication; Exhibit 1007. 12 A. Could you repeat that -- paragraph 250? 13 Q. It's 250. So it's on the bottom of page 132 14 and goes over to the top of page 133? 15 A. Great. Thank you. 16 Q. And so the sentence that you quote in 17 paragraph 208 -- excuse me, 209 is at the top of 18 page 233 -- excuse me, 133 of Exhibit 1007. 19 Do you see that? 20 A. I see that, yes. 21 Q. And the full sentence says: 22 [As Read] Importantly, AAV 2/8 provides a	Page 130 1 substantial advantage over the other serotypes 2 in terms of efficiency of gene transfer to 3 liver that until now has been relatively 4 disappointing. 5 And it goes on from there; right? 6 A. That's an accurate reading of that language, 7 yes. 8 Q. Okay. And so the inventors are saying in this 9 sentence that until AAV8 was found, gene transfer to the 10 liver had been relatively disappointing? 11 A. That is a fair interpretation of that 12 language. 13 Q. Okay. And so AAV met a need for a vector with 14 tropism to the liver; right? 15 ATTORNEY WILSON: Object to form. 16 THE WITNESS: I believe you said AAV met a 17 need? 18 BY ATTORNEY MORRISON: 19 Q. AAV -- I'm sorry, let me ask it again. AAV8 20 met a need for a vector with tropism to the liver? 21 ATTORNEY WILSON: Object to form. 22 THE WITNESS: Well, met a need is, you know,
Page 131 1 really as we've been talking about some of this language 2 is really relative. It's how good do you know to be to 3 be able to address a particular condition or be 4 successful in a particular application. 5 AAV8, as they indicate here, is superior to 6 prior AAV2s that had been described for liver, but one 7 would then have to analyze, you know, does it meet the 8 bar for using it for particular applications. 9 BY ATTORNEY MORRISON: 10 Q. So after this work that was done in the '772 11 publication, one would still have to analyze whether 12 AAV8 was actually good enough to achieve the goals of 13 delivering gene therapies to the liver? 14 ATTORNEY WILSON: Object to form. 15 THE WITNESS: Yes. So data within this 16 publication, you know, certainly highlight or indicate 17 the promise of different AAVs, you know, specifically 18 rh.10 which is called out and AAV8 which is called out 19 and AAV1 which is called out. 20 So it does highlight those -- the promise of 21 those vectors for the tissues that have been analyzed: 22 You know, muscle, lung, and liver. So one, a POSA,	Page 132 1 would be motivated to pursue examination of whether 2 those variants would be useful for given gene delivery 3 applications within those tissues. 4 BY ATTORNEY MORRISON: 5 Q. And by those variants, you mean AAV1, AAV8, 6 and AAV rh.10? 7 A. Rh.10, you know, according to the inventors, 8 the most prominent of these given its superb properties, 9 but AAV8 is interesting, or compelling, for liver and 10 AAV1, at least it says that -- and there's a comparison 11 between rh.10 and AAV1 in muscle here. And rh.10 they 12 indicated was the equal to the performance of AAV1 in 13 muscle. 14 (Discussion off the record.) 15 BY ATTORNEY MORRISON: 16 Q. So in paragraph 210, you say that -- oh, 17 strike that. 18 The '772 publication teaches that rh.10 has 19 excellent tropism in lung; right? 20 A. Can you refer to -- is that a quote from a 21 publication, or is that an interpretation of data? 22 Q. Paragraph 256 of the '772 publication --

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1 A. Ah, thank you.
 2 **Q. -- says:**
 3 **[As Read] The data from both experiments**
 4 **confirmed the superb tropism of clone 44.2 in**
 5 **lung-directed gene transfer.**
 6 **Right?**
 7 A. Yes. That's what paragraph 256 of '772 says.
 8 **Q. And clone 44.2 is rh.10.**
 9 A. Correct.
 10 **Q. So the '772 publication teaches that rh.10 has**
 11 **superb tropism in lung; right?**
 12 A. That's correct.
 13 **Q. And it also teaches that AAV8 has good tropism**
 14 **to the liver; right?**
 15 A. It shows data indicating that AAV8 has good
 16 tropism to liver and also spells that out, you know, for
 17 example, within paragraph 257.
 18 **Q. And so your opinion presented in your**
 19 **declaration at paragraph 210 and other places is that a**
 20 **person of skill in the art would be motivated to modify**
 21 **rh.10 with AAV8 to get even more efficient gene transfer**
 22 **in the liver; right?**

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1 own has superb tropism in lung and that it also had
 2 outstanding performance in liver and muscle; right?
 3 A. Superb tropism in lung comes from
 4 paragraph 256, and then outstanding in liver and muscle
 5 comes from paragraph 257 of the '772. That's a correct
 6 reading.
 7 **Q. So you would agree with me that the**
 8 **'772 publication teaches that rh.10 has superb tropism**
 9 **in lung and outstanding performance in liver and muscle;**
 10 **right?**
 11 A. That's what the inventor states in those two
 12 paragraphs.
 13 **Q. And that's what this publication teaches;**
 14 **right?**
 15 A. That's what the publication teaches as a
 16 result of the inventor stating that, yes.
 17 **Q. And in your opinion, a POSA would have not**
 18 **been motivated to improve the performance in the liver**
 19 **by modifying rh.10 based on AAV8.**
 20 A. Could you rephrase that because it sounded
 21 like "a POSA would not be motivated."
 22 **Q. I meant to say --**

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1 A. I believe, yes, that rh.10, as highlighted by
 2 the inventors, is a superb vector, an outstanding
 3 vector, using language they refer to elsewhere. And
 4 given its superiority within tissues, such as lung and
 5 muscle, one would want to preserve those properties and
 6 then learn from AAV8 in order to improve the properties
 7 of rh.10 within the liver.
 8 **Q. And the purpose of that would be to get even**
 9 **more efficient gene transfer in the liver for AAVrh.10;**
 10 **right?**
 11 A. Yeah. A goal for rh.10 engineering would be
 12 to take advantage of and preserve its properties within
 13 the lung and the muscle and then to try to further
 14 improve its properties within the liver to create a
 15 generally strong vector.
 16 **Q. And that's the reason that you've given in**
 17 **your declaration for modifying rh.10 with AAV8; right?**
 18 A. Yes. Myself and a POSA would be motivated to
 19 create a generally strong vector that is superb at
 20 multiple tissues to be able to utilize that vector for a
 21 variety of different applications.
 22 **Q. Well, the '772 publication says rh.10 on its**

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1 ATTORNEY WILSON: It did.
 2 BY ATTORNEY MORRISON:
 3 **Q. I believe what I said -- but I'll say it**
 4 **again.**
 5 A. Okay.
 6 **Q. It is your opinion that a POSA would have been**
 7 **motivated to improve the performance in the liver by**
 8 **modifying rh.10 based on AAV8.**
 9 A. It's my opinion that given the really
 10 compelling properties of rh.10 in muscle and in lung and
 11 its close second to AAV8, second best in the liver, that
 12 I would be motivated as a POSA to learn from AAV8, and
 13 to take modifications from AAV8 into rh.10 to preserve
 14 its properties within lung and muscle and improve its
 15 properties within liver.
 16 **Q. And what you say in your declaration at**
 17 **paragraph 210 is that the reason one would do that is to**
 18 **achieve even more efficient gene transfer in the liver;**
 19 **right?**
 20 A. Yes. In 210, and in general throughout the --
 21 my declaration, the goal would be to improve properties
 22 in liver while preserving the properties within lung and

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1 muscle.

2 **Q. Where do you say in paragraph 210 or anywhere**
3 **in your declaration that the goal would be to reserve**
4 **the properties in lung or in muscle?**

5 ATTORNEY WILSON: Object to form.

6 THE WITNESS: Yeah. So if there's a portion
7 within the document you'd like to discuss, I'd be happy
8 to, but I do discuss the idea that it would be very
9 compelling -- I would be strongly motivated to find a
10 vector that is generally good in multiple tissues.

11 BY ATTORNEY MORRISON:

12 **Q. So, Dr. Schaffer, I'll confess I didn't see in**
13 **your declaration anywhere where you said that the**
14 **motivation would be to preserve properties in lung and**
15 **in muscle while improving the properties in the liver;**
16 **so I was wondering if you could point me to where you**
17 **said that in your declaration.**

18 ATTORNEY WILSON: Object to form.

19 THE WITNESS: My apologies. I didn't bring my
20 reading glasses today.

21 BY ATTORNEY MORRISON:

22 **Q. Would you like mine?**

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1 A. Yes. I mean, in general throughout the entire
2 publication, I discuss the fact that as they do,
3 following upon their guidance, that rh.10 is a very
4 interesting vector, a very compelling vector to utilize
5 for multiple tissues. And the motivation would be to be
6 able to take that vector, preserve its properties for
7 other tissues, such as muscle and lung because it's
8 already strong within those tissues, and create a
9 generally good vector by trying to improve its
10 properties within liver.

11 **Q. Okay. So the motivation for choosing AAV8 as**
12 **a modifier is to improve the properties in liver; is**
13 **that right?**

14 A. That's correct. AAV8 is called out by the
15 inventors as the exemplary serotype in liver; so --

16 **Q. Is -- I apologize. I apologize.**

17 A. Sure. So one would want to learn from AAV8 in
18 order to improve the properties of rh.10 to make it good
19 at all three tissues.

20 **Q. Is there any other reason that you would**
21 **choose AAV8 to modify rh.10 other than to improve the**
22 **properties in liver?**

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1 ATTORNEY WILSON: Object to form.

2 THE WITNESS: Yes. AAV8 is an outstanding
3 vector, according to the inventors, within liver; so
4 it's the exemplar, if you will. It's the -- it's the
5 variant that one would want to learn from from liver in
6 order to make an otherwise superior serotype, such as
7 rh.10, even better within liver.

8 BY ATTORNEY MORRISON:

9 **Q. And so the motivation for choosing AAV8 is to**
10 **improve the properties in liver; right?**

11 ATTORNEY WILSON: Object to form.

12 THE WITNESS: Yeah. The motivation for
13 choosing AAV8 is to improve the properties in liver
14 while adding those properties on top of the already good
15 properties within lung and within muscle.

16 BY ATTORNEY MORRISON:

17 **Q. Right.**

18 **So I just want to focus on the choosing of**
19 **AAV8 as the -- strike that. Let me step back.**

20 **You have said multiple times -- and I**
21 **understand from your declaration -- that the reason you**
22 **allege you would choose rh.10 is for all the reasons**

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1 **we've already discussed, that it was superior in**
2 **multiple tissues.**

3 **Is that fair?**

4 A. I -- I would say I didn't choose rh.10. You
5 know, the inventors chose rh.10 by relatedly
6 highlighting it as a superb and as a outstanding vector.

7 **Q. But you chose it in your declaration as the**
8 **starting point for your analysis.**

9 A. I was guided --

10 ATTORNEY WILSON: Object to form.

11 THE WITNESS: -- by the inventors to focus on
12 rh.10 --

13 BY ATTORNEY MORRISON:

14 **Q. Okay.**

15 A. -- given how superb and exemplary it is.

16 **Q. Let me say it this way: You start your**
17 **analysis of the '772 publication with rh.10; right?**

18 A. Given that the inventors referred to it as
19 superb and outstanding, it's the natural place to start.
20 A POSA would start with rh.10.

21 **Q. Okay. And so the reason for choosing to**
22 **modify it with AAV8 instead of something else is to try**

35 (Pages 137 to 140)

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1 to improve the properties in the liver; right?

2 ATTORNEY WILSON: Object to form.

3 THE WITNESS: As the inventors call out, you
4 know, the exemplary serotypes for multiple tissues,
5 rh.10 itself is the exemplary serotype at this time in
6 lung. It's equal to the exemplary serotype within
7 muscle, namely AAV1, and is second-best to AAV8 for
8 liver. So the goal would be to learn from liver and
9 make substitutions from liver or modifications in rh.10,
10 based upon AAV8 to improve the properties of rh.10 in
11 liver --

12 BY ATTORNEY MORRISON:

13 Q. Right.

14 A. -- while preserving its properties in the
15 muscle and lung.

16 Q. So I'm want -- maybe I'm not asking my
17 question clearly. I want to focus on why you would
18 choose AAV8 as your modifier.

19 Do you understand where I'm going?

20 A. Yes. I --

21 Q. Okay.

22 A. -- I was believing --

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1 Q. So my --

2 A. Sorry. Go ahead.

3 Q. Oh, I'm sorry.

4 So my question is why would you choose AAV8 as
5 opposed to AAV7 or AAV1 to modified rh.10?

6 The reason you would do that is to improve the
7 properties in liver; right?

8 ATTORNEY WILSON: Object to form.

9 THE WITNESS: Yeah. The inventors of the
10 patents and the specification of the patents calls out
11 AAV8 as an exemplary vector for liver; so if I were
12 trying to take a vector and improve its properties in
13 liver while preserving its properties within lung and
14 muscle, I would try to learn from AAV8 -- or a POSA
15 would learn from AAV8 based upon the '772 specification.

16 BY ATTORNEY MORRISON:

17 Q. Is there anything -- any other reasons you
18 would choose AAV8 other than to try to improve the
19 properties in the liver?

20 A. AAV8 is called out by the inventors as being
21 an exemplary vector within liver; so I would want to
22 learn or a POSA would want to learn from AAV8 in order

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1 to inform the design of another serotype, such as rh.10.

2 Q. Okay. Other than AAV8's exemplary properties
3 in the liver, are there any other reasons you would
4 choose AAV8?

5 ATTORNEY WILSON: Object to form.

6 THE WITNESS: The inventors highlight AAV8
7 repeatedly as a model for liver, and so that is what I
8 would be guided by as a POSA to take rh.10 and learn
9 from RV8 -- AAV8 in order to improve the properties of
10 rh.10 within liver while preserving it in muscle and
11 lung.

12 BY ATTORNEY MORRISON:

13 Q. So other than the inventors highlighting
14 AAV8's properties in liver, are there any other reasons
15 for choosing AAV8?

16 ATTORNEY WILSON: Object to form.

17 THE WITNESS: Yeah. Perhaps you can suggest
18 some reasons one might consider because that's my
19 answer.

20 BY ATTORNEY MORRISON:

21 Q. Okay. You don't have any other reasons; is
22 that --

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1 ATTORNEY WILSON: Object --

2 BY ATTORNEY MORRISON:

3 Q. -- is that right?

4 ATTORNEY WILSON: Object to form.

5 THE WITNESS: I believe I answered the
6 question.

7 BY ATTORNEY MORRISON:

8 Q. So you don't -- other than modifying it to
9 improve the properties in liver, you don't have any
10 other reasons for choosing AAV8.

11 ATTORNEY WILSON: Object to form.

12 THE WITNESS: Yeah. I believe I answered the
13 question. I have probably nothing further to add to my
14 prior answer.

15 BY ATTORNEY MORRISON:

16 Q. Okay. So you have no other -- you have
17 nothing else to add based on -- strike that.

18 You have nothing else to add other than what
19 you've already said. Is that fair?

20 ATTORNEY WILSON: Object to form.

21 THE WITNESS: My prior answer is my opinion
22 about that -- the matter of that question.

36 (Pages 141 to 144)

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1 BY ATTORNEY MORRISON:
 2 **Q. Okay. Okay. And so you don't have anything**
 3 **else to add to that?**
 4 ATTORNEY WILSON: Object to form.
 5 THE WITNESS: I've provided my question to the
 6 answer -- or sorry -- my answer to the question. Thank
 7 you.
 8 BY ATTORNEY MORRISON:
 9 **Q. So, Dr. Schaffer, I'm just trying to make sure**
 10 **I have the full contours of your opinion. And if I've**
 11 **got them, that's great, and we can move on. That's all**
 12 **I'm trying to confirm is that you don't have anything**
 13 **else to add to what you've already said. Is that fair?**
 14 ATTORNEY WILSON: Object to form.
 15 THE WITNESS: My answer that I provided
 16 previously is my opinion about that question.
 17 ///
 18 BY ATTORNEY MORRISON:
 19 **Q. Okay. And you don't have anything else to**
 20 **add.**
 21 ATTORNEY WILSON: Object to form.
 22 THE WITNESS: The answer I provided before is

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1 my opinion about that question.
 2 BY ATTORNEY MORRISON:
 3 **Q. And you -- do you have anything else to add?**
 4 A. My answer -- I'm happy to continue to provide
 5 that answer.
 6 **Q. I don't want you to provide the same answer**
 7 **again. I just want to make sure you don't have anything**
 8 **else you want to say about why would you would choose**
 9 **AAV8, other than what you've already said, which I**
 10 **understand.**
 11 ATTORNEY WILSON: Object to form.
 12 THE WITNESS: I've provided answer to the
 13 question.
 14 BY ATTORNEY MORRISON:
 15 **Q. Okay. I understand from that that you don't**
 16 **have any else to add.**
 17 A. I've proved my answer --
 18 ATTORNEY WILSON: Object to the colloquy.
 19 That's not even a question.
 20 You don't have to answer that.
 21 BY ATTORNEY MORRISON:
 22 **Q. So you don't have anything else to add?**

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1 ATTORNEY WILSON: Object to form.
 2 THE WITNESS: I provided my answer to the
 3 question.
 4 BY ATTORNEY MORRISON:
 5 **Q. Okay.**
 6 **Where -- so in your declaration, you only**
 7 **refer to AAVrh.10's properties in muscle in paragraphs**
 8 **208 and 294; is that right?**
 9 A. You said paragraph 208. And then what was the
 10 second paragraph you mentioned?
 11 **Q. 294.**
 12 A. I can confirm that I referred to its muscle
 13 properties within those paragraphs. And while I have,
 14 you know, certainly supervised the writing of this
 15 document and spent time with it, I would want to go
 16 through with it verbatim to be able to comment on
 17 whether I used the word "muscle" elsewhere within the
 18 document, given the length of the document.
 19 **Q. Okay.**
 20 A. But I certainly do refer to the muscle tropism
 21 in 208 and in 294.
 22 **Q. Okay. In paragraph 211, you say that you**

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1 **would only modify a single amino acid at a time:**
 2 **[As Read] For fear of damaging or**
 3 **destroying the desirable properties of**
 4 **AAVrh.10.**
 5 **Right?**
 6 A. That's an accurate reading of paragraph 211.
 7 **Q. And isn't it true that a single amino acid**
 8 **substitution could damage or destroy some of the**
 9 **desirable properties of AAVrh.10?**
 10 ATTORNEY WILSON: Object to form.
 11 THE WITNESS: So some substitutions, some
 12 amino acid substitutions can improve function. Some can
 13 deleteriously impact function.
 14 BY ATTORNEY MORRISON:
 15 **Q. Okay. That's true of even a single amino**
 16 **acid, the substitution could improve function or it**
 17 **could make function worse; right?**
 18 ATTORNEY WILSON: Object to form.
 19 THE WITNESS: I think that, as a general
 20 principle of protein science, some amino acid
 21 substitutions are beneficial for a given function, and
 22 some are deleterious for a given function.

37 (Pages 145 to 148)

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1 BY ATTORNEY MORRISON:

2 **Q. And it's also true that changing many amino**
3 **acids might not damage or destroy function; right?**

4 ATTORNEY WILSON: Object to form.

5 THE WITNESS: There are likely cases. If you
6 could, you know, highlight some, that would be useful,
7 cases where changing many amino acids could impact --
8 adversely impact the function of a protein; so my
9 guidance would be to do a small number at a time,
10 starting with one.

11 BY ATTORNEY MORRISON:

12 **Q. So if you changed 48 amino acids in rh.10,**
13 **you'd have AAV8; right?**

14 A. Yes. Rh.10 and AAV8 differ at 48 amino acids.

15 **Q. And there are instances in the literature**
16 **where changing a fragment improves function; right?**

17 ATTORNEY WILSON: Object to form.

18 THE WITNESS: If you could refer to a given,
19 you know, publication, that would be helpful. I don't
20 know of a -- it would be especially helpful to refer to
21 one that was before, I believe, April of 2005 when I --
22 you know, a POSA would have formed their opinion about

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1 this case.

2 BY ATTORNEY MORRISON:

3 **Q. Sure.**

4 **You cite -- in your declaration at**
5 **paragraph 211, you cite the Wu reference, Exhibit 1032?**

6 A. Yes. Would you like to turn to that
7 reference?

8 **Q. Yes. Let's look at the Wu reference, which is**
9 **Exhibit 1032.**

10 ATTORNEY WILSON: Can I grab a copy of Wu.
11 Thank you.

12 ATTORNEY MORRISON: Mm-hmm.

13 THE WITNESS: Running out of real estate.

14 BY ATTORNEY MORRISON:

15 **Q. If you'd like a separate one, I'm always happy**
16 **to get that to you.**

17 A. Thank you.

18 Wu is Exhibit Number 1032.

19 BY ATTORNEY MORRISON:

20 **Q. 1032.**

21 A. Thank you.

22 I'm at Wu.

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1 **Q. Okay. And you know that Wu taught a number of**
2 **different types of substitutions, and you can see that**
3 **in the abstract; right?**

4 A. That's right. Wu made several different kinds
5 of substitutions.

6 **Q. And those included:**

7 **[As Read] Epitope tag or ligand insertion**
8 **mutants, alanine scanning mutants, and epitope**
9 **substitution mutants.**

10 **Right?**

11 A. Is this within the abstract somewhere?

12 **Q. It is within the abstract. It's the third or**
13 **fourth sentence that starts "Several types."**

14 A. Okay.

15 **[As Read] Epitope tag or ligand insertion**
16 **mutants, alanine scanning mutants, and epitope**
17 **substitution mutants.**

18 Yes. That's an accurate reading of the
19 abstract.

20 **Q. And so Wu made mutants where fragments were**
21 **inserted or changed that did not damage or destroy**
22 **function; right?**

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1 ATTORNEY WILSON: Object to form.

2 THE WITNESS: Yes. If you could point to
3 particular parts of the publication that teach that, I'd
4 be happy to try to comment.

5 BY ATTORNEY MORRISON:

6 **Q. Sure.**

7 **Well, let's start with this: A number of WU's**
8 **mutants, Numbers 1 through 48, were alanine scanning**
9 **mutants; right?**

10 ATTORNEY WILSON: Object to form.

11 THE WITNESS: And this is in a particular
12 table? Are you referring to --

13 ///

14 BY ATTORNEY MORRISON:

15 **Q. It's table -- I'm referring to Table 1.**

16 A. So Table 1 refers to MUT 1 through MUT 48, and
17 the second column refers to them as ALA sub.

18 **Q. And Wu says in the abstract that those are**
19 **alanine scanning mutants; right?**

20 A. I believe they are referring to that class of
21 mutants as alanine scanning.

22 **Q. And you'd agree with me that making mutations**

38 (Pages 149 to 152)

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1 by alanine scanning was common at the time of the Wu
2 publication?

3 ATTORNEY WILSON: Object to form.

4 THE WITNESS: So alanine scanning, a POSA
5 would have been familiar with that as an approach within
6 the field.

7 BY ATTORNEY MORRISON:

8 **Q. And you are familiar with it as an approach**
9 **within the field at the time of the '274 patent?**

10 A. I was familiar with it as an approach within
11 the field.

12 **Q. Have you ever heard the term "wreck and**
13 **check"?**

14 A. I'm not familiar with that term.

15 **Q. Okay. So Table 1 lists the mutants that Wu**
16 **made for the experiments that are described in this**
17 **publication; right?**

18 A. Table 1 lists the mutants that were considered
19 in the publication, yes.

20 **Q. And the first 48 of those are all alanine**
21 **substitutions; right?**

22 A. MUT through 48 are listed within Table 1 as

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1 ALA sub, which according to their key is alanine
2 substitution.

3 **Q. And, in fact, if you look at the third column**
4 **of Table 1 of Wu, it lays out exactly what substitutions**
5 **were made; correct?**

6 A. The third column lists -- it appears, the
7 first part of it, the amino acids that naturally occur
8 within the capsid for a given set of positions. And
9 then there's a hyphen, and then it refers to amino acids
10 that were introduced in place --

11 (Clarification inquiry by The Court Reporter.)

12 THE WITNESS: -- that were introduced in place
13 of those naturally occurring amino acids within the
14 capsid.

15 BY ATTORNEY MORRISON:

16 **Q. And so just taking Mutant 1 as an example,**
17 **there was a five amino acid stretch, and three of those**
18 **five amino acids were changed to alanine; right?**

19 A. Yes. It appears that positions 1, 4, and 5 in
20 their mutations, in their mutants was changed from the
21 original position or identity of the amino acid to
22 alanine.

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1 **Q. And so, for example -- again, using Mutant 1**
2 **as an example, the first amino acid position was an**
3 **aspartic acid, and it was changed to an alanine in this**
4 **mutant?**

5 A. That appears to be the case, a D2A mutation at
6 that position.

7 **Q. And I won't go through all of them, but**
8 **similar nomenclature is used throughout this table,**
9 **right, for how the mutants were made.**

10 A. Similar nomenclature was used, yes. The
11 original amino acid and, in some cases, a substitution
12 with an alanine for a MUT 1 through 48.

13 **Q. And so in all of the MUT 1 through 48, there's**
14 **alanine substitutions made.**

15 A. I haven't gone through them all one by one,
16 but following on the notation of the table where they're
17 all classified as alanine substitutions, that indicates
18 that the authors did intend to each of these -- for each
19 one of these to just be an alanine substitution.

20 **Q. Okay. And for the first -- just, again,**
21 **taking MUT 1 as an example, the phenotype of Mutant 1 is**
22 **WT, which is wild type; right?**

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1 A. Yes. The last column refers to the phenotype,
2 what happens to the particle upon trying to package a
3 version that has that substitution. And below the
4 table, there's a key to what all those abbreviations
5 mean, and I'm just going to confirm that WT means wild
6 type.

7 (Clarification inquiry by The Court Reporter.)

8 THE WITNESS: Yeah. The figure for the table
9 doesn't -- it doesn't define WT. WT is a standard
10 abbreviation within the field that refers to wild type;
11 so my interpretation is that WT is wild type. But it
12 would be helpful to go through the rest of the
13 publication to see if they explicitly define that term
14 elsewhere.

15 BY ATTORNEY MORRISON:

16 **Q. I think I can help you, Dr. Schaffer. If you**
17 **go to Figure 1. And the table at the bottom of**
18 **Figure 1, it says "Class 1," and it lists a number of**
19 **mutants. And then it says "Primary phenotype, wild**
20 **type."**

21 **Do you see that?**

22 A. Great. I'll assume that they mean -- WT means

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1 wild type, then, for the rest of the publication. They
 2 don't show the abbreviation, but that's a fair
 3 assumption, based upon -- a POSA would conclude that
 4 that would be the definition.
 5 **Q. And indeed, Mutant 1 in Table 1 is listed as**
 6 **Class 1, which we just learned from Figure 1 is wild**
 7 **type; right?**
 8 A. By comparison to the two -- Figure 1 in
 9 Table 1, that's correct.
 10 **Q. Okay. All right. So of these 48 alanine**
 11 **scanning substitutions that were made, Mutants 1 through**
 12 **48, most of them, 44 out of 48, more than one amino acid**
 13 **was mutated from its natural form to an alanine; right?**
 14 A. That --
 15 ATTORNEY WILSON: Object to form.
 16 THE WITNESS: That appears to be the case. I
 17 would want to go through them to ensure that -- you
 18 know, line by line, that multiple amino acids were
 19 changed from their original identity to an alanine.
 20 But, you know, going through the first couple as an
 21 example, yeah, it's three in the first one, two in the
 22 second one. I could repeat that exercise throughout the

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1 table if that would be helpful.
 2 BY ATTORNEY MORRISON:
 3 **Q. Well, let's look at the ones where only one**
 4 **amino acid -- well, strike that.**
 5 **If you look at -- if you look at Mutant 29,**
 6 **there's -- only a single amino acid changed, an arginine**
 7 **to an alanine?**
 8 A. Yes.
 9 **Q. And that substitution resulted in wild type**
 10 **phenotype; right?**
 11 A. Yes. That's what the table says.
 12 **Q. And Mutant 31, again, an arginine was chained**
 13 **to an alanine; right?**
 14 A. That's correct.
 15 **Q. But for that mutation, there was not an**
 16 **infectious virus formed; right?**
 17 A. NI, I believe, stands for noninfectious.
 18 Empty particle speaks for itself. It would a particle
 19 without a genome inside.
 20 **Q. And by a particle, that's a capsid.**
 21 A. A capsid particle, yes.
 22 **Q. So Mutant 31 forms a capsid, but it's not**

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1 **infectious.**
 2 A. That's what the table indicates, yes.
 3 **Q. Okay. Mutant 45, where a lysine is mutated to**
 4 **an alanine, that results, again, in a wild type**
 5 **phenotype; correct?**
 6 A. Correct. 656.
 7 **Q. And then Mutant 48, which is the fourth of**
 8 **four single amino acid mutations in Wu, is a Class 2A**
 9 **mutation.**
 10 **Do you see that?**
 11 A. I see that.
 12 **Q. And if --**
 13 A. Let me --
 14 **Q. If you go to -- so if you go to page 4 of Wu,**
 15 **that's the page numbers in Exhibit 1032, and if you go**
 16 **to the left-hand column, the paragraph that starts**
 17 **"Infectious titer assays revealed four general classes."**
 18 **Do you see where I am?**
 19 A. I do see where you are, yes.
 20 **Q. Okay. At the bottom of that paragraph, it**
 21 **explains what each of the classes are.**
 22 **Do you see that?**

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1 A. I see that it enumerates Class 1, 2, 3, and 4.
 2 **Q. And Class 2, it says:**
 3 **[As Read] Contained partially defective**
 4 **mutants with infectious titers two to three**
 5 **levels lower than the wild type titer.**
 6 **Right?**
 7 A. Yes.
 8 **Q. And if you go to the right-hand column on that**
 9 **same page at the last full paragraph in that column, it**
 10 **explains what a Class 2A mutation is in the sentence**
 11 **beginning "The rest of the immunities in Class 2."**
 12 **Do you see where I am?**
 13 A. I don't -- I'm seeing a paragraph that starts
 14 with "Three Class 4B mutants."
 15 **Q. Yes.**
 16 **So go to the bottom of that paragraph, the**
 17 **second-to-last sentence.**
 18 A. I'm at the second-to-last sentence.
 19 **Q. And it says:**
 20 **[As Read] The rest of the mutants in**
 21 **Class 2 that bind to heparan, h-e-p-a-r-a-n,**
 22 **were classified as Class 2A partially**

40 (Pages 157 to 160)

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1 **defective and heparan-binding positive.**

2 A. Yes. That's an accurate reading of the
3 publication.

4 **Q. So a Class 2A mutant has a infectious titer**
5 **that's two to three logs lower than wild type, but it**
6 **does bind heparan; right?**

7 A. That appears to be the text within the
8 publication, yes.

9 **Q. So it's a partially defective mutant.**

10 A. And -- yes. That's what the key in Table 2 as
11 well says. PD is partially defective.

12 **Q. So all of the mutants that Wu made, he**
13 **mutates -- in these first 48, he mutates the wild type**
14 **amino acid to alanine; right?**

15 A. That's correct.

16 **Q. And he doesn't ever make any mutation in these**
17 **first 48 mutants of a -- of the wild type amino acid to**
18 **some other amino acid other than alanine; right?**

19 ATTORNEY WILSON: Object to form.

20 THE WITNESS: For the ones that we went
21 through, the single amino acid mutations, it appears to
22 be a mutation from the original amino acid to an

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1 alanine.

2 BY ATTORNEY MORRISON:

3 **Q. And that's true of all of Mutants 1 through**
4 **48; right?**

5 ATTORNEY WILSON: Object to form.

6 THE WITNESS: Yeah. I believe we were talking
7 about single amino acid changes or -- could you rephrase
8 your question. I didn't quite gather.

9 BY ATTORNEY MORRISON:

10 **Q. Well, if you go to -- I'm talking about not**
11 **just the single amino acids, but all of the mutations in**
12 **1 through 48, those were all mutations where the wild**
13 **type amino acid was mutated to alanine; correct?**

14 A. That is correct.

15 **Q. All right. Now, Wu also teaches that the**
16 **mutations that abolished capsid formation were located**
17 **predominantly -- or entirely, actually -- in capsid**
18 **protein VP3.**

19 ATTORNEY WILSON: Object to form.

20 THE WITNESS: Yeah. It would be great if you
21 could highlight where that conclusion is mentioned.

22 BY ATTORNEY MORRISON:

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1 **Q. Sure.**

2 **So if you go to the abstract of Wu, and about**
3 **halfway down in the abstract, there's a sentence that**
4 **starts "Among."**

5 **It's between a third and halfway down, right**
6 **in the middle of the page. "Among the Class 4 mutants"?**

7 A. "Among the Class 4 mutants, a subset"? Yes.

8 **Q. Yes.**

9 A. Okay.

10 **Q. So it says -- Wu says:**

11 **[As Read] Among the Class 4 mutants, a**
12 **subset completely abolished capsid formation.**
13 **These mutants were located predominantly, but**
14 **not exclusively, in what are likely to be**
15 **beta-barrel structures in the capsid protein**
16 **VP3.**

17 A. Yes. That's what the abstract reads.

18 **Q. And if we look at Figure 2 of Wu, which is on**
19 **page 6 at the bottom, Figure 2 shows those 48 alanine**
20 **scanning mutations that we were looking at; right?**

21 A. I'm seeing the 48 alanine scanning mutations
22 along the horizontal.

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1 **Q. And Mutants 1 through 12 are in VP1; right?**

2 A. That appears to be the case, yes.

3 **Q. And Mutants 13 through 17 are in VP2; correct?**

4 A. That also appears to be the case.

5 **Q. And then Mutants 18 through 48 are in VP3;**
6 **right?**

7 A. That is correct.

8 **Q. And so the check mark in Figure 2 indicate**
9 **noninfectious mutants, and you can see that at the end**
10 **of the key for Figure 2:**

11 **[As Read] Noninfectious mutants are**
12 **indicated by check mark.**
13 **Right?**

14 A. I see that text, yes.

15 **Q. All of the check marks are in VP3; right?**

16 A. That is the case, yes.

17 **Q. So all of the mutants that Wu made that were**
18 **noninfectious were in VP3; right?**

19 ATTORNEY WILSON: Object to form.

20 THE WITNESS: It appears that all the check
21 marks are present within the VP3.

22 BY ATTORNEY MORRISON:

41 (Pages 161 to 164)

Page 165 1 Q. So all the noninfectious mutants of Mutants 1 2 through 48 were mutants made in the VP3 region of the 3 capsid protein; right? 4 ATTORNEY WILSON: Object to form. 5 THE WITNESS: Yeah. According to the 6 publication, all the check marks which are indicative of 7 noninfectious mutants are within the VP3 region. 8 BY ATTORNEY MORRISON: 9 Q. Okay. And that's also true for all the 10 temperature-sensitive mutants. All of those were also 11 located in VP3, according to Figure 2 of Wu; right? 12 ATTORNEY WILSON: Object to form. 13 THE WITNESS: Yeah. Could you define 14 "temperature-sensitive mutant." 15 BY ATTORNEY MORRISON: 16 Q. Sure. 17 So the Figure 2 legend says: 18 [As Read] Asterisks indicate 19 temperature-sensitive mutants. 20 Right? 21 A. That's what the text reads as, yes. 22 Q. And all of those asterisks are located on	Page 166 1 mutants that were made in the VP3 region of the capsid 2 protein; right? 3 A. That appears to be the case, but, you know, to 4 provide any sort of additional thoughts on this, one 5 would want to see what "temperature sensitive" is 6 defined as by these authors. 7 Q. And you don't know how the authors defined 8 "temperature sensitive" sitting here right now? 9 A. Temperature sensitive typically refers to 10 something that if you end up elevating the temperature 11 relative to some starting point, the properties of it 12 change, but I would want to see the exact definition 13 that they use in analyzing the properties of these 14 particles. What is their definition of "temperature 15 sensitive"? It depends on the temperatures. 16 Q. Do you see in Figure 2 of Wu that at the 17 bottom of the figure, it says "32 degrees Celsius"? And 18 at the top, it says "39.5 degrees Celsius"? 19 A. I see that, yes. 20 Q. And for each of the -- there are five 21 temperature-sensitive mutants indicated by five 22 asterisks?
Page 167 1 A. I see five asterisks, yes. 2 Q. Yes. 3 And so for three of the five asterisks, the 4 mutant had -- the MUT was active at 32 degrees but not 5 at 39.5; right? 6 A. That appears to be the case. MUT 26, 27, 33 7 all have asterisks. 8 Q. And the opposite is true for Mutants 28 and 9 35. Those were active at 39 and a half degrees Celsius 10 but not at 32 degrees Celsius; right? 11 A. That appears to be the case. 12 Q. And so according to Figure 2 of Wu, all of the 13 noninfectious mutants and all of the 14 temperature-sensitive mutants were located in the VP3 15 region of the capsid protein; correct? 16 A. Yeah. 17 ATTORNEY WILSON: Object to form. 18 THE WITNESS: So all their checks and 19 asterisks are within the VP3 region. 20 BY ATTORNEY MORRISON: 21 Q. Now, Wu does talk about mutations to alter 22 tropism in addition to its alanine scanning mutations;	Page 168 1 right? 2 A. Could you highlight where they cite that. 3 Q. Yeah. 4 So if you go to the Wu paper, Exhibit 1032 at 5 page 9, there's a heading in the left column saying 6 "Changing the Tropism of AAV." 7 Do you see where that is? 8 A. I see that heading. 9 Q. And Wu goes on to say that: 10 [As Read] To determine whether we can 11 change the tropism of our AAV by inserting a 12 novel receptor ligand into the capsid, we 13 constructed two new -- that contained a serpin 14 and receptor ligand. 15 Do you see that? 16 A. I see that text. 17 Q. And so Wu doesn't suggest that its alanine 18 scanning mutations would change tropism, does it? 19 ATTORNEY WILSON: Object to form. 20 THE WITNESS: They -- they had a section where 21 they teach or cover the idea where they choose one 22 strategy for changing tropism, which is by insertion of

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1 this serpin ligand, FVFLI, cited within the publication.

2 BY ATTORNEY MORRISON:

3 **Q. Mm-hmm.**

4 **And you would agree with me that relatively**
 5 **minor sequence changes, like a single amino acid, would**
 6 **be unlikely to alter tropism; right?**

7 ATTORNEY WILSON: Object to form.

8 THE WITNESS: I actually don't agree with
 9 that.

10 ATTORNEY MORRISON: Okay. Let's take a look.

11 Would you mark this as 2023.

12 (Exhibit 2023 was marked for identification.)

13 BY ATTORNEY MORRISON:

14 **Q. So I've asked the court reporter to mark as**
 15 **Exhibit 2023 to these proceedings, a new exhibit, which**
 16 **is a paper written by Melissa Bartel, David Schaffer,**
 17 **and Hildegard B ning entitled, "Enhancing the Clinical**
 18 **Potential of AAV Vectors by Capsid Engineering to Evade**
 19 **Preexisting Immunity."**

20 **Do you have that in front of you,**

21 **Dr. Schaffer?**

22 A. Yes. I see this publication in front of me.

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1 **Q. And the second author, David Schaffer, that's**
 2 **you; correct?**

3 A. That is me. That's correct.

4 **Q. And this is a publication that was -- came out**
 5 **in Frontiers in Microbiology in October of 2011?**

6 A. That's correct.

7 **Q. And who is Melissa Bartel?**

8 A. Melissa Bartel, now Melissa Kotterman, was a
 9 graduate student within my lab.

10 **Q. And who is Hildegard -- I apologize if I'm**
 11 **butchering the last name -- B ning?**

12 A. B ning. I'm sure I'm butchering it as well.

13 She's a colleague, a professor within the field at --
 14 within Cologne, Germany. Cologne.

15 **Q. And do you recall this paper?**

16 A. I recall this paper.

17 **Q. And what was the general point of this paper,**
 18 **if you recall?**

19 ATTORNEY WILSON: Object to form.

20 THE WITNESS: I'm happy to go through the
 21 abstract. It's been probably 13 years since I've read
 22 this paper.

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1 But, yeah, as the title indicates, the goal is
 2 to be able to overcome this problem of preexisting
 3 immunity -- or try to mitigate this problem of
 4 preexisting immunity against AAV capsids by capsid
 5 engineering.

6 BY ATTORNEY MORRISON:

7 **Q. Okay. So I want to look at a couple of places**
 8 **in -- in this paper.**

9 **Well, before we do that, let me ask you: This**
 10 **paper was published in October of 2011; right?**

11 A. That's correct.

12 **Q. And so that's about six years after the**
 13 **priority date of the invention in this case; right?**

14 A. That sounds right, yes.

15 **Q. Okay. And would you agree with me that any**
 16 **paper you publish is generally accurate and complete,**
 17 **but that's at least your goal when publishing papers?**

18 A. It's accurate at the time of publication. The
 19 field, of course, changes and our data changed.

20 **Q. Sure.**

21 **But when you publish something, you intend for**
 22 **it to be accurate, complete?**

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1 A. The intention is for it to be, you know, as
 2 accurate as possible, a view of the field at the time.

3 **Q. And you wouldn't publish something that you**
 4 **thought at the time to be untrue; correct?**

5 A. I would not intentionally publish something
 6 that I thought to be untrue at the time.

7 **Q. Okay.**

8 **All right. So -- and I think we already**
 9 **discussed. This paper is about evading preexisting**
 10 **immunity to AAV; right?**

11 A. That's correct, as summarized within the title
 12 of the paper.

13 **Q. And if -- so if you turn to page 4 of the**
 14 **paper, in the left-hand column, there's a paragraph that**
 15 **starts:**

16 **[As Read] Other human viruses also face**
 17 **challenges.**

18 **Do you see that?**

19 A. I see that paragraph starting there, yes.

20 **Q. And this paragraph is talking about work that**
 21 **was done in another laboratory; right?**

22 A. That first sentence, let me scan through.

43 (Pages 169 to 172)

Page 173 1 Croyle, De Geest, Mok, Kasman, Fisher, or 2 Green, none of those publications are from my 3 laboratory. 4 Q. Okay. And so in this paragraph, you're 5 talking about using polymer coatings to deal with 6 preexisting immunity; right? 7 A. That is correct. 8 Q. And you say in this paragraph that -- in the 9 sentence that starts "Furthermore, since polymer 10 coatings." 11 Do you see where I am? 12 A. Is it further below in the same paragraph? 13 Q. It's in the same paragraph. It's about 14 two-thirds of the way down. 15 A. I see it. "Furthermore, since polymer 16 coatings." 17 Q. Mm-hmm. So you say: 18 [As Read] Since polymer coatings can 19 block regions responsible for natural viral 20 tropism, this modification afforded the 21 further opportunity to retarget the virus. 22 And it goes on; right?	Page 174 1 A. That's correct. And that's a correct reading. 2 Q. And so you note in this paper that one way to 3 change tropism is -- would be with a polymer coating to 4 block natural tropism; right? 5 ATTORNEY WILSON: Object to form. 6 THE WITNESS: Yes. This paragraph summarizes 7 that other investigators within the field were using a 8 combination of polymer coatings and retargeting ligands 9 to be able to alter tropism. 10 BY ATTORNEY MORRISON: 11 Q. Okay. And then in the same page, the 12 right-hand column, in the -- under the heading that's in 13 all caps that starts "Generic Modification." 14 A. Yes. I see that section. 15 Q. You talk about -- about half down, there's a 16 sentence that starts "In addition, capsid variability." 17 A. I see that. "In addition, capsid variability 18 among serotypes." 19 Q. Mm-hmm. 20 And in that sentence, you say something we've 21 already talked about today, right, that: 22 [As Read] Capsid variability among
Page 175 1 serotypes affects not only antigenicity but 2 also tropism so the different serotypes could 3 not be readily alternated. 4 Right? 5 ATTORNEY WILSON: Object to form. 6 THE WITNESS: Let me read the paragraph. 7 /// 8 BY ATTORNEY MORRISON: 9 Q. Mm-hmm. 10 A. Thank you. I've read the paragraph. 11 Q. Okay. And so in the middle of the paragraph, 12 you say that: 13 [As Read] Capsid variability among 14 serotypes affects not only antigenicity but 15 also tropism so the different serotypes could 16 not readily be altered -- could not be readily 17 alternated. 18 A. That's what the sentence reads, yes. 19 Q. Okay. And then last, I'd like to go to the 20 very end of the paper in the conclusion section. And 21 I'm looking at the very last paragraph, and I'll give 22 you a chance to read the paragraph.	Page 176 1 A. Okay. 2 Q. And then I have a couple of questions about 3 it. 4 A. Great. Thank you. 5 Q. All right. And in this paragraph, you talk 6 about an AAV mutation that was made to the AAV2 capsid 7 protein; is that right? 8 A. In the conclusion paragraph? 9 Q. In the -- I'm sorry. I've pointed you to the 10 wrong paragraph. 11 On the page with the conclusion -- 12 A. I see. 13 Q. -- in the paragraph in the left column that 14 starts "To date, AAV libraries based on error-prone." 15 Do you see where I am? 16 A. I do see it, yes. 17 Q. That's the paragraph. 18 A. Okay. 19 Q. I apologize. 20 A. I'll read it. 21 Great. Thank you. 22 Q. Sure.

Page 177 1 So in this paragraph, you're talking about 2 some mutations to the AAV2 capsid protein; right? 3 A. That is correct, the publications that relate 4 to AAV2. 5 Q. And, again, you are talking about publications 6 from another laboratory, right, in this paragraph? 7 A. One publication is mine. 8 Q. Which one is yours? 9 A. Maheshri 2006. 10 Q. Okay. 11 And here, you say -- towards the bottom of the 12 paragraph, you note some mutations that were made to 13 AAV2, and you note that two of them "were significantly 14 less neutralized." 15 Do you see where I am? I'm about two thirds 16 of the way down. 17 A. Yes. 18 [As Read] Two of these mutants were 19 significantly less neutralized. 20 Q. Yes. That's where I am. 21 [As Read] Two of these mutants were 22 significantly less neutralized by human sera	Page 178 1 from single donors and by IVIG compared to 2 AAV2. 3 And another AAV2 mutant; right? 4 A. That's how the sentence reads, yes. 5 Q. And so two of the mutants that were being 6 studied in these publications did better as a matter of 7 antibody immunogenicity than AAV2 or the -- an earlier 8 AAV2 immunity study. Is that fair? 9 A. Yes, referring to the Perabo 2006 publication. 10 Q. Mm-hmm. 11 And then you go on to say: 12 [As Read] In agreement with the initial 13 hypothesis that the level of immune evasion 14 can be improved if an optimal amino acid 15 substitution is introduced to disrupt an 16 immunogenic epitope, both mutants contained 17 novel substitutions at positions 459, 493, and 18 551. 19 Right? 20 A. Yes. That's what the text reads. 21 Q. So there were three substitutions made to AAV2 22 at three different positions. Is that fair?
Page 179 1 A. I would want to go back and read the Perabo 2 publication. It's probably been 15 years since I've 3 read it, but that's an accurate reading of the material 4 here. 5 Q. And then in the last sentence, you say that: 6 [As Read] In addition, the relatively 7 minor sequence changes -- compared, for 8 example, to the 120 amino acid differences 9 between AAV2 and AAV1 -- likely did not change 10 the mutant's tropism relative to AAV2. 11 Right? 12 A. That's how it reads, yes. 13 Q. Okay. And going back to the Wu paper -- you 14 can set that the one aside for now. 15 A. Okay. 16 Q. Going back to the Wu paper. I think we 17 already discussed that Wu discusses at page 9 of Exhibit 18 1032, changing tropism by insertion of a novel serpin 19 receptor ligand? 20 A. I'm back at the section called "Changing the 21 Tropism of AAV," and it describes the insertion of the 22 serpin ligand into AAV2 in Wu.	Page 180 1 Q. All right. And you also wrote a review paper 2 in 2007 that discussed various strategies for changing 3 tropism. 4 Is that -- do you recall that? 5 A. If you could cite the paper or show the paper. 6 I've written a number of review articles over the years. 7 ATTORNEY MORRISON: You don't recall every 8 review article you've written since 2007? 9 Can we mark this as Exhibit 2024 to these 10 proceedings. 11 (Exhibit 2024 was marked for identification.) 12 THE WITNESS: Thank you very much. 13 BY ATTORNEY MORRISON: 14 Q. Okay. So we've just marked as Exhibit 2024 to 15 this IPR a review paper written by -- and I apologize. 16 I'm not going to try to pronounce the first names -- 17 Jang, Lim and you, David V. Schaffer; is that right? 18 A. That's correct, Jae-Hyung Jang and Kwang-il 19 Lim. 20 Q. And this was published in Biotechnology and 21 Bioengineering in October of 2007? 22 A. That's the date, October 2017 -- 07, yes.

45 (Pages 177 to 180)

Page 181 1 Q. Okay. And who are -- is it Drs. Jang and Lim? 2 A. Drs. Jang and Lim were post-doctoral fellows 3 in my lab at that time. 4 Q. Okay. And this is a review paper talking 5 about directed evolution approaches to viral vectors; is 6 that right? 7 A. Yes. As indicated in the title, it's -- 8 includes "Directed evolution approaches to engineers 9 viral vectors." 10 Q. What's directed evolution? 11 A. Directed evolution a technology invented in 12 the early 1990s where the idea is that there's several 13 ways in which one could pursue for engineering novel 14 properties into a protein. There's a set of approaches 15 called rational approaches, and then there's another 16 approach which is a library and diversity approach. 17 So in that case for the second approach, the 18 alternate cert strategy, you would -- instead of making 19 rational changes to a sequence in assessing functions, 20 you would end up making large libraries of randomized 21 mutations and then selecting or analyzing the function 22 of those variants and pulling out the ones that had a	Page 182 1 desired change in function. Then take those -- in some 2 cases, perform additional genetic diversification or 3 mutation, screen that new library to pull out ones that 4 had functional differences that were of interest, and 5 going through that iterative process of genetic 6 diversification and selection, you could significantly 7 alter the function of a protein. 8 That -- oh. That approach was originally 9 invented as applied to enzymes and subsequently lead to 10 the Nobel prize in chemistry in 2018. 11 Q. And the directed evolution approach, as it 12 relates to AAV, that's an approach that you use in your 13 lab; is that right? 14 A. We were the first to use that approach in AAV. 15 Q. And the approach that you describe in your 16 declaration is a rational -- I think you called it a 17 rational approach? 18 A. Rational design approach, yes. 19 Q. Okay. So the approach in your declaration is 20 not directed evolution. It's rational design; right? 21 A. It's a different design strategy. It's not a 22 directed evolution strategy.
Page 183 1 Q. Okay. And would you call the approach you -- 2 that you describe in your declaration a rational design 3 approach? 4 A. The approach used in the declaration is one 5 type of rational design approach. 6 Q. Okay. 7 All right. And is Dr. -- is it Jang or 8 "Yong"? I don't know. 9 A. It's Jang, yes. 10 Q. Is he still working in the field? Do you 11 know? 12 A. I'm actually unaware if he's -- he's a 13 professor in Korea right now. I haven't analyzed his 14 publications recently; so I'm unaware if he's still 15 working with AAV. 16 Q. What about Dr. Lim? 17 A. Dr. Lim is also a professor in Korea. I'm 18 actually -- also have not analyzed his publications in 19 the past five years or; so I'm unaware if he's still 20 working with AAV. 21 Q. Fair enough. 22 But both are still professors?	Page 184 1 A. Both are professors working on -- I believe 2 both are still working on gene delivery. 3 Q. All right. 4 And, again, when you write and publish a paper 5 in a journal, you intend for it to be accurate and 6 scientifically valid. Is that fair? 7 A. I want it to be an accurate representation of 8 thoughts at the time, yes. 9 Q. And October -- I think I already asked this 10 but -- so I apologize if I did. But October 2007 is 11 about two years after the date of the '274 patent that 12 we're talking about today. 13 A. Yes. It's two years after the date of the 14 patent, yes. 15 Q. Okay. So if you could go to page 520 of the 16 publication that we've marked as Exhibit 2024, under 17 "Transductional Targeting of AAV." 18 Do you see where I am? 19 A. I see where you're talking about, yes. 20 Q. And I want to ask you some questions about 21 this first paragraph under that section; so I'll give 22 you a chance to read it.

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1 A. Okay.
 2 Great. Thank you.
 3 **Q. Okay. So in the third sentence in this**
 4 **paragraph, it says:**
 5 **[As Read] Several such strategies to**
 6 **modify AAV tropism include.**
 7 **Do you see where I am?**
 8 A. I see, yes.
 9 **Q. Okay. The first one is:**
 10 **[As Read] Association with 'adaptor'**
 11 **bispecific antibodies, with one arm directed**
 12 **against AAV and the another against a target**
 13 **receptor.**
 14 A. I see that, yes.
 15 **Q. And so one strategy that you discuss for**
 16 **modifying tropism is to essentially use an antibody that**
 17 **would bind with both the AAV and a target receptor to**
 18 **overcome the natural tropism of AAV; is that right?**
 19 ATTORNEY WILSON: Object to form.
 20 THE WITNESS: That's right.
 21 BY ATTORNEY MORRISON:
 22 **Q. And so that wouldn't involve changing the**

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1 **amino acid sequence of an AAV at all; right?**
 2 A. That's right. At that time, that was a
 3 pursued approach including -- by Jeff Bartlett, who's
 4 listed as the author on that citation.
 5 **Q. Okay. The second approach you describe is:**
 6 **[As Read] Chemical or metabolic**
 7 **conjugation of biotin to the virus, followed**
 8 **by the addition of avidin and a**
 9 **biotinylated-targeting molecule.**
 10 **Do you see that?**
 11 A. I see that language, yes.
 12 **Q. And so, again, that's using a strategy that's**
 13 **not a modification of the sequence of the amino acids of**
 14 **the AAV capsid; right?**
 15 A. I see that, yes.
 16 **Q. Okay. And then the third strategy is:**
 17 **[As Read] Genetic modification of the**
 18 **viral capsid structures through the insertion**
 19 **of defined peptide sequences.**
 20 A. I see that, yes.
 21 **Q. And so that third one is modification of the**
 22 **amino acid sequence of the AAV capsid protein; right?**

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1 A. That's correct.
 2 **Q. But it's inserting certain peptide sequences**
 3 **into the capsid in order to change the tropism. Is that**
 4 **fair?**
 5 A. That's a fair statement of that language, yes.
 6 **Q. Okay. There's nothing in this paper or**
 7 **nothing in this section, anyway, that's discussing**
 8 **changing a single amino acid in order to change tropism.**
 9 **Is that fair?**
 10 A. It includes -- it says -- discusses "several
 11 such strategies to modify AAV tropism include." It
 12 doesn't say those are the only strategies, but the three
 13 listed do not mention substitutions.
 14 **Q. Okay. The paper goes on to note in the same**
 15 **paragraph that:**
 16 **[As Read] Capsid modifications can result**
 17 **in significantly reduced viral infectivity.**
 18 **Do you see that?**
 19 A. I see that sentence, yes.
 20 **Q. And that is in line with what we looked at in**
 21 **Wu where some of the substitutions significantly -- some**
 22 **of the modifications Wu made also impacted infectivity;**

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1 **right?**
 2 A. Yes. I think it was the -- as we discussed
 3 earlier, it's a general principle of protein science
 4 that some modifications can be deleterious and some can
 5 be advantageous to a given function of a protein.
 6 **Q. And the paper, the 2024 -- that we've marked**
 7 **as 2024, the Jang paper, goes on to say in the next**
 8 **sentence:**
 9 **[As Read] In many cases, one may not know**
 10 **a suitable, specific receptor to exploit for**
 11 **targeted delivery to a given cell type, and**
 12 **binding to the cell surface may not be the**
 13 **sole determinant of tropism.**
 14 **Right?**
 15 A. That is -- can you point out where that was
 16 said.
 17 But I'll mention one thing is that when you
 18 started with the description of the paper, you said
 19 2024, and this is 2007.
 20 **Q. Yeah. I'm sorry.**
 21 A. No worries.
 22 **Q. It's Exhibit 2024 --**

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1 A. Got it.

2 **Q. -- to the proceedings --**

3 A. Okay.

4 **Q. -- published in 2007. I appreciate the**

5 **clarification, though.**

6 A. All right.

7 **Q. So I'm back on page 520 --**

8 A. Mm-hmm.

9 **Q. -- same paragraph we were in before, and it's**

10 **now the --**

11 A. I see.

12 **Q. -- second-to-last sentence says:**

13 **[As Read] In many cases, one may not know**

14 **a suitable, specific receptor to exploit for**

15 **targeted delivery to a given cell type, and**

16 **binding to the cell surface may not be the**

17 **sole determinant of tropism.**

18 **Right?**

19 A. I see that, yes.

20 **Q. And so some of these -- the paper is**

21 **explaining that some of these tropism-changing**

22 **strategies might change tropism but cause a different**

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1 **problem, like reduction of infectivity.**

2 ATTORNEY WILSON: Object to form.

3 BY ATTORNEY MORRISON:

4 **Q. Is that fair?**

5 A. For that particular sentence, or are you

6 talking about a particular sentence within --

7 **Q. I'm talking about this paragraph that we just**

8 **looked at. It's -- this paragraph is saying that there**

9 **are strategies to change tropism, but those strategies**

10 **for changing tropism might then cause a different**

11 **problem.**

12 A. The sentence says:

13 **[As Read] Such capsid modifications can**

14 **result in significantly reduced viral**

15 **infectivity.**

16 So that's a risk.

17 **Q. Okay. All right. You can set that one aside.**

18 **Let's go back to the '772 publication. And I**

19 **apologize. I know you've got a lot of paper now.**

20 **Are you okay to keep going? I just realized**

21 **what time it is. I've been talking to you for a long**

22 **time.**

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1 **Would you like to take a break?**

2 A. Do you have a sense of how much longer this

3 line of questioning may be or --

4 ATTORNEY MORRISON: It's a little while. I

5 can keep going, but I've realized -- well, let's just go

6 off the record for a minute.

7 (Discussion off the record.)

8 BY ATTORNEY MORRISON:

9 **Q. Welcome back, Dr. Schaffer.**

10 A. Thank you. Welcome to yourself.

11 **Q. Did you discuss the substance of your**

12 **testimony with your counsel over the break?**

13 A. We did not.

14 **Q. Okay. Could you turn in your declaration to**

15 **page 81, and that's the page in the center of the bottom**

16 **of your declaration.**

17 A. Okay.

18 **Q. And paragraph 214.**

19 A. Yes. I'm at paragraph 214.

20 **Q. Okay. And I should've asked this earlier, but**

21 **all the documents in your binders that you brought in --**

22 **those are all clean copies with no marks or anything on**

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1 **them; right?**

2 A. There are no marks aside from the print.

3 **Q. Okay. Great.**

4 **Okay. So starting in paragraph 214, you**

5 **discuss some expert reports that were submitted on**

6 **behalf of patent owners in a litigation on**

7 **U.S. Patent 10,526,617; is that right?**

8 A. That's right. This -- let me read through the

9 paragraph real quick to refresh.

10 So it talks about an expert report of an

11 expert witness in that situation.

12 **Q. Okay.**

13 **All right. And so going to paragraph 215, you**

14 **say that:**

15 **[As Read] Patent owners contend that a**

16 **person of skill in the art would understand**

17 **the alignment of AAV capsid protein sequences**

18 **in figure 2 to teach the creation of**

19 **artificial sequences, where an amino acid --**

20 **excuse me -- an amino acid in a naturally**

21 **occurring sequence (e.g., AAVrh.10) has been**

22 **substituted with the amino acid appearing in**

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Page 193 1 the corresponding position in the capsid 2 sequence of a different variant in the 3 alignment. 4 Do you see that? 5 A. I see that paragraph, yes. 215. 6 Q. Okay. And is it your opinion, Dr. Schaffer, 7 that the '772 publication in figure 2 teaches the 8 creation of artificial capsid sequence where you would 9 substitute amino acids from one naturally occurring 10 sequence into another one? 11 A. That -- the subsequent material or analysis of 12 figure 2 within that patent specification does teach the 13 formation of artificial sequences based upon sequence 14 alignments. 15 Q. Okay. So you would agree with what patent 16 owners contend in the underlying litigation on the '772 17 that figure 2 teaches the creation of artificial 18 sequences where you would substitute in amino acids from 19 one sequence into another. 20 Is that fair? 21 ATTORNEY WILSON: Object to form. 22 THE WITNESS: Yeah, the '772 patent talks	Page 194 1 about the formation of artificial sequences based upon 2 swapping sequences between AAVs. And, you know, I 3 believe as well expert -- the expert report of Dr. Leone 4 further goes into that in a little bit more detail. 5 BY ATTORNEY MORRISON: 6 Q. Okay. So you say -- in paragraph 216, you 7 talk about Dr. Leone's report. 8 Do you see that? 9 A. I see that. 10 Q. And so you say that she explains that based on 11 figure 2: 12 [As Read] A person of skill could readily 13 identify "conserved" and "nonconserved" 14 regions. 15 Do you see that? 16 A. That is a quote from her report. 17 Q. And do you agree that looking at figure 2 a 18 person of skill in the art could identify conserved and 19 nonconserved regions among the sequences in figure 2? 20 A. Let me take a look at -- so, for example, I 21 believe this excerpt is from figure 2 of '772. So, yes. 22 She highlights, for example, the regions that are not in
Page 195 1 red and calls those "nonconserved" regions, and then 2 also notices the regions within red which she refers to 3 as "conserved" regions. 4 Q. Right. 5 A. So I -- it's her opinion -- while I agree -- 6 that it's -- a POSA would have known how to do that. 7 Q. Okay. And you pointed to Dr. Leone as -- an 8 excerpt on -- your declaration from Dr. Leone's report 9 where she highlighted certain portions in red and called 10 those "conserved"; and then certain portions aren't red, 11 and those are "nonconserved"; right? 12 A. That's a quote from her -- from her 13 documentation as well, yes. 14 Q. And, again, you -- you would agree that a 15 person of skill in the art could do this sort of 16 analysis, which ones are conserved and which ones are 17 nonconserved, across the sequences? 18 ATTORNEY WILSON: Object to form. 19 THE WITNESS: So, for example, I think it is 20 possible to align sequences and identify ones that are 21 conserved and ones that are not conserved. That's 22 taught within '772, and Dr. Leone agrees with that.	Page 196 1 BY ATTORNEY MORRISON: 2 Q. Okay. And you would agree -- well, let me ask 3 you. 4 Do you agree with Dr. Leone that a person of 5 skill in the art would avoid changes in the red 6 conserved regions and focus on making changes in the 7 nonconserved regions? 8 A. I think that -- so Dr. Leone, as well as '772, 9 are teaching a particular path to take to be able to 10 modify capsids and alter the properties of capsids. So 11 if one is following their path, it does make sense, you 12 know, following their advice, and I think a POSA would 13 agree to -- if one wants to be able to, you know, confer 14 properties of one capsid on another capsid, they would 15 choose the regions that are not conserved and make swaps 16 accordingly. 17 Q. Okay. And so looking now at paragraph 217 in 18 your declaration, you say "Dr. Leone explains" -- 19 Oh, sorry. I'll let you get there. 20 A. Oh, please go ahead. 21 Q. Okay. Yeah. 22 [As Read] Dr. Leone explains that for

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1 those positions where substitutions may be
 2 made, figure 2 guides a person of skill in the
 3 art as to which alternative amino acids to
 4 choose.
 5 **Do you see that?**
 6 A. Yes. Dr. Leone teaches, really, you know,
 7 three steps. You know, the first is to do the
 8 alignments, you know, as -- as exemplified in '772. The
 9 second is to find positions that are conserved and
 10 nonconserved. And then the third is to, you know, based
 11 upon those positions, make a minimum number of
 12 substitutions from one serotype onto another to be able
 13 to try to confer properties of one serotype onto
 14 another.
 15 **Q. And in your opinion, the '772 teaches making**
 16 **those kinds of substitutions?**
 17 A. Yes. The '772 teaches making those
 18 substitutions, as Dr. Leone agrees.
 19 **Q. Okay.**
 20 **Now, is the method that you just described in**
 21 **this section of your declaration following the '772 to**
 22 **make changes in the nonconserved regions -- is that**

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1 **how -- if you were trying to improve in your lab at the**
 2 **time of the invention rh.10, is that the approach you**
 3 **would have followed?**
 4 ATTORNEY WILSON: Object to form.
 5 THE WITNESS: There were -- there were
 6 approaches that were, you know, within the art of the
 7 field; so I think different labs were pursuing different
 8 approaches.
 9 I was pursuing an alternate approach, which
 10 was the directed evolution approach. Some were pursuing
 11 an approach involving sequence alignment.
 12 BY ATTORNEY MORRISON:
 13 **Q. Okay. And so in your lab, you were not**
 14 **pursuing this sort of -- I think what you called a**
 15 **rational design approach. You were pursuing a different**
 16 **kind of approach called "directed evolution"?**
 17 ATTORNEY WILSON: Object to form.
 18 THE WITNESS: Yeah, within my lab, we were
 19 focusing on directed evolution. It was a small lab at
 20 the time, but that's how we decided to focus.
 21 BY ATTORNEY MORRISON:
 22 **Q. Okay. And that was in -- when did you start**

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1 **your lab at Berkeley, if you can remind me?**
 2 A. 1999.
 3 **Q. Okay. And so in 2005, you were focused on**
 4 **directed evolution as opposed to rational design.**
 5 **Is that fair?**
 6 A. There are alternate approaches to be able to
 7 pursue within the field, and our work was following the
 8 directed evolution approach.
 9 **Q. Okay. And that was -- I just want to make**
 10 **sure I understand. That was true both in 2005, and it's**
 11 **still true today.**
 12 **Is that fair?**
 13 A. There's a lot of scientific nuance in that
 14 question. I'm happy to go into -- into the scientific
 15 detail, but it's -- we opt towards directed evolution
 16 more so than rational design at this time, yet I
 17 recognize the validity of both approaches.
 18 **Q. Okay. And -- okay.**
 19 **Did you -- as part of your analysis, did you**
 20 **study the -- so Dr. Leone's opinions rely on a copy of**
 21 **figure 2 that's from the issued patent, '617, which is**
 22 **the same as figure 2 from the '772 publication; right?**

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1 A. I believe that's the case.
 2 **Q. Yeah. Did you study the '617 patent that**
 3 **issued through a series of applications from the '772**
 4 **publication?**
 5 ATTORNEY WILSON: Object to form.
 6 THE WITNESS: The -- the specification, I
 7 believe, of '617 is identical to that of '772. I don't
 8 recall the claims. I'm happy to -- to -- I believe that
 9 we have -- I don't recall if we have '617 as a exhibit
 10 here. You know, the '772 specification, which would be
 11 the majority of '617, is present here.
 12 But I haven't reviewed the claims of '617
 13 recently.
 14 BY ATTORNEY MORRISON:
 15 **Q. Okay. If you'd like to look at them, it's**
 16 **Exhibit 1014, which is previously marked.**
 17 A. Mm-hmm.
 18 ATTORNEY WILSON: Do you have a copy, Susan?
 19 ATTORNEY MORRISON: I do.
 20 ATTORNEY WILSON: If you could pass that out.
 21 THE WITNESS: Great.
 22 Is it towards the end of -- or would you like

50 (Pages 197 to 200)

Page 201 1 me to page to the claims? 2 BY ATTORNEY MORRISON: 3 Q. The claims are all the way at the end of 4 the -- 5 A. Okay. Thank you. 6 Q. And so did you study -- I guess the question 7 really is did you study the claims when you were forming 8 your opinions? 9 ATTORNEY WILSON: Object to form. 10 THE WITNESS: Yes. I read these claims; 11 however, these -- these claims were not, you know, 12 material to my -- most of my opinion was focused on '772 13 along with, as you mentioned, Xie and Snowdy; so these 14 claims I didn't view as, you know -- a significant part 15 of my opinion. It was based on '772. 16 BY ATTORNEY MORRISON: 17 Q. Okay. Now, among the -- and I'm sorry to have 18 made you turn to that to just walk away from it again, 19 but among the mutations that are in -- strike that. 20 Let's go back to the '772 patent. Apologies. 21 That is 1007. 22 Excuse me, it's the '772 publication.	Page 202 1 A. Mm-hmm. 2 I'm at the '772 publication. 3 Q. Okay. I'd like to walk through some of the 4 data in the '772 publication with you. 5 A. Sure. 6 Q. So let's start with paragraph 122 of the 7 specification, which is on page 19 -- 119. 8 A. Which paragraph did you say? 9 Q. I'm sorry. It's paragraph 122 of your 10 declaration if you'd like to look at it, but it's 11 paragraph 256 in the '772. We've already looked at this 12 once. 13 A. All right. 14 Q. This is on page 133 of the '772. 15 A. Great. Thank you. 16 Q. And I think, as we discussed before, the '772 17 states that: 18 [As Read] Rh.10 has superb tropism in 19 lung-directed gene transfer. 20 A. That's what paragraph 256 says, yes. 21 Q. And if you go back to paragraph 253, there's a 22 similar statement that:
Page 203 1 [As Read] Clone 44.2 -- 2 Which is rh.10; right? 3 [As Read] -- was found to be a very 4 potent gene-transfer vehicle in all three 5 tissues with a big lead in the lung tissue 6 particularly. 7 A. That's what -- yes, that's an excerpt from 8 paragraph 253 of '772. 9 Q. Okay. And '772, as we have already discussed, 10 also says that AAV8 is particularly strong in liver. 11 A. 257 reports that, you know, rh.10 was close to 12 the performance of AAV8 for liver, but is AAV8 was the 13 best liver transducer. 14 Q. So let's go back and go through some of these 15 examples starting with examples 3 and 4, which are on -- 16 they begin on page 129 of Exhibit 1007, the '772 17 publication. 18 A. Okay. 19 Q. Okay. So examples 3 and 4 discuss the 20 creation of a pseudotyped new AAV vector which combines 21 capsid sequences from AAV7 with other sequences from 22 AAV2; is that right?	Page 204 1 A. Let me read the example really quickly to 2 confirm. 3 Q. Mm-hmm. 4 And if you need to look at your declaration, 5 it's in paragraph 124. 6 A. Thank you. 7 ATTORNEY WILSON: Do you want to look at this 8 copy? 9 THE WITNESS: Yeah, I'm going to look at the 10 second copy of the -- thank you. 11 ATTORNEY WILSON: And you'll pull your 12 declaration up. 13 BY ATTORNEY MORRISON: 14 Q. So it's page 129 of 1007. 15 A. And, Counsel, could you kindly repeat that 16 number. 17 Q. It's -- in your declaration, it's 124. 18 A. Page 124 or paragraph? 19 Q. Paragraph 124, which is on page 46 of the 20 declaration. The page number's in the center on bottom 21 of page 46. 22 A. I'm at paragraph 124 in my declaration.

Page 205 1 Q. Okay. So you'd agree with me that in 2 examples 3 and 4, the '772 publication is talking about 3 creating pseudotyped or chimeric packaging constructs 4 where the rep gene from AAV2 is being fused with cap 5 sequences from a different variant? 6 A. That's a accurate reading of my paragraph 124. 7 Q. Okay. And you'd agree that's what examples 3 8 and 4 in the '772 were talking about; right? 9 A. '77 -- or Example 3 of '772 talks about 10 production of an AAV7 vector or packaging of an AAV7 11 vector, and it does contain as part of that, as you 12 noted, within paragraph 221, the formation of a -- let 13 me sure I get the language right. 14 Well, they're talking about an AAV2 vector 15 inside of an AAV7 capsid. 16 Q. Mm-hmm. 17 A. And then let me scan through Example 4 just to 18 confirm my understanding -- or review my understanding. 19 Example 4 is talking about the rescue of 20 latent AAVs and then the cloning of those sequences. 21 Q. Okay. And then moving to Example 5 in '772 22 patent, which you discuss in paragraph 127 of your	Page 206 1 declaration if you'd like to look at it. 2 Example 5 discusses creating different 3 pseudotyped vectors combining -- well, using the AAV1, 4 AAV5, or AAV8 capsid proteins to produce -- to package 5 an AAV2 vector; is that right? 6 A. The first paragraph -- or second paragraph, 7 rather, of Example 5, namely paragraph 230, does talk 8 about digesting a plasmid containing the AAV2, rep and 9 cap, excising AAV2 cap and swapping into its place AAV8, 10 AAV1, AAV5 cap. So the results would be a chimeric AAV2 11 rep, and then a different serotype of a cap. 12 Q. Okay. And then in Example 6, they -- the 13 inventors look at whether these new capsid proteins have 14 any cross-immunologic reactivity? 15 A. Yes. Example 6 talks about serologic analysis 16 of the pseudotyped vectors. 17 Q. And so essentially what Example 6 is looking 18 at is, for example, whether antibodies to AAV7 will 19 neutralize an antibody from another AAV like AAV8; 20 right? 21 A. Let me jump into the data. 22 Q. And it's in Table 5 if that helps.
Page 207 1 A. Thank you. 2 So Table 5 in the second column describes, as 3 you suggest, creating sera against AAV1 capsid, AAV2 4 capsid, et cetera, the immunization vector, and then 5 testing whether those resulting sera do neutralize other 6 AAVs. 7 Q. Okay. And Table 5 shows that none of the 8 vectors cross-neutralize any other vector? 9 ATTORNEY WILSON: Object to form. 10 THE WITNESS: Can you explain what you mean by 11 "cross-neutralize." 12 BY ATTORNEY MORRISON: 13 Q. Sure. So the data in Table 5 shows that, for 14 example, the sera from the AAV2 and AAV1 chimera only 15 neutralizes that same chimera and not any of the other 16 ones that were created; right? 17 A. As indicated by the first row showing 00, 18 meaning it fully neutralizes it, and the rest of the 19 rows showing 100, indicating it doesn't neutralize those 20 serotypes. 21 Q. So the sera from patients immunized with the 22 AAV1 chimera, that only -- that only neutralizes the	Page 208 1 AAV1 chimera and on any of the other ones that were 2 created; is that right? 3 A. I'm going to check really quickly to see how 4 the sera were created. That's described in 234, I 5 believe. 6 I agree with what you say with the exception 7 you mentioned "patients," which implies human; so these 8 were mice. 9 Q. And I actually didn't intend for it to imply 10 human, but okay. So the mouse sera used in the 11 experiment shown in Table 5, the -- each sera only 12 naturalized the same capsid and not any of the other 13 capsids? 14 A. In this experiment, that's correct. 15 Q. Okay. And so there wasn't any 16 cross-reactivity among these five capsids tested in 17 Table 5? 18 A. In this experiment, that's correct. 19 Q. Okay. And rh.10 was not tested in this 20 experiment shown in Table 5 Example 6 of '772? 21 A. Rh.10 does not appear to be in Table 5. 22 Q. Okay. Now, in paragraph 236 on -- of the '772

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1 publication, the inventors note that they also tested
2 the AAV7 and AAV8 chimeric vectors against human sera
3 from 52 normal subjects.

4 Do you see that?

5 A. I see that, yes.

6 Q. And those human sera from 52 normal subjects
7 did not neutralize the AAV7 or AAV8 chimeras; is that
8 right?

9 A. In this experiment, yes.

10 Q. Okay. But that human sera did neutralize AAV2
11 and AAV1; right?

12 A. As reported in this paragraph, yes.

13 Q. Okay. And so what that means is that the --
14 at least those 52 normal subjects did not have
15 antibodies to AAV7 or 8?

16 A. At least at the levels that were tested. They
17 talk about 20 percent and 10 percent serum. So these
18 neutralizing assays really depend upon the details. So
19 at least at that level or that dosage of the serum or of
20 the antibodies, there was no detectable neutralization.

21 (Clarification inquiry by The Court Reporter.)

22 THE WITNESS: Clarification. I said -- or

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1 intended to say "sera."

2 BY ATTORNEY MORRISON:

3 Q. And that's just the plural of "serum"?

4 A. Yes.

5 Q. Okay. Perfect. Okay. Let's go on to

6 Example 7, which is the next one in the '772

7 publication. So in Example 7, the inventors tested for

8 muscle- and liver-directed gene transfer in -- in mice;

9 correct?

10 A. Let me scan through to confirm.

11 That's right. The Example 7 does describe

12 experiments to test the delivery efficiency of several

13 serotypes to muscle and to liver.

14 Q. And those serotypes that were tested were AAVs

15 1, 2, 5, 7, and 8; right?

16 A. That's right. Those are the ones that appear,

17 for example, in Table 6 and in Table 7.

18 Q. Okay. So let's go to Table 6, which presents

19 some of the results from this experiment. And let me

20 know when you're there.

21 A. I'm there, thanks.

22 Q. Okay. All right. Table 6 shows that the AAV7

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1 construct is about three times better in the muscle than
2 the previous best muscle transducer AAV1?

3 A. That's what Table 6 indicates.

4 Q. And it shows that AAV7 is also the second best
5 in the liver?

6 A. Again, what these data show. I agree.

7 Q. And it shows it's far better than any of the
8 previously -- excuse me. Let me ask a better question.

9 It shows that AAV7 is better than any of the
10 previously known constructs in liver; right?

11 ATTORNEY WILSON: Object to form.

12 THE WITNESS: Yeah, could you specify because
13 7 and --

14 BY ATTORNEY MORRISON:

15 Q. Yeah. Let me -- let me ask a better question.

16 A. Okay.

17 Q. Table 6 shows that AAV7 is better in liver
18 than AAVs 1, 2, or 5; right?

19 A. That's correct.

20 Q. All right. And in paragraphs 249 and 250 of

21 the '772 publication, the inventors talk about the

22 advantages of AAV7 in muscle and AAV8 in liver; right?

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1 A. You said 249 and 250?

2 Q. Yes.

3 A. Yes. Those talk about the advantages relative

4 to muscle and to liver.

5 Q. And in your report on page 51 -- or excuse me,

6 your declaration on page 51 at paragraph 138, you quote

7 paragraphs 249 and 250; right?

8 A. I say that, yes.

9 Q. And in 250, you have an ellipsis.

10 Do you see that?

11 A. In paragraph 250? Yes.

12 Q. And so I want to look at what you cut out. So

13 paragraph 250 starts:

14 [As Read] The tropism of each new vector

15 is favorable for in vivo applications.

16 Right?

17 A. I see that, yes.

18 Q. You quote that part; right?

19 A. Yes.

20 Q. And then paragraph 250 goes on to say that:

21 [As Read] The AAV2/7 vectors appear to

22 transduce skeletal muscle as efficiently as

53 (Pages 209 to 212)

Page 213 1 AAV2/1, which is the serotype that confers the 2 highest level of transduction in skeletal 3 muscle of the primate AAVs tested to date. 4 Do you see that? 5 A. Are you talking about 249 or 250 the 6 paragraph -- 7 Q. I'm talking about 250 in the publication. 8 That's what it says. It's the second sentence. 9 A. I see that, yes. 10 Q. But you didn't quote that in your declaration; 11 right? 12 A. That is correct. 13 Q. Why did you cut that out of your declaration? 14 A. Because I was following the guidance of the 15 inventors who really described the importance of AAV8 16 for transducing liver. 17 Q. Well, the inventors also describe the 18 importance of AAV7 for transducing skeletal muscle; 19 right? 20 ATTORNEY WILSON: Object to form. 21 THE WITNESS: The -- the goal for, you know, 22 this particular passage was to really follow the	Page 214 1 guidance of the inventors in the selection of AAV8 as a 2 model vector for liver. 3 BY ATTORNEY MORRISON: 4 Q. So you don't think the inventors gave guidance 5 about the importance of AAV7 for muscle? 6 ATTORNEY WILSON: Object to form. 7 THE WITNESS: Yeah, they -- you know, the two 8 paragraphs that provide the strongest guidance for me, 9 which are pretty definitive, are paragraphs 256 and 257. 10 BY ATTORNEY MORRISON: 11 Q. Mm-hmm. Right. But I'm asking about 12 paragraph 250 right now. 13 And so I'm asking why you didn't quote that 14 sentence. Was it because you didn't think it was 15 important to your analysis, or some other reason? 16 ATTORNEY WILSON: Object to form. 17 THE WITNESS: I focused on the AAV8 because it 18 was described as -- by the inventors as the most 19 important vector and the most potent vector for being 20 able to mediate gene delivery to liver. 21 BY ATTORNEY MORRISON: 22 Q. Okay. And so you didn't include that sentence
Page 215 1 because you were looking at liver transduction not 2 muscle; is that right? 3 A. Yes. Going back to the -- you know, the 4 guidance that the '772 publication provides, it guides a 5 POSA to be able to take vectors that have really 6 interesting properties and be able to take, you know, 7 the identities of amino acids from one, substitute it to 8 the other to try to make an improved vector. 9 So I was starting with the best vector that 10 they reported in their own language for lung and for 11 muscle and then taking the best vector, again reported 12 in their language, for liver and making substitutions 13 from the latter into the former. 14 Q. So the sentence that you cut out with the 15 ellipsis wasn't important to your analysis because you 16 were looking for increased liver transduction; is that 17 right? 18 ATTORNEY WILSON: Object to form. 19 THE WITNESS: Yes. I was simply following the 20 guidance, the bottom-line conclusions of the inventors, 21 who really focused on rh.10 as a generally useful 22 vector. And if you compare that to AAV8 -- and perhaps	Page 216 1 we'll get to those data -- AAV8 is not as effective 2 within muscle or within lung, but it is effective within 3 liver. 4 So starting with rh.10, which is the best in 5 muscle -- the best in lung. For rh.10, they state later 6 is the equal to the best within muscle, and it is the 7 best within lung. And then taking the other AAV8 -- 8 which is the best in liver, not as good in muscle and 9 lung -- I would be guided as a POSA to be able to take 10 amino acids present in AAV8 and substitute them into 11 rh.10 to try to make something that's better within 12 liver while preserving muscle and lung. 13 BY ATTORNEY MORRISON: 14 Q. So in your opinion, the '772 publication says 15 AAVrh.10 is best in muscle? 16 A. It says -- I'll quote this. Yeah, it doesn't 17 have to be my opinion. 18 They say that: 19 [As Read] Performance of clone 44.2 -- 20 You know, namely, rh.10. 21 [As Read] -- in liver and muscle-directed 22 gene transfer was also outstanding, close to

Page 217 1 that of the best liver transducer, AAV8, and 2 the best muscle transducer, AAV1. 3 Q. Mm-hmm. 4 A. So from that I would conclude that rh.10 is 5 the best in -- you know, from prior -- the 6 paragraph 256, it appears to be the best in lung. And 7 then based upon 257, it is outstanding and equal to that 8 of AAV1, which is the best previous transducer within 9 muscle. 10 Q. So, again, let's go back to Table 6, which is 11 page 132 of Exhibit 1007. 12 In this experiment, AAV7 is about three times 13 better than AAV1 in muscle; right? 14 ATTORNEY WILSON: Object to form. 15 THE WITNESS: So the number for muscle that 16 appears for AAV7 is "14.2 plus or minus 2.4," and it 17 looks like AAV1 is "4.5 plus or minus 2.1." 18 BY ATTORNEY MORRISON: 19 Q. So AAV7 has about three times the transduction 20 into muscle as AAV1 -- right? -- based on Table 6? 21 ATTORNEY WILSON: Object to form. 22 THE WITNESS: So it appears for that	Page 218 1 particular data point that AAV7 was higher in value 2 compared to AAV1. 3 BY ATTORNEY MORRISON: 4 Q. About three times higher; right? 5 ATTORNEY WILSON: Object to form. 6 THE WITNESS: I'd be happy to pull out a 7 calculator. You know, 3 times 4 and a half is, what, 13 8 and a half? 9 BY ATTORNEY MORRISON: 10 Q. Mm-hmm. So 3 times 4 and a half is 13 and a 11 half; and AAV7's 14.2? 12 A. That is correct. 13 Q. So it's a little better than three times 14 better -- AAV7 is a little bit better than, three times 15 better, AAV1 in muscle? 16 ATTORNEY WILSON: Object to form. 17 THE WITNESS: It appears to be better than 18 muscle, yes. 19 BY ATTORNEY MORRISON: 20 Q. Okay. 21 A. Or better than AAV1 in muscle according to 22 that data.
Page 219 1 Q. Let's look at Table 8 now in Example 9. 2 And I think you point this out in your 3 declaration: There is no Example 8 in the '772 4 publication; right? 5 A. That's right. 6 Q. So the next example is Example 9; right? 7 A. That's correct. 8 Q. And in Example 9 AAV7, is not being tested, 9 but AAV8 still is; right? 10 A. That's correct. 11 Q. And there's also four new vectors that are 12 being tested in Example 9; right? 13 A. That's right. 14 Q. And one of those new vectors is rh.10; right? 15 A. That's correct. 16 Q. Now, Table 8 shows that in -- excuse me -- in 17 lung -- rh.10 is the best performer in lung in the -- in 18 the experiment shown in Table 8; right? 19 A. That's correct. 20 Q. And in Table 8, it shows that in muscle rh.10 21 performs the same as AAV1; right? 22 A. That's right.	Page 220 1 Q. Okay. And then Tables 9 and 10 result -- 2 excuse me. 3 Tables 9 and 10 report the results of further 4 experiments on rh.10; right? 5 A. Rh.10 as well as a number of other variants. 6 Q. And in paragraph 254, it describes those 7 experiments that are reported in Tables 9 and 10 saying: 8 [As Read] A couple of other experiments 9 were then performed to confirm the superior 10 tropism of AAV 42 -- 44.2 in the lung tissue. 11 A. That's where -- or how to -- paragraph 254 12 starts, yes. 13 Q. And then -- so in Tables 9 and 10, the 14 inventors are confirming the superior performance of 15 rh.10 in the lung; right? 16 A. That appears to be the goal of at least 17 they -- in this Table 9 in paragraph 254; so at least to 18 that one. They don't say that that's the purpose of 19 Table 10. 20 But as a general idea, this is showing 21 quantification of gene delivery to the lung for a number 22 of serotypes.

Page 221 1 Q. And that's true for both Tables 9 and 10? 2 They're both showing delivery to the lung for a variety 3 of serotypes; right? 4 A. That's correct. 5 Q. And they're comparing all the other serotypes 6 to rh.10? 7 A. They're comparing all the serotypes, at least 8 the ones listed here, to one another. 9 Q. In last column of both Tables 9 and 10, there 10 is a heading that compares the relative gene transfer as 11 compared to rh.10; right? 12 A. That's correct. 13 Q. So in Tables 9 and 10, the inventors are 14 comparing the performance of a variety of vectors to 15 rh.10 in lung tissue specifically? 16 A. Yeah. It's my opinion that they're comparing 17 them to each other as a result of the earlier columns; 18 so the third and fourth column of Table 9 and the second 19 column of Table 10 shows relative gene expression for 20 all these variants compared to each other. And then 21 they call out specifically rh.10 in that final column of 22 each table --	Page 222 1 Q. Okay. 2 A. -- to compare relative delivery efficiency to 3 rh.10. 4 Q. And both Tables 9 and 10 are in lung tissue 5 specifically; right? 6 A. That is correct. 7 Q. Okay. 8 All right. So let's move on to the next 9 example, which is Example 10. 10 And there's actually two Example 10s. I think 11 you point that out in your declaration; is that right? 12 A. There's a double count, it appears. Minor 13 typo. 14 Q. And the first Example 10 is a mouse model of 15 hypercholesterolemia; right? 16 A. That's what paragraph 263 says, yes. 17 Q. And hypercholesterolemia is a fancy word for 18 high cholesterol, basically; right? 19 A. That's correct. 20 Q. Okay. And so that's a disease of the liver? 21 A. It's -- I would characterize it as a disease 22 of the entire body. It's caused by mutations with a
Page 223 1 gene -- within a gene expressed within the liver. 2 Q. Okay. So hypercholesterolemia is a mutation 3 of a gene that's expressed within the liver. Fair? 4 A. That's correct. 5 Q. Okay. And so the target of the gene therapy 6 would be the liver; correct? 7 ATTORNEY WILSON: Object to form. 8 THE WITNESS: Yes. I don't know enough about 9 familial hypercholesterolemia to know whether one could 10 correct the disease by expressing the LDL receptor -- 11 the gene whose mutation causes this form -- or causes 12 this disease in tissues aside from the liver, but it 13 does appear -- let me confirm. 14 They actually don't describe within the 15 example, unless you could highlight it, what their 16 target tissue was. 17 BY ATTORNEY MORRISON: 18 Q. Well, under paragraph 274, they looked at LDL 19 receptor expression in frozen liver sections? 20 A. That's correct. 21 Q. So at least in that portion of the experiment, 22 they were looking at expression in the liver?	Page 224 1 A. They were looking at expression within the 2 liver, yes, in that particular part of the experiment. 3 Q. And the conclusion of this experiment, which 4 you discussed, if you'd like to look at it, in 5 paragraph 155 of your declaration, but it's in 6 paragraph 284 of the patent -- or, excuse me, of the 7 '772 publication. 8 A. Yes. I'm at paragraph 155 of my declaration. 9 Q. And in paragraph 155 of your declaration, 10 which discusses paragraph 284 of the '772 publication, 11 the conclusion is that both of the AAV7 and AAV8 vectors 12 lowered total cholesterol, LDL, and triglycerides; 13 right? 14 A. Could you cite that paragraph again. 15 Q. Sure. It's 284 in the '772. 16 A. That's what 284 says, yes. 17 Q. So both AAV7 and AAV8 were effective at 18 transducing the liver in this experiment? 19 ATTORNEY WILSON: Object to form. 20 THE WITNESS: "Effective" is a relative word, 21 again. 22 BY ATTORNEY MORRISON:

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1 **Q. Mm-hmm. The '772 publication doesn't note any**
 2 **difference between the transduction of AAV7 and AAV8 in**
 3 **this particular experiment, the first Example 10?**

4 ATTORNEY WILSON: Object to form.

5 THE WITNESS: Paragraph 284 says, in simply
 6 reading:

7 [As Read] All the vectors pseudotyped in
 8 AAV2/8 or AAV2/7 capsid lowered cholesterol,
 9 LDL, and triglycerides as compared to the
 10 control.

11 BY ATTORNEY MORRISON:

12 **Q. And so it doesn't say that one was better than**
 13 **the other -- right? -- in this particular experiment?**

14 A. In 284, in the concluding paragraph for that
 15 example, it says both were capable of doing so. Were --
 16 both lowered. It doesn't talk about relative amounts.

17 **Q. Okay. And rh.10 was not -- rh.10 was not**
 18 **tested in this mouse model; right?**

19 A. Rh.10 was not tested within this particular
 20 model.

21 **Q. Okay. Let's look at the second Example 10.**

22 **This is about a expression of a functional factor IX**

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1 **gene to correct hemophilia?**

2 A. Thank you. Yes.

3 **Q. Right?**

4 **And, again, factor IX -- or excuse me --**

5 **hemophilia, this is another place where you would want**
 6 **to target the liver; right?**

7 ATTORNEY WILSON: Object to form.

8 THE WITNESS: Yes. Factor IX is ordinarily
 9 expressed from the liver.

10 ///

11 BY ATTORNEY MORRISON:

12 **Q. Mm-hmm.**

13 A. However, it's not clear that one would need to
 14 express factor IX from the liver in order to be able to
 15 treat the disease. In fact, alternate strategies have
 16 been attempted within the field.

17 **Q. But in paragraph 287 of the '772 publication,**
 18 **at the very least, they note that they were using a**
 19 **"liver-specific promoter"; right?**

20 A. That's correct. In paragraph 287, they refer
 21 to a liver-specific promoter.

22 **Q. And in paragraph 289, it notes that the**

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1 **different serotypes or -- excuse me, the vectors of**
 2 **different serotypes were delivered in an interportal**
 3 **injection into the liver; right?**

4 A. 289 states that, yes.

5 **Q. So at least in this experiment, they were**
 6 **testing delivery of these vectors to the liver; right?**

7 A. In that experiment, they were focusing on
 8 delivery to the liver for the factor IX mini-gene.

9 **Q. In paragraph 296 of the '772 patent states**
 10 **that both AAV7 and AAV8 worked well in delivering the**
 11 **gene to the liver?**

12 ATTORNEY WILSON: Object to form.

13 THE WITNESS: I'll simply read it and say:

14 [As Read] Lowest sustained clotting times
 15 were observed in the animals with 2V -- AAV2/8
 16 and AAV2/7.

17 I'm simply reading the document.

18 BY ATTORNEY MORRISON:

19 **Q. And the same is true for -- if you go back to**
 20 **paragraph 292 of the '772 publication, it states:**

21 [As Read] The highest levels of
 22 expression were observed for the AAV2/8 and

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1 **AAV2/7 constructs.**

2 **Right?**

3 A. Let me take a minute to read the full example
 4 so I can place everything in context.

5 Okay. Thank you. Could you repeat your
 6 question, please.

7 **Q. Sure. Paragraph 292 of the '772 publication**
 8 **states that the highest levels of expression in this**
 9 **experiment were found with the AAV2/8 and 2/7**
 10 **constructs; right?**

11 A. That's what it states, yes.

12 **Q. And so, again, it's explaining that both AAV7**
 13 **and AAV8 in this experiment have high levels of**
 14 **expression in the liver; right?**

15 ATTORNEY WILSON: Object to form.

16 THE WITNESS: Yeah. Paragraph 292, as you
 17 indicated, says that:

18 [As Read] The highest levels of
 19 expression were observed for the AAV2/8 and
 20 the AAV2/7 constructs.

21 BY ATTORNEY MORRISON:

22 **Q. And that's after injection into the**

57 (Pages 225 to 228)

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1 **intraportal vein into the liver; right?**

2 A. That experiment followed what was stated in
3 paragraph 289, presumably, which is intraportal
4 injection.

5 **Q. And rh.10 was not tested in this second**
6 **Example 10 either; right?**

7 A. There are no data on rh.10 within this
8 example.

9 **Q. Dr. Schaffer, AAV2 -- or excuse me, AAVs**
10 **generally are always liver-directed in the sense that**
11 **the liver's the default destination for AAV?**

12 ATTORNEY WILSON: Object to form.

13 THE WITNESS: Yes. It'd be helpful to be able
14 to do a, you know, biodistribution study. If you would
15 like to, you know, analyze how much goes to the liver,
16 the experiment would be to do an intravenous injection
17 and follow the distribution.

18 This -- to my knowledge, this '772 publication
19 does not report an experiment like that.

20 BY ATTORNEY MORRISON:

21 **Q. You'd agree with me that for**
22 **systemically administered viruses the liver is often the**

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1 **default destination, which can represent a barrier when**
2 **other organs are the intended targets?**

3 A. It sounds like --

4 ATTORNEY WILSON: Object to form.

5 THE WITNESS: It sounds like you're reading
6 from a citation. It would be helpful if you could note
7 that.

8 BY ATTORNEY MORRISON:

9 **Q. Sure.**

10 **It's actually Exhibit 1030.**

11 ATTORNEY WILSON: Do you have a copy, Susan?
12 I don't think we have that one out yet.

13 ATTORNEY MORRISON: I do.

14 ATTORNEY WILSON: Great. Thank you.

15 ATTORNEY MORRISON: Mm-hmm.

16 BY ATTORNEY MORRISON:

17 **Q. Okay. So the document that has already been**
18 **marked in these proceedings as Exhibit 1030, this is a**
19 **paper by Melissa Kotterman, and you talk -- called --**
20 **oh, boy -- "Engineering adeno-associated viruses for**
21 **clinical gene therapy."**

22 A. That's correct.

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1 **Q. And Melissa Kotterman, I think you said**
2 **earlier, is the same as Melissa Bartel --**

3 A. Bartel.

4 **Q. -- which was a paper we looked at earlier?**

5 A. That's correct.

6 **Q. Okay.**

7 **Okay. If you go to Box 1 on page 3 under**
8 **"Transport to and tropism for target cells" --**

9 **Do you see that?**

10 A. I do.

11 **Q. Do you see where I am?**

12 **The first sentence says:**

13 **[As Read] For systemically administered**
14 **viruses, the liver is often the default**
15 **destination, which can represent a barrier**
16 **when other organs are the intended targets.**

17 **Do you see that?**

18 A. I see that.

19 **Q. Okay.**

20 **All right. And in this paper, you again**
21 **discuss ways to change or redirect tropism. And in**
22 **particular, I'm talking about -- on the same page of**

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1 **Exhibit 1030, in the middle column, the paragraph that**
2 **starts "In another example."**

3 **(Clarification inquiry by The Court Reporter.)**

4 THE WITNESS: I see that paragraph, yes.

5 BY ATTORNEY MORRISON:

6 **Q. And here you talk about:**

7 **[As Read] The incorporation of**
8 **high-affinity ligands into the AAV capsid can**
9 **deteriorate confer binding to alternative cell**
10 **surface receptors and therefore restrict --**
11 **excuse me -- and thereby restrict or redirect**
12 **viral tropism.**

13 **Right?**

14 A. Yes. That's an accurate -- accurate read of
15 the sentence -- of the sentence.

16 **Q. And you don't discuss in this paragraph**
17 **altering tropism by making a -- changes to the --**
18 **changes to the amino acid sequence of the existing**
19 **capsid protein; right?**

20 A. Let me read really quick. It's been a while
21 since we wrote this.

22 Could you rephrase that, please.

58 (Pages 229 to 232)

Page 233

1 **Q. Sure. So you don't discuss in this paper**
 2 **altering a single amino acid residue in the AAV capsid**
 3 **to change tropism; right?**

4 A. I would have to take time to reread the paper.
 5 It's 10 years old; so I'd have to refresh my memory.

6 **Q. And that's a good point. This paper is from**
 7 **20 -- July 2014; right?**

8 A. That's correct.

9 **Q. So about nine years after the priority date of**
 10 **the '274 patent that we're talking about today?**

11 A. That sounds correct.

12 **Q. Okay. You can set that the one aside for now.**
 13 **The --**

14 A. Actually, can I amend what I said? I'm
 15 scanning through here a little bit.

16 **Q. Well, there's not a question pending, but --**
 17 ATTORNEY WILSON: Do you want to revise one of
 18 your earlier answers?

19 THE WITNESS: I'd like to revise one of my
 20 earlier answers.

21 I said I would have to go reread this.

22 BY ATTORNEY MORRISON:

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1 **Q. Mm-hmm.**

2 A. I certainly would have to reread it in its
 3 entirety to be providing a complete analysis.

4 But, for example, at the beginning of
 5 "Rational Design," it talks about the introduction of
 6 mutations from a tyrosine to a phenylalanine by
 7 site-directed mutagenesis to be able to alter tropism to
 8 increase infectivity.

9 ///

10 BY ATTORNEY MORRISON:

11 **Q. Now, is increasing -- in your opinion, is**
 12 **increasing infectivity the same as altering tropism?**

13 A. Yes.

14 **Q. Okay. And the papers that are cited there,**
 15 **it's cites 20 -- footnotes 21 and 22.**

16 **Do you see that?**

17 A. I do see that.

18 **Q. So let's look at those, and footnote 21 is a**
 19 **paper by Zhong, et al.; right?**

20 A. Yes.

21 **Q. From 2008?**

22 A. That's right.

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1 **Q. So three years after the priority date of the**
 2 **patent-in-suit -- or excuse me, the patent we're talking**
 3 **about today?**

4 A. That's correct.

5 **Q. And exhibit -- cite 22 is another paper by**
 6 **Zhong, et al.**

7 A. That's correct.

8 **Q. And it's also from 2008?**

9 A. That's correct.

10 **Q. So neither of those would be prior art to the**
 11 **'274 patent; right?**

12 A. That's correct.

13 ATTORNEY WILSON: Object to form.

14 BY ATTORNEY MORRISON:

15 **Q. And you don't cite those papers as knowledge**
 16 **in the field from before the time of the '274 patent;**
 17 **right?**

18 ATTORNEY WILSON: Object to form.

19 THE WITNESS: Yeah, those two papers are after
 20 the priority date of the -- of the matter in question.

21 BY ATTORNEY MORRISON:

22 **Q. Okay.**

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1 **All right. You can set that one aside.**

2 **And you'd agree with me, Dr. Schaffer, that on**
 3 **systemic administration, "natural serotypes of AAV**
 4 **typically exhibit tropism for liver, or alternatively,**
 5 **for multiple organs, which renders targeted delivery to**
 6 **other tissues difficult"; right?**

7 ATTORNEY WILSON: Object to form.

8 THE WITNESS: It sounds like you're reading
 9 from a -- from a citation again. It'd be helpful if you
 10 could point out where that came from.

11 BY ATTORNEY MORRISON:

12 **Q. Sure. I'd be happy to.**

13 **But do you generally agree with the statement**
 14 **that I just made?**

15 ATTORNEY WILSON: Object to form.

16 THE WITNESS: I would like to be able to read
 17 the full passage from where -- from which that's
 18 excerpted so I can really ascertain the context.

19 BY ATTORNEY MORRISON:

20 **Q. So without reading the full passage, you can't**
 21 **tell me whether you agree or disagree with that**
 22 **statement.**

59 (Pages 233 to 236)

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1 **Is that fair?**
 2 A. I'd refer to read the full passage --
 3 **Q. Okay.**
 4 A. -- to ensure that it's a accurate
 5 representation of the context in which that sentence
 6 comes.
 7 **Q. Okay. So -- but without reading the full**
 8 **paper, you can't tell me whether you agree with that**
 9 **statement?**
 10 ATTORNEY WILSON: Object to form.
 11 THE WITNESS: I'd prefer to read the full
 12 passage prior to being able to offer an opinion on that
 13 passage.
 14 ATTORNEY MORRISON: Okay.
 15 Can we mark this as Exhibit 2025.
 16 (Exhibit 2025 was marked for identification.)
 17 BY ATTORNEY MORRISON:
 18 **Q. Okay. Exhibit 2025 is a comment written by**
 19 **you, David V. Schaffer, called "AAV shuffles to the**
 20 **liver: commentary on Lisowski, et al."; right?**
 21 A. That's correct.
 22 **Q. And this is from 2014 in the American Society**

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1 **of Gene & Cell Therapy; right?**
 2 A. Amendment to that. The -- the society runs
 3 the journal, but that's actually not the name of the
 4 journal.
 5 **Q. Oh, my apology. The journal is named?**
 6 A. "Molecular Therapy Methods & Clinical
 7 Development."
 8 **Q. Thank you.**
 9 **And so this is -- you're the sole author of**
 10 **this comment; correct?**
 11 A. That's correct.
 12 **Q. And if you go to the second full paragraph,**
 13 **you say:**
 14 **[As Read] That being --**
 15 **And, again, before I get there, when you**
 16 **publish something, your intention is it that it is**
 17 **scientifically accurate and correct; right?**
 18 A. At the time that it's published, yes.
 19 **Q. And so -- and, again, the time this was**
 20 **published would have nine years after the priority date**
 21 **of the '274 patent; right?**
 22 A. That is correct. Roughly nine years.

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1 **Q. Okay. And so now looking at that second full**
 2 **paragraph, you say:**
 3 **[As Read] That being said, numerous**
 4 **delivery hurdles pose challenges for extending**
 5 **current successes to future indications.**
 6 **You see that?**
 7 A. The beginning of the -- the third full
 8 paragraph.
 9 **Q. Sorry. Third full paragraph, yes.**
 10 A. I see that passage, yes.
 11 **Q. And you say:**
 12 **[As Read] For example, upon systemic**
 13 **administration, natural serotypes typically**
 14 **exhibit tropism for liver, or alternatively**
 15 **for multiple organs, which renders targeted**
 16 **delivery to other tissues difficult.**
 17 **Right?**
 18 A. I see that passage.
 19 **Q. All right. You can put that aside.**
 20 **Dr. Schaffer, if you mutate or alter an AAV**
 21 **viral -- AA -- let me start over.**
 22 **If you alter the sequence of an AAV capsid**

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1 **protein to increase tropism to the liver, but your**
 2 **target tissue is, say, lung --**
 3 **Are you with me so far?**
 4 A. Mm-hmm.
 5 **Q. Okay.**
 6 **-- isn't it true that you might need to**
 7 **administer more of that vector to get the desired effect**
 8 **in lung?**
 9 ATTORNEY WILSON: Object to form.
 10 THE WITNESS: I -- I actually don't agree with
 11 that.
 12 BY ATTORNEY MORRISON:
 13 **Q. Okay. If you had a vector, for example, that**
 14 **was good in lung and you altered it to be better in**
 15 **liver, isn't it possible that you would have to**
 16 **administer more of the drug to get an effect?**
 17 ATTORNEY WILSON: Object to form.
 18 THE WITNESS: The only way to determine that
 19 would be to do the experiment.
 20 BY ATTORNEY MORRISON:
 21 **Q. Okay. So you wouldn't know without doing the**
 22 **experiment?**

60 (Pages 237 to 240)

Page 241 1 ATTORNEY WILSON: Object to form. 2 THE WITNESS: Yeah. There's a path that is 3 suggested within '772 to be able to make modifications 4 to vectors. So my goal -- or a POSA would be guided by 5 '772 to be able to take the best performer in lung and 6 muscle, you know, namely rh.10, and it would be 7 desirable also have a variant that had high efficiency 8 in muscle and in lung in addition being able to mediate 9 delivery to the liver. 10 So there's a -- a path to be able to achieve 11 that as guided by '772. 12 BY ATTORNEY MORRISON: 13 Q. Right. I'm stepping back from '772 -- 14 A. Mm-hmm. 15 Q. -- and whatever path you believe is laid out 16 there. 17 Isn't it possible that, if your vector is good 18 at delivering to the lung and you change it to make it 19 better to the liver, that you might have to administer 20 more because some of your viral vector is now going to 21 the liver instead of to the lung? 22 ATTORNEY WILSON: Object to form.	Page 242 1 THE WITNESS: I believe the standard for, you 2 know, whether or not an experiment would be worthwhile 3 doing, at least from a legal setting, is that there's a 4 reasonable chance for success. 5 And in my opinion, following the path that's 6 taught in '772 -- taking a variant which is really good 7 in muscle and really good in lung and adding 8 substitutions in a very surgical way, you know, guided 9 by sequence alignment and taking one amino acid at a 10 time -- has a reasonable chance of success of being able 11 to improve the tropism for liver while preserving that 12 within lung and muscle. 13 BY ATTORNEY MORRISON: 14 Q. So that's not my question. Not even close to 15 my question. 16 So I'm going to ask you to focus on what I'm 17 asking. Okay? 18 Do you understand? 19 ATTORNEY WILSON: All right. That's not a 20 question. Argumentative. 21 ATTORNEY MORRISON: It's not meant to be 22 argumentative.
Page 243 1 ATTORNEY WILSON: Fine. Then just ask your 2 question. 3 ATTORNEY MORRISON: Okay. 4 BY ATTORNEY MORRISON: 5 Q. I'm going to use totally different tissues. 6 Okay? 7 Let's say that your target tissue is the 8 bladder, and you have a vector that's really good at 9 delivering to the bladder -- 10 You with me so far in my hypothetical? 11 A. Indeed. 12 Q. Okay. 13 -- and you alter it to make it really good at 14 delivering to the central nervous system. 15 Do you understand? Are you with me still? 16 A. With you. 17 Q. Okay. Isn't it possible that by altering that 18 vector to make it better at the central nervous system 19 when your target is the bladder that you might have to 20 deliver more vector in order to get the effect in the 21 bladder? 22 ATTORNEY WILSON: Object to form.	Page 244 1 THE WITNESS: I think that there's a path 2 where one could make substitutions or modifications to 3 one vector to be able to improve its properties for the 4 CNS while having a reasonable chance of success in 5 preserving the properties for the bladder. 6 BY ATTORNEY MORRISON: 7 Q. But isn't it possible that you would then have 8 to inject more vector, more virus in order to get that 9 effect on the bladder? 10 ATTORNEY WILSON: Object to form. 11 THE WITNESS: If it were my lab, I would tell 12 my students, "Do the experiment. There's a reasonable 13 chance of success." 14 /// 15 BY ATTORNEY MORRISON: 16 Q. But isn't it possible that you would have to 17 give more vector in order to get the effect in the 18 bladder? That's my question. 19 ATTORNEY WILSON: Object to form. 20 THE WITNESS: My standard is that -- is there 21 a reasonable chance of success for doing the experiment? 22 Because you could, you know, hypothesize any conceivable

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1 outcome for an experiment, but I would say, "Is there a
 2 reasonable chance of success in doing this experiment?"
 3 And I would want to do it.
 4 BY ATTORNEY MORRISON:
 5 **Q. How do you define "reasonable chance of**
 6 **success"?**
 7 A. I believe it's a legal term.
 8 **Q. Mm-hmm.**
 9 A. So it'd be helpful if, you know -- since I'm
 10 probably one of the few people in the room that's not a
 11 lawyer, how would -- how does the field define
 12 "reasonable chances of success"?
 13 **Q. Well, I'm asking you. When you're saying you**
 14 **have a "reasonable chance of success," you had counsel**
 15 **explain the law to you; right?**
 16 A. Yes. It's --
 17 **Q. So when you're saying -- I'm sorry. I didn't**
 18 **mean to interrupt you, but I just want to make sure my**
 19 **question's clear.**
 20 A. Mm-hmm.
 21 **Q. When you're saying you believe that there's a**
 22 **"reasonable chance of success," what are you defining?**

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1 **How do you define that?**
 2 A. It's a qualitative thing. It's not like a,
 3 you know, coin toss. It's a qualitative thing that I
 4 think it's worthwhile for a POSA -- or a POSA would
 5 think it's worthwhile to try out the experiment to see
 6 if it would work.
 7 And in addition, the experiments we're
 8 discussing here are not overly difficult; so making
 9 individual substitutions, for example, is very routine
 10 and not very difficult. So the amount of time one would
 11 invest to be able to potentially get a really compelling
 12 result is not that much. It's worthwhile doing the
 13 experiment.
 14 **Q. So my question, then, is isn't there also a**
 15 **reasonable chance that by making that modification to**
 16 **improve your vector to make it better to deliver to the**
 17 **central nervous system, isn't it also reasonable that**
 18 **you might have to administer more to get the effect in**
 19 **the bladder?**
 20 ATTORNEY WILSON: Object to the form.
 21 THE WITNESS: Yeah, I think for any given
 22 experiment, there's no guarantee it's going to work. If

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1 there's a reasonable chance of doing the experiment, you
 2 do the experiment.
 3 BY ATTORNEY MORRISON:
 4 **Q. Mm-hmm. And so it's -- it might work; it**
 5 **might not. Is that fair?**
 6 ATTORNEY WILSON: Object to form.
 7 THE WITNESS: Yeah, I think that that's
 8 inherent in "reasonable chance." The chances are good
 9 that something might work out, which means that it's
 10 worthwhile to do it to a POSA or to me.
 11 BY ATTORNEY MORRISON:
 12 **Q. Okay. So you believe that there's a**
 13 **reasonable -- well, strike that.**
 14 **You'd agree with me that it's a difficult --**
 15 **excuse me, strike that.**
 16 **You would agree with me that it is difficult**
 17 **to control AAV tropism in transgene expression; right?**
 18 ATTORNEY WILSON: Object to form.
 19 THE WITNESS: Yeah, "difficult" is a relative
 20 word.
 21 BY ATTORNEY MORRISON:
 22 **Q. Mm-hmm.**

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1 A. It's -- depends on the application. If we'd
 2 like to talk about specific applications, I'm happy to
 3 provide more guidance.
 4 **Q. Is "difficult" a word that you would use in**
 5 **your writing? Would you say, "It's difficult to control**
 6 **AAV tropism and transgene expression"?**
 7 ATTORNEY WILSON: Object to form.
 8 THE WITNESS: It sounds like you're citing
 9 from a particular publication. Happy to talk about that
 10 publication, if you can --
 11 BY ATTORNEY MORRISON:
 12 **Q. Right. So my question is is that a word you**
 13 **would use?**
 14 **You're saying it's a relative word. Is**
 15 **"difficult" a word you would use in your writing?**
 16 ATTORNEY WILSON: Object to form.
 17 THE WITNESS: Yeah, I have over 250
 18 publications; so I can't remember every word that I've
 19 used.
 20 BY ATTORNEY MORRISON:
 21 **Q. Sure. But certainly you've used the word**
 22 **"difficult"; right?**

Page 249 1 ATTORNEY WILSON: Object to form. 2 THE WITNESS: Again, I can't recall every word 3 that I've used in our publications. 4 /// 5 BY ATTORNEY MORRISON: 6 Q. You can't recall ever having used the word 7 "difficult" in one of your publications? 8 A. I can't recall whether I've used the word 9 "difficult" in publications. 10 Q. In 250 publications, you think it's possible 11 you've never used the word "difficult"? 12 ATTORNEY WILSON: Object to form. 13 THE WITNESS: I would have to sit down and 14 reread the 250 publications to be able to answer that 15 question accurately. 16 ATTORNEY MORRISON: Okay. 17 Let's look at this and see if you've ever used 18 the word "difficult" before. 19 So I'm going to mark a new exhibit. It's 20 going to be 2026. 21 (Exhibit 2026 was marked for identification.) 22 THE WITNESS: Thank you.	Page 250 1 ATTORNEY MORRISON: I've asked the court 2 reporter to mark as Exhibit 2006 to these proceedings a 3 paper from 2014 in the journal "The Neuroscientist" 4 called "Adeno-Associated Virus Vectors and Neurological 5 Gene Therapy." 6 BY ATTORNEY MORRISON: 7 Q. Do you have that in front of you, 8 Dr. Schaffer? 9 A. Yes. I have a copy of this publication. 10 Q. And this was written by -- the first author is 11 someone named David S. -- is it "Ojala"? 12 A. He goes by "Ojala." 13 Q. Ojala. Thank you. 14 And you are the last author on this paper? 15 A. I'm the last author on the publication, yes. 16 Q. And who is Dr. Ojala? 17 A. Dr. Ojala was a graduate student at my lab. 18 Q. And the second author, Dominic Amara? 19 A. Dominic was a undergraduate working in the lab 20 with David. 21 Q. Okay. And, again, when you publish a 22 manuscript, you do your best at the time to make sure
Page 251 1 it's scientifically accurate and correct; right? 2 A. At the time of publication, yes, the intention 3 is for it to be accurate. 4 Q. And, again, this was published in 2014; so 5 nine years after the priority date for the '274 patent; 6 right? 7 A. That's correct. Roughly nine years 8 afterwards. 9 Q. Okay. If you could turn to the second page 10 under targeting the CNS. 11 Do you see where I am? 12 A. I do, yes, thank you. 13 Q. If you could go about halfway down that 14 paragraph there's a sentence that starts "In addition"? 15 A. I see that paragraph -- or that sentence. 16 Q. Mm-hmm. So this says: 17 [As Read] In addition, the ability to 18 target specific cell types and regions in the 19 CNS that are implicated in disease is 20 important for safe and effective therapies for 21 several indications. 22 Right?	Page 252 1 A. I see that passage, yes. 2 Q. And it says -- goes on to say: 3 [As Read] However, it is difficult to 4 control AAV tropism in transgene expression. 5 Right? 6 A. I see that phrase. 7 Q. And it goes on to say: 8 [As Read] AAV vectors have an excellent 9 safety record, though the implementation of 10 new routes of administration in serotypes 11 could increase the risk of an immune response 12 to the vector and/or transgene. 13 Right? 14 A. I see that phrase, yes. 15 Q. And so it goes on to say: 16 [As Read] These challenges motivate the 17 careful selection of natural AAV serotypes and 18 engineering of novel AAV variants to yield 19 transduction profiles that are optimally 20 suited to specific therapeutic needs. 21 Right? 22 A. That's a correct reading of the passage, yes.

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1 ATTORNEY MORRISON: Okay. You can set that
2 aside.
3 Okay. I'm going to move on to Ground 2; so
4 why don't we take a break before we do that.
5 ATTORNEY WILSON: Sounds good.
6 (A break was taken.)
7 BY ATTORNEY MORRISON:
8 **Q. Welcome back, Dr. Schaffer.**
9 **Did you talk to your counsel about the**
10 **substance of your testimony during the break?**
11 A. I didn't.
12 **Q. Okay. You would agree with me there are 48**
13 **amino acid differences between rh.10 and AAV8; right?**
14 A. The sequence alignment between AAV8 and
15 rh.10 -- I'm going to page to that.
16 Yes. Indicates 48 differences.
17 **Q. Okay. And in your analysis in Ground 1, you**
18 **didn't provide any opinion on any of -- any change other**
19 **than changing the serine at 665 to a asparagine; right?**
20 ATTORNEY WILSON: Object to form.
21 THE WITNESS: I discussed the 48 modifications
22 that could be made, you know, using AAV8 as a guide to

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1 be able to change the sequence of rh.10; so all 48 of
2 those are disclosed, for example, in the exhibits and
3 are referred to within the declaration.
4 BY ATTORNEY MORRISON:
5 **Q. But in your Ground 1 analysis in your**
6 **declaration, you don't provide any discussion of whether**
7 **a POSA would make any of those other 47 changes; right?**
8 ATTORNEY WILSON: Object to form.
9 THE WITNESS: The -- the document as a whole
10 provides a lot of information about both my opinion
11 about how this could be done, which is based upon '772,
12 and, you know, it's consistent with the testimony of
13 Leone, the expert witness, on analyzing those
14 48 modifications -- those 48 positions and making
15 modifications one at a time.
16 BY ATTORNEY MORRISON:
17 **Q. So in your opinion you would -- well, strike**
18 **that.**
19 **In your ground -- I want to focus just on your**
20 **Ground 1 analysis. Okay?**
21 A. Mm-hmm.
22 **Q. In your Ground 1 analysis, you don't provide**

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1 **any opinion on any of the other 47 changes; right?**
2 ATTORNEY WILSON: Object to form.
3 THE WITNESS: Let me page -- sorry.
4 ATTORNEY WILSON: Sorry.
5 THE WITNESS: Let me move to the Ground 1.
6 BY ATTORNEY MORRISON:
7 **Q. Sure.**
8 **And it starts on page 74 of Exhibit 1005?**
9 A. Yeah, it's a long document. I could sit and
10 read it in detail to be able to address your question or
11 if there are particular citations that would be -- or
12 regions or parts of this that would be helpful, I'd be
13 happy to discuss them.
14 But as a whole, my declaration does talk about
15 all 48 possible modifications that could be made to
16 rh.10 based upon AAV8.
17 **Q. Did you consider whether all 48 of those**
18 **modifications would form a capsid?**
19 A. The guidance that's provided by '772 and which
20 is agreed to by Leone indicates that it's a reasonable
21 path, a compelling path to follow to be able to make
22 modifications to rh.10 based upon AAV8, and if one made

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1 modifications at those nonconservative residues, the
2 indication is that those would be likely to form a
3 capsid.
4 **Q. Okay. And what about -- would they be able to**
5 **package a transgene?**
6 A. The guidance -- one moment, please.
7 What I'm specifically looking for is in '772.
8 It's, you know, not -- this is the teaching of '772; so
9 it's -- I'd like to follow that and not use my own
10 opinion.
11 '772 does teach the formation of such capsids.
12 **Q. You keep saying you don't want to give your**
13 **own opinion and instead rely on '772.**
14 **But you understand Sarepta is relying on your**
15 **opinions, Dr. Schaffer, in support of their arguments in**
16 **this petition?**
17 A. Ground 1 through Ground 6 are my opinions --
18 **Q. Mm-hmm.**
19 A. -- about obviousness of those claims.
20 However, it's based upon a lot of material within '772
21 and teachings of '772.
22 **Q. Okay.**

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1 A. So I'd like -- oh, sorry.
 2 **Q. Oh, I'm sorry. Go ahead.**
 3 A. I'd like to differentiate between things that
 4 are my opinion, such as within the grounds, parts of the
 5 grounds, and parts or considerations that are, you know,
 6 the opinion of the inventors on which I'm basing my
 7 opinion.
 8 **Q. Okay. And you understand that Dr. Leone's**
 9 **opinion that you rely on results in a lot more than just**
 10 **the 48 modifications that you're talking about; right?**
 11 ATTORNEY WILSON: Object to form.
 12 THE WITNESS: Well, as I talk about within my
 13 specification --
 14 Could you please repeat your question.
 15 BY ATTORNEY MORRISON:
 16 **Q. You understand that Dr. Leone's opinion that**
 17 **you rely upon would result in a lot more than just the**
 18 **48 modifications that you discuss in your clarification;**
 19 **right?**
 20 ATTORNEY WILSON: Object to form.
 21 THE WITNESS: Dr. Leone provides guidance
 22 which, as we discussed beforehand, involves starting by

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1 putting alignments together of different AAV sequences;
 2 identifying which regions are conserved, which
 3 regulations are not conserved; and then making, you
 4 know, alternate amino acid choices at one of the
 5 nonconserved positions from the correspond -- from the
 6 corresponding position of another AAV capsid into the
 7 original or first capsid.
 8 And she further advises that this actually be
 9 done, not in a sweeping fashion, but advises that it be
 10 done, like, one amino acid at a time.
 11 So that's -- you asked about her particular
 12 opinion.
 13 I -- I happen to agree with that; that it's a
 14 good opinion. But you asked about her opinion, and
 15 that's the guidance she provides.
 16 BY ATTORNEY MORRISON:
 17 **Q. And what you just testified to, that's your**
 18 **understanding of Dr. Leone's opinion?**
 19 ATTORNEY WILSON: Object to form.
 20 THE WITNESS: The portion of Dr. Leone's
 21 testimony, which is following those three steps, happens
 22 to agree well with the approach that a POSA would take

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1 at a time and that '772 teaches.
 2 BY ATTORNEY MORRISON:
 3 **Q. Okay. Let's talk about Ground 2. And**
 4 **Ground 2 relies upon a reference to -- in addition to**
 5 **the '772 a reference to Xie, which is Exhibit 1008 to**
 6 **this proceeding.**
 7 ATTORNEY WILSON: Thank you.
 8 THE WITNESS: Thanks. I'm at Ground 2 of my
 9 declaration.
 10 BY ATTORNEY MORRISON:
 11 **Q. Okay. And so Ground 2 relies on your Ground 1**
 12 **analysis and then adds the analysis of -- on Xie; right?**
 13 A. That's correct.
 14 **Q. Okay. And, again, the same as for Ground 1,**
 15 **the reason to modify AAVrh.10 with AAV8 would be to**
 16 **improve tropism to the liver; right?**
 17 A. While preserving tropism in muscle and lung,
 18 yes.
 19 **Q. Okay. And Xie is about AAV2; right?**
 20 A. Well, Xie is a crystal structure of an AAV.
 21 It's the first time that a crystal structure of AAV has
 22 been reported.

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1 **Q. It's the crystal structure of AAV2; right?**
 2 A. It happens to be AAV2, but it's a crystal
 3 structure of an AAV. And it's a general principle in
 4 protein science that sequences that have similar amino
 5 acid content have very similar structures.
 6 **Q. The crystal structure of other AAVs were known**
 7 **at the time of the '274 patent; right?**
 8 ATTORNEY WILSON: Object to form.
 9 THE WITNESS: If you could point to the
 10 particular crystal structures. I can't recall the
 11 timing. AAV -- AV -- this particular AAV crystal
 12 structure came out in 2002, I believe. If I could take
 13 a look at the exhibit.
 14 BY ATTORNEY MORRISON:
 15 **Q. Yes. You are -- you are correct. It's**
 16 **published -- the Xie paper was published August 6, 2002.**
 17 **Does that sound right?**
 18 A. That sounds right. I can't recall when
 19 additional AAV structures started coming out.
 20 **Q. Are all crystal structures of AAVs the same?**
 21 ATTORNEY WILSON: Object to form.
 22 THE WITNESS: So it's a -- a general principle

65 (Pages 257 to 260)

Page 261 1 of protein science that, you know, proteins that have a 2 similar primary amino acid sequence tend to have very 3 close crystal structures. 4 BY ATTORNEY MORRISON: 5 Q. You'd agree with me that: 6 [As Read] Although the sequence of amino 7 acids in a protein determines the protein's 8 structure, the structure cannot be accurately 9 predicted from knowing the sequence alone. 10 Right? 11 A. Could you indicate -- 12 ATTORNEY WILSON: Object to form. 13 THE WITNESS: -- where you're drawing that 14 from. 15 /// 16 BY ATTORNEY MORRISON: 17 Q. It's paragraph 49 of your declaration at 18 page 22 of Exhibit 1005. 19 A. Thank you. 20 And could you cite, please, which paragraph 21 that that was drawn from. 22 Q. Paragraph 49 --	Page 262 1 A. Great. 2 Q. -- on page 22 of Exhibit 1005. 3 A. Mm-hmm. 4 Q. You'd agree with me that: 5 [As Read] Although the sequence of amino 6 acids in a protein determines the protein's 7 structure, the structure cannot be accurately 8 predicted from knowing the sequence alone. 9 Right? 10 A. There's been an enormous amount of progress 11 here. In fact, a Nobel prize given three weeks ago for 12 accurate determination of structure based upon sequence. 13 So that is something. There is a lot of progress. 14 But "accurately," I suppose, is the operative 15 word there. 16 Do you want a, you know, 2-angstrom crystal 17 structure or a 5-angstrom crystal structure? So it 18 really depends on how accurate one would want it to be. 19 Q. Dr. Schaffer, you wrote that sentence; right? 20 A. I did write that sentence. 21 Q. Okay. So you'd agree that that sentence is 22 true -- right? -- or you wouldn't have written it and
Page 263 1 signed it in your declaration; right? 2 A. There -- 3 ATTORNEY WILSON: Object to form. 4 THE WITNESS: There are a lot of words that 5 we've been using, you know, such as "targeting" and 6 "reasonable chance." These end up being, at some point, 7 you know, a matter of semantics. 8 So "accurately" -- if you would like to, you 9 know, describe what "accurately" means, I think that a 10 structure can be reasonably accurately determined from 11 the sequence based upon modern innovations at the time 12 of, you know, the filing of -- at the time of 2005, 13 definitely. Yes, it would have been difficult to 14 accurately predict the structure from the sequence 15 alone. 16 BY ATTORNEY MORRISON: 17 Q. Okay. 18 A. With -- in the absence of another crystal 19 structure to use as a reference. 20 Q. Dr. Schaffer, you chose the word "accurately"; 21 right? 22 A. I chose the word "accurately."	Page 264 1 Q. Okay. And you would agree with me that in 2 2005 the sentence that you wrote choosing all the words 3 in this sentence was true; right? 4 ATTORNEY WILSON: Object to form. 5 THE WITNESS: It has to be considered in the 6 context of other material that's present here. 7 So based just on the sequence, it'd be 8 difficult to determine the structure; but if you have 9 the sequence and a reference structure of a similar 10 sequence, then it becomes a lot, you know, more readily 11 available to predict the structure accurately. 12 BY ATTORNEY MORRISON: 13 Q. Where does it say that in your declaration, 14 sir? 15 A. That's a principle of protein science. You 16 know, for example, I refer to Alberts. 17 Q. Dr. Schaffer, where does it say that in your 18 declaration? 19 ATTORNEY WILSON: Susan, don't interrupt the 20 witness. 21 ATTORNEY MORRISON: He's not answering my 22 question.

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1 ATTORNEY WILSON: Object to the form.
 2 It doesn't -- he is answering your question,
 3 and it doesn't justify you interrupting his answer.
 4 THE WITNESS: In the next paragraph, I refer
 5 to Alberts. I'd be happy to talk about Alberts.
 6 Alberts talks about a process called hemology
 7 modeling, which was well known and taught to
 8 undergraduates at that time, where you can take a known
 9 crystal structure and thread through at the sequence a
 10 very similar crystal structure to be able to predict the
 11 structure of that new sequence.
 12 BY ATTORNEY MORRISON:
 13 **Q. Where in your declaration does it talk about**
 14 **hemology modeling? In your declaration, this 1005,**
 15 **where does it talking about hemology modeling?**
 16 ATTORNEY WILSON: Object to form.
 17 THE WITNESS: Yeah, hemology modeling was a
 18 very, very well-known process at the time. A POSA would
 19 be very, very familiar with it.
 20 BY ATTORNEY MORRISON:
 21 **Q. Where does it say that in your declaration?**
 22 ATTORNEY WILSON: Object to form.

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1 BY ATTORNEY MORRISON:
 2 **Q. So I would like you to cite me a paragraph**
 3 **where it says that in your declaration.**
 4 ATTORNEY WILSON: Argumentative. Object to
 5 form.
 6 BY ATTORNEY MORRISON:
 7 **Q. That's what I'm asking.**
 8 A. Yeah, I don't believe I mentioned what
 9 transfer RNAs are in my declaration, yet it's common
 10 knowledge to anybody who's taken a course in cell
 11 biology or biochemistry.
 12 **Q. So you'd agree not mentioning hemology**
 13 **modeling in your declaration.**
 14 **Is that fair?**
 15 ATTORNEY WILSON: Object to form
 16 argumentative.
 17 THE WITNESS: It's a commonly very well-known
 18 approach, both at that time and currently.
 19 BY ATTORNEY MORRISON:
 20 **Q. Sir, is my question unclear?**
 21 ATTORNEY WILSON: Again, you're interrupting
 22 the witness, Susan. You need to let him finish his

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1 answer.
 2 BY ATTORNEY MORRISON:
 3 **Q. Go ahead. Finish.**
 4 A. I don't talk about many things that are true
 5 in the world within this declaration. It's a limited
 6 amount of page length.
 7 **Q. Okay.**
 8 A. So it's very, very well known to a POSA at
 9 that time that hemology modeling can be utilized to be
 10 able take a new sequence and based on that, you know,
 11 using a structure of an analogous sequence with high
 12 similarity, make an accurate prediction of the sequence
 13 of the new protein.
 14 **Q. You understand, Dr. Schaffer, that everything**
 15 **that you wanted to testify about in this case had to be**
 16 **in this declaration; right? You understood that when**
 17 **you were putting it together?**
 18 ATTORNEY WILSON: Object to form.
 19 BY ATTORNEY MORRISON:
 20 **Q. Did you understand that?**
 21 ATTORNEY WILSON: Same objection.
 22 THE WITNESS: The declaration -- so I can't

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1 cite off the top of my head how many pages Alberts has.
 2 I certainly didn't include every page of Alberts within
 3 the text of my declaration to be able to cite things
 4 that a POSA would've known at the time because they're
 5 taught it in undergraduate class.
 6 BY ATTORNEY MORRISON:
 7 **Q. So you believe you can talk about now anything**
 8 **a POSA would have known, even if it's not in your**
 9 **declaration, because it would've been taught in an**
 10 **undergraduate class and you didn't have to put that in**
 11 **your declaration? Is that your understanding?**
 12 ATTORNEY WILSON: Object to form.
 13 THE WITNESS: I think a POSA would have known
 14 what hemology modeling is because it's taught in
 15 undergraduate class.
 16 BY ATTORNEY MORRISON:
 17 **Q. But you didn't talk about hemology modeling in**
 18 **your declaration -- in the words in this declaration,**
 19 **Exhibit 1005.**
 20 **Those words don't appear; right?**
 21 ATTORNEY WILSON: Object to form.
 22 THE WITNESS: A POSA would have known what

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1 hemology modeling is because it was common knowledge at
 2 the time.
 3 BY ATTORNEY MORRISON:
 4 **Q. But you don't say the words "hemology**
 5 **modeling" in your declaration; right?**
 6 ATTORNEY WILSON: Object to form.
 7 THE WITNESS: A POSA would've known what
 8 hemology modeling is because it was common knowledge at
 9 the time.
 10 BY ATTORNEY MORRISON:
 11 **Q. Where is the words "hemology modeling" in your**
 12 **declaration?**
 13 ATTORNEY WILSON: Objection.
 14 ///
 15 BY ATTORNEY MORRISON:
 16 **Q. They're not there; right?**
 17 ATTORNEY WILSON: Object to form.
 18 THE WITNESS: A POSA would've known what
 19 hemology modeling is because it's cited and described in
 20 detail in Alberts.
 21 BY ATTORNEY MORRISON:
 22 **Q. So anything that's in Alberts is incorporated**

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1 **within your declaration?**
 2 ATTORNEY WILSON: Object to form.
 3 THE WITNESS: Alberts is cited here for
 4 material that is relevant. And in addition, Alberts
 5 provides a lot of information that is of general use to
 6 the field and to a POSA.
 7 BY ATTORNEY MORRISON:
 8 **Q. Okay. So anything in Alberts is fair game, in**
 9 **your opinion?**
 10 ATTORNEY WILSON: Object to form.
 11 THE WITNESS: Hemology modeling is described
 12 in Alberts in detail, and, as a result, it would have
 13 been known to a POSA.
 14 BY ATTORNEY MORRISON:
 15 **Q. Okay. Let's go back to Xie.**
 16 **Xie, the title says it's the atomic structure**
 17 **of adeno-associated virus in 2; right?**
 18 A. One moment, please.
 19 ATTORNEY WILSON: Objection.
 20 ATTORNEY MORRISON: What's your objection,
 21 Counsel? I read the title.
 22 ATTORNEY WILSON: No, you didn't read the

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1 title, actually. You paraphrased the title. That's the
 2 objection.
 3 BY ATTORNEY MORRISON:
 4 **Q. Dr. Schaffer, when you get there, let me know.**
 5 **Okay?**
 6 A. Sure.
 7 **Q. This Xie paper is of:**
 8 **[As Read] The structure of the**
 9 **adeno-associated virus AAV2 to a 3-angstrom**
 10 **resolution by X-ray crystallography.**
 11 **Correct?**
 12 A. The first sentence of the abstract talks about
 13 determination of that structure to a 3-angstrom
 14 resolution.
 15 **Q. Okay.**
 16 **Do you know, Dr. Schaffer, that the crystal**
 17 **structure of AAV4 was first published in 2003?**
 18 A. I was -- perhaps I saw that at the time. I'm
 19 unaware at this time that AAV4 was published back in
 20 2003.
 21 **Q. Okay.**
 22 A. I can't recall the chronology of the

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1 publication of the crystal structures.
 2 **Q. But you don't cite in your declaration the**
 3 **crystal structure of AAV4; right?**
 4 A. I don't believe I cite the structure of AAV4.
 5 **Q. Okay. And the structure of AAV5 was first**
 6 **published 2004.**
 7 **Is that -- do you recall that?**
 8 A. I don't recall the timing; but if -- if you
 9 can cite the publication, I'll take your word for it.
 10 **Q. Sure. And you don't -- but you don't cite the**
 11 **publication of the crystal structure of AAV5 in your**
 12 **declaration; right?**
 13 A. I don't cite the publication of crystal
 14 structure AAV5.
 15 **Q. And the crystal structure of AAV8 was also**
 16 **published late in 2005.**
 17 **Do you recall that?**
 18 A. I recall that it was published; and if you
 19 indicate the date, then I'll -- I'll take your word for
 20 it.
 21 **Q. Okay. But you don't cite the crystal**
 22 **structure of AAV8 in your declaration; right?**

68 (Pages 269 to 272)

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1 A. I don't cite it in my declaration.
 2 **Q. Now, Xie discloses the crystal structure of**
 3 **the VP3 portion of AAV2 along with regions that overlay**
 4 **that.**
 5 A. Could you clarify what you mean by "regions
 6 that overlay that."
 7 **Q. Sure.**
 8 **You can look at --**
 9 **It's on page 2 of Xie. And it's in your**
 10 **footnote 6, but I don't have a page number for that, and**
 11 **I apologize.**
 12 **Your footnote 6 on page 100 of your**
 13 **declaration.**
 14 **Would you like me to give you a separate copy**
 15 **of Xie? Would that make it easier?**
 16 A. It might be helpful to have a separate copy,
 17 yes. Thank you.
 18 **Q. There you go.**
 19 A. Thank you.
 20 **Q. And if you go to page 100 of your declaration,**
 21 **Exhibit 1005, at footnote 6.**
 22 A. I'm at footnote 6.

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1 **Q. You cite in footnote 6, right in the middle,**
 2 **Xie at page 2, where it talks about the VP2 numbering of**
 3 **parvoviral structures.**
 4 A. Yes. I see a passage from Xie quoted there
 5 about the numbering.
 6 **Q. And it says:**
 7 **[As Read] Although we follow the**
 8 **convention of VP2 numbering for parvoviral**
 9 **structures, it is the 533-residue VP3 that is**
 10 **visualized, along with the corresponding**
 11 **regions of VP1 and VP2 occupying equivalent**
 12 **positions in the capsid and not the N termini**
 13 **unique to the minority proteins.**
 14 **Right?**
 15 A. Yes. That's an accurate part of the passage.
 16 **Q. And that's your declaration quoting from the**
 17 **Xie paper; right?**
 18 A. That's correct.
 19 **Q. So what Xie visualized was the VP3 portion of**
 20 **the capsid protein; right?**
 21 A. That's correct.
 22 **Q. Okay.**

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1 **All right. AAV2 has three fewer amino acids**
 2 **than either rh.10 or AAV8; right?**
 3 ATTORNEY WILSON: Object to form.
 4 THE WITNESS: So if one compared or aligned
 5 AAV2 versus rh.10 or AAV8, yes, there's a small number
 6 of differences in the length between the three.
 7 ///
 8 BY ATTORNEY MORRISON:
 9 **Q. So rh.10 and AAV8 have 738 total amino acids?**
 10 A. I believe that to be the case.
 11 Looking now at the alignment between rh.10 and
 12 AAV8 and -- yes, 738 amino acids.
 13 **Q. And AAV2 has 735 amino acids; right?**
 14 A. It may have.
 15 **Q. And it's also in your footnote 6,**
 16 **Dr. Schaffer, if that's helpful.**
 17 A. That's correct, yes.
 18 **Q. And you say that right at the beginning of**
 19 **footnote 6 in your declaration; right?**
 20 A. Mm-hmm. That is correct.
 21 **Q. And so you would agree with me that position**
 22 **665 in AAV8 or AAVrh.10 corresponds with 662 in AAV2;**

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1 **right?**
 2 A. Yes, I believe that's correct.
 3 **Q. And, again, you say that right in footnote 6**
 4 **of your declaration; right?**
 5 A. That's correct.
 6 **Q. And later on in that same footnote, you talk**
 7 **about how Xie uses the VP2 numbering; right?**
 8 A. That's correct. Xie --
 9 ATTORNEY WILSON: Object to form.
 10 THE WITNESS: Xie -- their amino acid number 1
 11 corresponds to the first amino acid of VP2.
 12 BY ATTORNEY MORRISON:
 13 **Q. Which is number 138?**
 14 A. I believe that's correct, yes, for AAV2 as
 15 well.
 16 **Q. And so to correlate that position 662 to the**
 17 **numbering Xie uses, you have to subtract 137 amino**
 18 **acids?**
 19 A. That is correct.
 20 **Q. So what Xie calls in the paper "position 525"**
 21 **is the same as the position that we've been talking**
 22 **about, position 665 in rh.10 and AAV8?**

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1 (Clarification inquiry by The Court Reporter.)

2 THE WITNESS: Yeah, so I'm looking at
3 Exhibit 1023, which talks about the numbering system and
4 tries to clarify the inconvenient numbering system
5 utilized by Xie, which has been the source of some angst
6 within the field over the past 20 years.

7 Although I'm grateful for their crystal
8 structure.

9 BY ATTORNEY MORRISON:

10 Q. All right. So I've just given your counsel a
11 copy of 1023 as well just to make things easier, and if
12 you'd like an extra one, I have it.

13 All right. So having laid that groundwork,
14 Xie teaches that at that position we're talking about,
15 position what's called 525 in Xie and which would be 665
16 in rh.10, there's a -- there is a serine at -- in AAV2
17 at that position; right?

18 A. That is correct.

19 Q. Okay. We're going to come back to 1023; so
20 just hold on to that for a minute.

21 But if you go back to your declaration for a
22 moment and look at paragraph 256, which is at the top of

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1 page 99 --

2 A. Thank you.

3 Q. And you say -- in the second sentence, you
4 say:

5 [As Read] Xie teaches that the amino
6 acids that lie on the surface of the capsid,
7 quote, "govern interactions with antibodies
8 and cellular receptors."

9 Do you see that?

10 A. That's excerpted from Xie, yes.

11 Q. So let's look at -- you cite Xie at page 3?

12 A. That's correct.

13 Q. Okay. So let's look at that, and let's start
14 at the very bottom of page 2 of Xie --

15 A. Gotcha.

16 Q. -- which is the page that -- and it's -- the
17 page numbers I'm referring to, Dr. Schaffer, are the
18 little page numbers that say "Sarepta Exhibit 1008
19 page 2."

20 A. Oh, page 2 up here? Great.

21 Q. Yeah. Okay. So let's start at the very
22 bottom of page 2. The -- there's a beginning of a

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1 paragraph that runs over onto page 3.

2 Do you see where I am?

3 A. Does it begin with "Structure Determination"?

4 Q. No. It begins with "The long interstrand
5 loops of AAV."

6 A. So just for clarification, am I supposed to be
7 following Sarepta --

8 Q. Yes.

9 A. -- exhibit page 2?

10 Q. So that sentence that starts at the very
11 bottom of the right-hand column, "The long interstrand
12 loops of AAV."

13 A. I see that, yes.

14 Q. Okay. It says:

15 [As Read] The long interstrand loops of
16 AAV, which together comprise about 60 percent
17 of the structure, contain beta-ribbons and
18 other additional elements of secondary
19 structure, about half of which are found in
20 the autonomous viruses like canine parvovirus.
21 Right?

22 A. That's an accurate reading of the passage,

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1 yes.

2 Q. Okay. And then it goes on to say:

3 [As Read] Thus, the loops have quite
4 different structures in the different
5 parvovirus genres, consistent with the lower
6 sequence identity outside the more conserved
7 beta-barrel -- excuse me -- barrel
8 beta-strands.

9 Right?

10 A. That's also an accurate read, yes.

11 Q. And then it goes on to say -- and this is the
12 part I believe you're citing:

13 [As Read] These loops constitute the
14 surface features of the virus that govern
15 interactions with antibodies and cellular
16 receptors.

17 Right?

18 A. Yes. Also an accurate reading of the passage,
19 yes.

20 Q. So it's the long interstrand loops of AAV that
21 constitute the surface features of the virus that govern
22 interactions with antibodies and cellular receptors;

70 (Pages 277 to 280)

Page 281 1 right? 2 A. Those loops are very important determinants of 3 the interactions with antibodies and cellular receptors. 4 Q. Okay. 5 If you could go to the Xie paper at page 1, 6 and in the right-hand column, the first full paragraph 7 that starts "AAV2 is one of 5 distinct serotypes." 8 Do you see where I am? 9 A. I see that, yes. 10 Q. Okay. That sentence states that serotypes -- 11 I'm sorry, that paragraph of that sentence. 12 That paragraph states: 13 [As Read] Serotypes 1, 2, and 3 share 14 approximately 85 percent capsid sequence 15 identity, with 2 and 3 likely using the same 16 cellular receptor. 17 Right? 18 A. That's what the passage says, yes. 19 Q. Okay. And then it notes that: 20 [As Read] Serotypes 4 and 5 are more 21 distantly related and use different receptors. 22 Right?	Page 282 1 A. That's -- that's what the sentence reads, yes. 2 Q. Okay. And you don't -- oh, sorry. 3 And if you could look at page 5 of Xie and 4 again I'm using the little Sarepta page numbers. 5 A. Okay. 6 Q. And page 5 notes the same thing in the section 7 on "Receptor Attachment and Antigenicity." 8 Do you see where that -- do you see where I 9 am? 10 A. I see that passage starting in bold, yes. 11 Q. Okay. And it notes that: 12 [As Read] The primary receptor for AAV2 13 on the cell surface is heparan sulfate 14 proteoglycan. 15 A. That's an accurate reading of the passage, 16 yes. 17 Q. And the next sentence says that: 18 [As Read] Serotype 3 likely uses the same 19 cellular receptor. 20 Right? 21 A. That's what the next sentence reads. 22 Q. And then it says:
Page 283 1 [As Read] Serotypes 4 and 5 likely use 2 different receptors. 3 A. Again, what the rest of the sentence reads 4 accurately. 5 Q. And that's consistent with what Xie said 6 earlier on page 1; right? 7 A. That's correct. 8 Q. And you don't talk in your declaration at all 9 about what cellular surface receptor AAVrh.10 uses? 10 A. I don't believe I talk about the cellular 11 surface receptor. 12 Q. And -- okay. All right. Let's go back to 13 this Table 1023, and I want to look at this table with 14 the Xie paper. 15 A. Okay. 16 Q. So if you need a separate copy of this I'm 17 happy to give it to you. 18 A. Okay. 19 Q. All right. And I want to look at figure 2 in 20 the Xie reference, which is on page 3 in the little 21 Sarepta page numbers at the bottom. 22 A. Okay.	Page 284 1 Figure 2, you say? 2 Q. Figure 2, yes. 3 A. Thank you. 4 Yes. 5 Q. Okay. So figure 2 has a -- has the amino acid 6 sequence of AAV2 and canine parvovirus lined up with one 7 another; right? 8 A. That's correct. 9 Q. Okay. And in the caption for figure 2, the 10 last sentence of the caption describes what the little 11 triangles under the various residues mean; right? 12 A. That's correct. 13 Q. Okay. And so it says that: 14 [As Read] The triangles are shaded 15 according to each residue's accessibility. 16 Right? 17 A. That's correct. 18 Q. And so the red triangles are the least 19 accessible; is that right? 20 ATTORNEY WILSON: Object to form. 21 THE WITNESS: Are you saying that the red 22 triangles are between 20 -- 20 angstrom squared and

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1 50 angstrom squared compared to cyan and green and blue?

2 BY ATTORNEY MORRISON:

3 Q. Yes.

4 A. I see that passage.

5 Q. So the -- the red triangles are the least
6 accessible, cyan next, then green, then blue?

7 A. That is correct interpretation of this
8 passage.

9 Q. Okay. And so we discussed before, based on
10 your 1023, that the position that we're talking about
11 here that corresponds to position 665 in AAVrh.10 is
12 position 525; right?

13 A. Let me review the -- that's correct.

14 Q. And position 525 in figure 2 is a serine in
15 AAV and a proline in canine parvovirus?

16 A. My apologies. My eyes are failing me a little
17 bit here. Could you point to the -- the position within
18 that alignment you're referring to.

19 Q. Yeah, I'd be happy to.

20 Do you see where the -- it's in the bottom
21 row. Do you see where the 520 is?

22 A. I do see where 520 is, yes.

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1 Q. And if you count five over to the right,
2 there's -- in a yellow-highlighted box, that's position
3 525?

4 A. I see that position, thank you.

5 Q. And it's marked with a red triangle; right?

6 A. Correct.

7 Q. Okay. And so some of your other -- I want to
8 look at a couple of other positions of the 1023 chart in
9 figure 2. So position 411 in -- which is on the second
10 page of 1023. It's a -- it's a glutamate, I believe.

11 A. 411 following Xie numbering?

12 Q. Yes.

13 A. That's I think glutamic acid, I'd interpret
14 that.

15 Q. Mm-hmm. And that glutamic acid, if you look
16 at figure 2, has a blue triangle. It's marked in red on
17 the third line up from the bottom.

18 A. I see that, yes.

19 Q. Okay. And position 419 in Xie, which is
20 another one you highlighted in yellow in your
21 Exhibit 1023?

22 A. 419, I see that, yes.

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1 Q. Mm-hmm. That is marked in figure 2 with a
2 green triangle?

3 A. Correct. That appears to be marked with a
4 green triangle.

5 Q. Okay.

6 All right. Let's go to figure 4 of Xie, which
7 is on the next page. It's on page 4 of Exhibit 1008.

8 And the serine -- and so in this figure, blue
9 indicates positions that are closest to the center and
10 red indicates positions that are furthest from the
11 center; right?

12 A. That appears to be the scale in the upper
13 right-hand side of that panel.

14 Q. Okay. And the serine at 525, which is on the
15 right-hand side of the map near where the letter E is --
16 Do you see it?

17 A. I do see it. The figure wants for resolution,
18 but you can distinguish those words.

19 Q. And it's marked in, like, a light blue;
20 correct?

21 A. That is correct.

22 Q. Okay.

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1 All right. Now, Xie in page -- if you go to
2 the next page of Xie, page 5, Xie points to an analysis
3 done by Wu of "mutants that were deficient in heparan
4 binding."

5 Do you see that? It's in the left-hand column
6 under "Receptor Attachment in Antigenicity."

7 A. You're saying the left-hand column of that
8 section?

9 Q. Of page 5, yes. It's about five or six
10 sentences down:

11 [As Read] Of five hep-negative mutants
12 that are deficient.

13 Do you see where I am?

14 A. I see that correctly.

15 Q. And Xie talks about five different mutants
16 made by Wu and where those mutations are located in the
17 crystal structure; right?

18 A. Xie is referring to, yes, heparan-negative
19 mutants present within Wu. I think I have Wu bookmarked
20 here by an earlier discussion.

21 Q. Yeah. I believe it's 1030.

22 And so Xie, by way of Wu, points to several

72 (Pages 285 to 288)

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1 references on the surface that might be important
 2 locations.
 3 ATTORNEY WILSON: Object to form.
 4 THE WITNESS: Could you rephrase that and
 5 refer specifically to the passage in Wu you're
 6 considering.
 7 BY ATTORNEY MORRISON:
 8 Q. Sure. I'm actually considering a passage in
 9 Xie --
 10 A. Okay.
 11 Q. -- that talks about "five mutants that are
 12 deficient in heparan binding," and it points to
 13 particular residues that were mutated by Wu; right?
 14 A. Correct. It points to particular residues,
 15 although it doesn't list all of the heparan-binding
 16 mutants.
 17 Q. It just lists five of them; right?
 18 A. Let me read this passage.
 19 Q. Mm-hmm.
 20 A. I'm just navigating back and forth between the
 21 numbering of Wu versus Xie.
 22 But at any rate, yes, I am seeing this text.

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1 Q. Okay.
 2 A. It talks about -- I would want to go through
 3 this analysis one by one to be able to confirm the
 4 analysis of Xie versus Wu.
 5 Q. Okay. So Xie mentions, though, five different
 6 mutants that he says that Wu did; right?
 7 A. Xie mentions five different mutants.
 8 Q. And one of them is at position 1 -- excuse me,
 9 451; right? It's the first one he mentions --
 10 A. He mentions a substitution at 451 -- sorry, at
 11 448 through 451.
 12 Q. At 448 through 451.
 13 And residue 451 in your Exhibit 1023 is a
 14 residue you point to that's different between AAVrh.10
 15 and AAV8; right?
 16 A. That is correct.
 17 Q. And Xie also points to an -- a hemagglutinin
 18 epitope insertion at 454; right?
 19 A. That is correct.
 20 Q. And then that's another position where you
 21 point to that AAV8 and AAVrh.10 have different
 22 residues -- amino acids?

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1 A. That is correct.
 2 Q. Okay.
 3 All right. Let's set Xie aside and talk about
 4 Snowdy.
 5 And I'll ask you. Do you know Dr. Xie? Have
 6 you ever met him?
 7 A. I don't know Dr. Xie. To my knowledge, I've
 8 never met him.
 9 Q. Okay.
 10 A. Perhaps at a poster session some point.
 11 Q. Do you know if he's still working in the
 12 field?
 13 A. I'm unaware of whether he's working in the
 14 field.
 15 Q. Do you know Dr. Snowdy?
 16 A. I do not know Dr. Snowdy personally.
 17 Q. Do you know if he is working in the field?
 18 A. I'm unaware of whether he's still working in
 19 the field.
 20 Q. Do you know if he's ever published anything
 21 since he finished his PhD?
 22 A. I have not done a analysis as to whether or

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1 not he's published anything since completing his degree.
 2 Q. Do you know that Dr. Snowdy got an MBA at the
 3 same time as his PhD and went on to become a venture
 4 capitalist?
 5 A. I was unaware --
 6 ATTORNEY WILSON: Object to form.
 7 THE WITNESS: I was unaware of that given that
 8 I don't know Dr. Snowdy.
 9 BY ATTORNEY MORRISON:
 10 Q. Okay. And so you don't know whether
 11 Dr. Snowdy is working in the field now or not?
 12 ATTORNEY WILSON: Object to form.
 13 THE WITNESS: I'm unaware of whether
 14 Dr. Snowdy is working within the field.
 15 BY ATTORNEY MORRISON:
 16 Q. Or whether he ever worked in the field after
 17 he finished his PhD; right?
 18 A. I'm unaware of whether he worked in the field
 19 while earning his PhD.
 20 Q. Okay. And the reference that you rely on --
 21 which I have a copy of for your counsel somewhere.
 22 ATTORNEY MORRISON: Unless I've already given

73 (Pages 289 to 292)

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1 to you.

2 ATTORNEY WILSON: I think you've given it to

3 me.

4 ATTORNEY MORRISON: I think I did. It's

5 Exhibit 1009.

6 BY ATTORNEY MORRISON:

7 Q. Is -- this is Dr. Snowdy's doctoral thesis;

8 right?

9 A. That is correct.

10 Q. And did you look to see if any of Dr. Snowdy's

11 research that was included in this thesis was published

12 in any peer-reviewed journal?

13 A. I did not determine whether it was published

14 in a peer-reviewed journal.

15 Q. Okay.

16 A. My knowledge of that material is based upon

17 presentations at conferences at the time.

18 Q. Okay. And Dr. Snowdy's thesis is broken

19 into -- I think he calls them chapters.

20 Is that fair?

21 Or sections.

22 A. Would you like me to refer to the table of

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1 contents of Snowdy?

2 Q. So he has different -- yes.

3 And Dr. Snowdy has different sections in his

4 thesis; is that right?

5 A. His table of contents organizes the material

6 into a number of sections and subsections.

7 Q. And -- and the -- each of the -- so the first

8 major section, subsection Roman numeral I, is an

9 introduction and background; right?

10 A. That's correct.

11 Q. And then section 2 has a set of experiments,

12 section 3 has another set of experiments, and section 4

13 has another set of experiments.

14 Is that reasonable?

15 A. That appears to be the case.

16 Q. And the portion of Snowdy that you relied upon

17 is in section 4; right?

18 A. That's correct.

19 Q. Okay. Now, Dr. Snowdy says in a number of

20 places -- well, strike that.

21 If you could turn to Dr. Snowdy's thesis at

22 page 27, which is page 27 of the page numbers that are

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1 in the middle of the page.

2 A. Mm-hmm.

3 Q. It's Sarepta exhibit page 41.

4 A. Okay. I'm at that page.

5 Q. Okay. So at that page, in the last paragraph,

6 "while it has been" --

7 Do you see where I am?

8 A. I see that passage, yes.

9 Q. Dr. Snowdy says:

10 [As Read] While it has been accepted that

11 AAV capsid proteins target the nucleus, the

12 mechanism through which AAV targets the

13 nucleus has received very little attention.

14 Do you see that?

15 A. I see that, yes.

16 Q. Okay. And if we turn to page 48 of

17 Dr. Snowdy's thesis -- and, again, I'm referring to the

18 pages at the bottom. That's page 62 of the Sarepta

19 exhibit numbering.

20 A. I see that page, yes.

21 Q. There's a paragraph that starts "There are

22 several trafficking events."

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1 Do you see where I am?

2 A. I do, yes.

3 Q. Okay. So at the top of the next page, there's

4 a sentence that begins "After trafficking"?

5 A. I see "After trafficking," yes.

6 Q. Okay. It says:

7 [As Read] After trafficking --

8 Boy.

9 [As Read] After trafficking in the

10 endosome, the virus must somehow escape the

11 endosome. Though little is known about how

12 endosomal escape may occur.

13 Right?

14 A. That's an accurate reading of the passage.

15 Q. Okay. So Dr. Snowdy first says that the

16 mechanism through which AAV targets the nucleus has

17 received little attention, and now he says that how

18 endosomal escape happens is unknown; right?

19 ATTORNEY WILSON: Object to form.

20 THE WITNESS: It says "little is known."

21 BY ATTORNEY MORRISON:

22 Q. "Little is known." All right. Just --

74 (Pages 293 to 296)

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1 All right. And, finally, if we go to
2 paragraph -- or page 53 of Dr. Snowdy's thesis, which is
3 Exhibit 1009, page 67.

4 A. I'm at that page.

5 Q. Okay. In the last paragraph, Dr. Snowdy again
6 says:

7 [As Read] Despite the importance of this
8 critical aspect of the AAV infection --
9 And I'll pause there.

10 By "this critical aspect," he's talking about
11 nuclear targeting; right?

12 A. I was reading the preceding paragraph to place
13 it in context, and that, together with the title for
14 section A.4, confirms, yes, he's talking about nuclear
15 targeting.

16 Q. He says:

17 [As Read] Very little is known of how AAV
18 provides the transport of its genome across
19 the nuclear envelope and how the progeny
20 capsid proteins gain access to the nucleus for
21 genome encapsidation and virion assembly.
22 Right?

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1 A. That is what the passage says.

2 Q. Okay.

3 All right. So in chapter of -- or section 4
4 of Dr. Snowdy's thesis, which starts on page 123 of --
5 now I'm referring to the Sarepta exhibit page. It's
6 page 109 of Dr. Snowdy's thesis.

7 A. You're referring to -- so page 109 of the
8 thesis?

9 Q. 109 of the thesis, and the Sarepta page
10 numbers is 123.

11 A. I'm at that page.

12 Q. Okay. So this is the -- the chapter or
13 section of Dr. Snowdy's thesis that you rely on in your
14 declaration; right?

15 A. This is the section on phosphorylation
16 consensus sites, yes.

17 Q. Okay. And this section spans from page 109 to
18 page 116 of Dr. Snowdy's thesis; right?

19 A. Let me confirm that.

20 Q. Mm-hmm.

21 A. That's correct. It spans 109 through 116.

22 Q. Okay. In this section, Dr. Snowdy is looking

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1 at nuclear localization signals; right?

2 A. Looking at putative nuclear localization
3 signals, yes.

4 Q. Mm-hmm. And in particular, he looked at a
5 putative -- and I'm looking now at page 11 under
6 "Results."

7 He looked at a putative nuclear localization
8 sequence in -- I'm sorry. He looked at a putative
9 nuclear localization sequence in AAV2.

10 A. Are you referring to the sequence in the box
11 that highlights a -- or where is the nuclear
12 localization sequence? Can you confirm that we have the
13 same understanding.

14 Q. Sure. So I'm just looking at the first
15 paragraph, and he says he:

16 [As Read] Used NetPhos to search the AAV2
17 capsid for high probability phosphorylation
18 kinase.

19 And I won't keep reading.

20 Do you see where I am?

21 A. I see where with you are, but you're referring
22 to a nuclear localization sequence. So I'd just like to

Page 300

1 confirm the identity of that sequence.

2 Q. Okay. The -- I think, Dr. Schaffer, the
3 nuclear localization sequence or the putative nuclear
4 localization sequence is shown in bold in the box on
5 page 111.

6 A. Great. Thank you.

7 Q. Do you see that?

8 A. I do, yes.

9 Q. Okay. And he looked at three cites: serine,
10 148; threonine, 159; and serine, 159; right?

11 A. That's mentioned in the line above that boxed
12 sequence; correct.

13 Q. And in the boxed sequence, he marks those
14 residues with the kinase that might phosphorylate it;
15 right?

16 A. That -- it is marked with a kinase that might
17 phosphorylate that residue.

18 Q. Mm-hmm. And each of those residues and this
19 nuclear localization sequence are in the VP1 portion of
20 the capsid protein of AAV2; right?

21 A. When you say it's by the numbering of VP1 --

22 Q. Mm-hmm.

75 (Pages 297 to 300)

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1 A. -- as -- as we discussed earlier, the VP1
 2 unique region has 137 amino acids.
 3 **Q. So these are in VP2?**
 4 A. They're within the VP2 -- they lie within VP1,
 5 but they're within the VP2 unique region.
 6 **Q. But these residues would not be in VP3; right?**
 7 A. These would not be present within VP3.
 8 **Q. Okay. So what Dr. Snowdy did is mutate each**
 9 **of these three residues either to an alanine or to an**
 10 **aspartic acid; correct?**
 11 A. Correct.
 12 **Q. And just to be clear, alanine the**
 13 **single-letter code is "A"; right?**
 14 A. It's an "A."
 15 **Q. And aspartic acid is a "D"; right?**
 16 A. Aspartic acid is a "D."
 17 **Q. Okay. So Dr. Snowdy didn't mutate any those**
 18 **residues to asparagine, which is "N"; right?**
 19 A. I don't believe he mutated those residues to
 20 an "N" in his publication -- or his chapter.
 21 **Q. Okay. Instead he mutated either a serine or a**
 22 **threonine to either an alanine or an aspartic acid;**

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1 **right?**
 2 A. That is correct.
 3 **Q. And two of those -- so he, in total, made 6**
 4 **mutants; right? And they're listed in that same**
 5 **paragraph?**
 6 ATTORNEY WILSON: Object to form.
 7 THE WITNESS: There are six mutants lifted in
 8 that -- listed in that paragraph.
 9 BY ATTORNEY MORRISON:
 10 **Q. And four of those six mutants had no impact on**
 11 **the capsid protein; right?**
 12 A. If you go to the next paragraph on the
 13 following page, 112 by the chapter's numbering, it does
 14 mention that -- four mutations, and it lists or
 15 enumerates those had little or no effect on the virus's
 16 ability to infect cells.
 17 **Q. And so the mutations at position 148 and 159**
 18 **had no effect or little effect on the virus's ability to**
 19 **infect?**
 20 A. The mutations that Snowdy introduced at those
 21 two positions -- you know, namely the S-to-A and S-to-D
 22 mutations had no effect or little effect on the virus's

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1 ability to infect the HeLa cells as quoted directly from
 2 the chapter.
 3 **Q. But for the mutations at position 181, those**
 4 **mutations had a large impact; right?**
 5 A. The last sentence of that paragraph, I think
 6 you provided a summary of, you know, happy to read
 7 that -- that passage.
 8 You know, the same number of particles
 9 containing the S181A mutation infected far more cells
 10 than did the wild-type. And the same number of
 11 particles containing the S181D mutation infected almost
 12 no cells at all.
 13 **Q. And so for the serine at position 181,**
 14 **mutating it to an alanine dramatically increased its**
 15 **infectivity; right?**
 16 A. That's what that sentence says. Correct.
 17 **Q. And mutating it to an aspartic acid**
 18 **dramatically decreased its infectivity; right?**
 19 A. That's also within that sentence; correct.
 20 **Q. But for the other two positions, as we already**
 21 **discussed, at -- the serine at 148 and the threonine at**
 22 **159, there was no impact of those mutations? Or**

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1 **little -- no or little effect.**
 2 ATTORNEY WILSON: Object to form.
 3 THE WITNESS: Yeah, two sentences prior, I
 4 believe we've read out that sentence again. And as you
 5 indicate, the quote says:
 6 [As Read] Had no effect or little effect
 7 on the virus's ability to infect the HeLa
 8 cells.
 9 BY ATTORNEY MORRISON:
 10 **Q. And to deliver the gene carried?**
 11 A. [As Read] And to deliver on the EGFP gene
 12 carried as their cargo.
 13 **Q. EGFP, just for clarity, that's a reporter gene**
 14 **that will -- it fluoresces; right?**
 15 A. It's -- I believe stands for "enhanced green
 16 fluorescent protein."
 17 **Q. Mm-hmm. So you can visualize it as Snowdy did**
 18 **in figure 23?**
 19 A. That's correct.
 20 **Q. So Dr. Snowdy's thesis shows that changing a**
 21 **phosphorylation site doesn't always have an impact on**
 22 **infectivity; right?**

Page 305 1 ATTORNEY WILSON: Object to form. 2 THE WITNESS: The three sites where there was 3 an introduction of a mutation, one of them dramatically 4 affected the infectivity. The other two had, as we 5 said, no effect or little effect on the virus's ability 6 to infect the HeLa cells. 7 BY ATTORNEY MORRISON: 8 Q. And I want to look at your declaration for a 9 minute at paragraph 276, which is where you're 10 discussing the Snowdy paper. 11 A. Are we going to be referring back to Snowdy? 12 Should I -- 13 Q. We are. If it helps, I can give you another 14 copy of Snowdy. And then you won't have to flip back 15 and forth. 16 A. Thank you. 17 Q. So if you can go to paragraph 276 of your 18 declaration, which is on page 106. 19 A. I'm at page 106 of my declaration. 20 Q. Mm-hmm. And do you see "paragraph 276" at the 21 bottom there? 22 A. I see paragraph 276, yes.	Page 306 1 Q. Okay. And you say in this paragraph that: 2 [As Read] Snowdy disclosed a method of 3 improving transaction of AAV vectors by 4 removing phosphorylatable sites in the capsid 5 proteins. 6 Right? 7 A. That's an accurate reading of the passage, 8 yes. 9 Q. And is that method of improving transaction -- 10 that was in isolated HeLa cells; right? 11 A. Snowdy's data refers to HeLa cells, talks 12 about infectivity as read out or measured in HeLa cells. 13 Q. And it doesn't talk about impact in in vivo. 14 This is an in vitro experiment; right? 15 A. This is an in vitro experiment. 16 Q. And so it doesn't talk about specific tissues 17 within a mammal or a subject; right? 18 A. This doesn't talk about specific tissues 19 within a subject. It talks about the general property 20 of infectivity. 21 Q. Okay. And Snowdy does say, though, that, at 22 page 28 -- and that's page 28 of Snowdy's thesis. It's
Page 307 1 page 42 of Sarepta's exhibit page numbers. 2 A. I'm there. 3 Q. He says in the first full paragraph in the 4 middle of the page that: 5 [As Read] Data from our laboratory and 6 data emerging in the literature suggests that 7 AAV serotypes have transduction efficiencies 8 that are dependent upon -- excuse me -- 9 dependent on the tissue type. 10 Right? 11 A. You're reading "Data from our laboratory and 12 data emerging in the literature"? 13 Q. Mm-hmm. 14 A. This sentence starting with that? 15 Q. Yes. 16 A. Or the -- with that passage? 17 Q. I was, yes. 18 A. That's a correct reading of that sentence. 19 Q. Okay. And so Dr. Snowdy's explaining that 20 transduction efficiency can be dependent upon tissue 21 type; right? 22 A. That's a recurring theme today, and Snowdy	Page 308 1 agrees with it. 2 Q. Okay. 3 Okay. And Snowdy does discuss receptor 4 binding, but notes -- and I'm -- and I'm at page 118 of 5 Snowdy. And I apologize for jumping all over the place. 6 But 118. And, again, I'm referring to the page of the 7 thesis. 8 A. I'm at page 118 of the thesis. 9 Q. Okay. And in his -- and this -- this portion 10 of his thesis is in a final chapter or section called 11 "Future Directions," which starts on the preceding page; 12 right? 13 A. I agree with that. 14 Q. Okay. And so he says that: 15 [As Read] A great deal of work remains in 16 establishing the mechanisms through which AAV 17 variants and capsid proteins traffic through 18 their host cells. 19 Right? 20 A. You're starting with the top sentence on 21 page 118? 22 Q. I am.

Page 309 1 A. That's an accurate reading, yes. 2 Q. And he then goes on that: 3 [As Read] Very little of the pathway from 4 receptor binding to gene expression has been 5 unequivocally determined for the virus. 6 Right? 7 A. That's right. That's the next sentence. 8 Q. And then I'm going to paraphrase the next 9 sentence, partly for the court reporter's benefit, but 10 for AAV2 there's a dependence on heparan proteoglycan 11 for binding; right? 12 A. "For initial attachment to the target cell" is 13 how he phrases it, yes. 14 Q. And that's consistent with what we saw in Wu, 15 that that heparan binding site was the binding site for 16 AAV2? 17 A. That's the initial primary receptor on the 18 cell's surface. 19 Q. But then he goes on to say in the following 20 sentence: 21 [As Read] It is unknown what receptor 22 mediates infection by AAV1, AAV3, AAV7, and	Page 310 1 AAV8. 2 Right? 3 A. That's an accurate reading of that 4 paragraph -- or that sentence within that paragraph, 5 yes. 6 Q. And Dr. Snowdy is not talk -- Dr. Snowdy is 7 talking about transduction into the nucleus of the AAV 8 virus in his Chapter 4; right? 9 A. Let me page back to Chapter 4. 10 The title doesn't discuss nucleus. It 11 generically refers to AAV2 trafficking. The first 12 sentence of that introductory paragraph does talk about 13 nuclear localization sequences. 14 Q. And Chapter 4 is about changing amino acids 15 that are in the vicinity of a putative nuclear 16 localization signal; right? 17 A. That's correct. Changing the identity of 18 amino acids that are in proximity to a putative or 19 potential nuclear localization sequence. 20 Q. And the nuclear localization sequence is what 21 is responsible for moving -- the step that we talked 22 about in AAV infection, where the virus is moving
Page 311 1 through the cytoplasm and going into the nucleus; right? 2 ATTORNEY WILSON: Objection. 3 Go ahead. 4 THE WITNESS: Okay. 5 BY ATTORNEY MORRISON: 6 Q. Please correct me if I've got it wrong. 7 A. The nuclear localization sequence engages with 8 cellular machinery, you know, proteins inside the cell, 9 and that leads or initiates the process of importing 10 that material into the nucleus of the cell. 11 Q. Okay. And that's -- so that nuclear 12 localization sequence is important after the virus has 13 entered the cell; is that right? 14 A. It is important for that final -- well, 15 second-to-final step of that step of getting into the 16 nucleus. 17 Q. Okay. 18 Okay. And Dr. Snowdy is not talking in this 19 chapter about changing the tissue tropism of a 20 particular AAV virus; right? 21 ATTORNEY WILSON: Object to form. 22 THE WITNESS: Dr. Snowdy talks about --	Page 312 1 So without scanning the entire article, there 2 are places where he talks about AAV's ability to infect 3 a target cell. 4 BY ATTORNEY MORRISON: 5 Q. Mm-hmm. But in Chapter 4 he's talking about 6 an experiment done in vitro, not in vivo; so he's not 7 talking about tissue tropism; right? 8 ATTORNEY WILSON: Object to form. 9 THE WITNESS: So he's talking about AAV's 10 ability to infect a target cell, and that's an inherent 11 part of tropism. 12 BY ATTORNEY MORRISON: 13 Q. But he's not talking about changing the 14 tropism from one tissue to another in Chapter 4. He 15 doesn't mention that at all; right? 16 ATTORNEY WILSON: Object to form. 17 THE WITNESS: He's talking about the ability 18 to infect a target cell, which a POSA would recognize as 19 an important aspect of tropism. 20 BY ATTORNEY MORRISON: 21 Q. Okay. He's not talking about tissues within a 22 living being; right?

Page 313 1 ATTORNEY WILSON: Object to form. 2 THE WITNESS: Again, talking about the generic 3 ability to the infect a target cell, which is directly 4 related to tropism. 5 BY ATTORNEY MORRISON: 6 Q. Okay. But you'd agree with me his experiment 7 is in vitro not in vivo; right? 8 A. The experiment was in vitro. 9 Q. And it's in HeLa cells? 10 A. The experiment was in HeLa cells. 11 Q. And what are HeLa cells? 12 A. HeLa cells are derived, I believe, from the 13 cervix of the donor. 14 Q. And they're -- they're a cell line that you 15 can divide over and over and over again. They'll live 16 for a long time. 17 Is that fair? 18 A. That is fair to say, yes. 19 Q. And they live in a -- in a flask in an 20 incubator typically when you would be doing any 21 experiments with them; right? 22 A. That's correct. One would incubate HeLa cells	Page 314 1 in a flask in an incubator. 2 Q. Okay. All right. And you'd agree with me -- 3 well, strike that. 4 Dr. Snowdy, in his Chapter 4, doesn't test 5 whether any of the sites he's looking at are actually 6 phosphorylation sites. They're just putative 7 phosphorylation sites; right? 8 A. He identifies -- sorry. 9 ATTORNEY WILSON: Object to form. 10 THE WITNESS: He identifies three potential 11 sites for phosphorylation. And then analyzes the effect 12 of making mutations that would either prevent the 13 phosphorylation or emulate the presence of a 14 phosphorylation. 15 BY ATTORNEY MORRISON: 16 Q. But he doesn't ever determine whether in the 17 natural -- in its natural state whether any of those 18 sites are actually phosphorylation sites; right? 19 ATTORNEY WILSON: Object to form. 20 THE WITNESS: So it is a -- what's common 21 knowledge in the field at that time. A POSA would know 22 that if one identified a putative kinase site -- a
Page 315 1 putative phosphorylation site -- sorry -- that would be 2 the first step or a really critical step for analyzing 3 whether or not it was phosphorylated would be to do 4 these mutations such as guided by Jans and Jans or 5 others within the field to test whether or not a 6 phosphomimetic, you know, a amino acid that has a 7 negative charge, and as a result may behave like 8 something like -- that is phosphorylated would change 9 the function. 10 BY ATTORNEY MORRISON: 11 Q. Okay. So for the three sites that Dr. Snowdy 12 tested, two are serines; one's a threonine; right? 13 A. That's correct. 14 Q. All three of those are amino acids that can be 15 phosphorylated; right? 16 A. Serine, threonine, and then the second serine, 17 those are sites that, yes, could be potentially 18 phosphorylated. 19 Q. And the other amino acid that can be 20 phosphorylated is tyrosine; right? 21 A. That's correct. 22 Q. But just because those amino acids exist in a	Page 316 1 protein doesn't mean that they are going to be 2 phosphorylated. They just might be? 3 A. They would be -- 4 ATTORNEY WILSON: Object to form. 5 THE WITNESS: Yeah, the presence of -- well, 6 serine, threonine, and tyrosine are phosphorylatable 7 sites. So if they appear within a protein, it's 8 possible that they could become phosphorylated. 9 BY ATTORNEY MORRISON: 10 Q. Okay. But just because they could become 11 phosphorylated it does not mean in any particular 12 protein at any particular site they are phosphorylated; 13 right? 14 ATTORNEY WILSON: Object to form. 15 THE WITNESS: Their presence indicates that 16 they're candidates for phosphorylation if there is a, 17 you know, particular kinase that attempts to 18 phosphorylate residue at those sites. 19 BY ATTORNEY MORRISON: 20 Q. Okay. And I think we already agreed on it 21 this, but Snowdy did not make any serine-to-asparagine 22 mutation; right?

Page 317 1 A. Snowdy did not make a serine-to-asparagine 2 mutation within this work. 3 Q. Okay. He only mutated serine to alanine or 4 serine to aspartic acid; right? 5 ATTORNEY WILSON: Object to form. 6 THE WITNESS: The three sites where he 7 mutated, he did a serine to alanine at positions 148, 8 159, and 181, and also made a serine-to-aspartic-acid 9 mutation at those three positions. 10 BY ATTORNEY MORRISON: 11 Q. And just for clarity, the position 159 is 12 actually a threonine to alanine or aspartic acid. 13 A. My apologies. I think I said serine. 14 Q. Okay. And Snowdy -- you -- you note that 15 Snowdy references Jans and Jans, which I think is 16 publication you also just referenced a moment ago; is 17 that right? 18 A. That's correct. Jans and Jans was right here 19 in the middle of the paragraph that I was taking a look 20 at -- 21 Q. Okay. 22 A. -- and --	Page 318 1 Q. And you say at paragraph -- in your 2 declaration paragraph 274, in the last sentence of that 3 paragraph, which is at the top of page 106, you say: 4 [As Read] Snowdy also teaches the 5 substitution of asparagine (N) as a 6 non-phosphorylatable amino acid to remove a 7 phosphorylation site. 8 A. That's an accurate reading of that passage, 9 yes. 10 Q. And you cite Snowdy at pages 28 through 29; 11 right? 12 And I believe those pages are the pages -- the 13 Sarepta pages and not the thesis pages. 14 A. Thank you. 15 I'm at pages 28 and 29 according to the 16 Sarepta numbering. 17 Q. Which is pages 14 and 15 of the thesis; right? 18 A. That's correct. 19 Q. Okay. And so at those pages, Dr. Snowdy says: 20 [As Read] A phosphorylated serine or 21 threonine can be mimicked by substitution of 22 the residue with asparagine resulting in a
Page 319 1 constitutively phosphorylated residue. 2 A. That's what the passage reads. A POSA would 3 know that that's actually a typographical error. 4 Q. And should be, not asparagine, but aspartic -- 5 A. Aspartic acid. 6 Q. Okay. So what you say at paragraph 106 -- or 7 excuse me, paragraph 274 on 106 the point -- the part 8 you point to in Snowdy doesn't teach -- this passage in 9 Snowdy -- I'm going to get to Jans and Jans. 10 This passage in Snowdy does not teach the 11 substitution of asparagine? 12 A. What I'm indicating is that on pages 28 to 29 13 there's a citation of Jans and Jans. 14 Q. Okay. 15 A. And then by citing that, there's a instruction 16 about that potential modification. 17 Q. Okay. So you agree, though, that this passage 18 in Snowdy at pages -- top of page 29, that's a typo; 19 right? 20 A. I agree that that's a typographical error. 21 Q. Okay. So let's look at Jans and Jans, which 22 is Exhibit 1017, and I can get -- let me give you	Page 320 1 another one so you can look at your declaration. 2 A. Okay. 3 ATTORNEY WILSON: Thank you. 4 THE WITNESS: Thank you. 5 BY ATTORNEY MORRISON: 6 Q. Okay. 7 All right. So Jans and Jans has already been 8 marked in this proceeding as Exhibit 1017. 9 So Jans and Jans is not about AAV. We can 10 agree on that; right? 11 A. Correct. It's not about AAV. It's about a 12 different viral protein, the SV40 large T antigen. 13 Q. Okay. And Jans and Jans does not make a 14 substitution of an asparagine for a serine; right? 15 ATTORNEY WILSON: Object to form. 16 THE WITNESS: So I can cite some places with 17 where a substitution into an asparagine is made and that 18 is to be able to change an aspartic acid to an 19 asparagine. 20 BY ATTORNEY MORRISON: 21 Q. So -- right. So if you look at Table 1 -- in 22 the description of Table 1, which is on page 3,

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1 according to the Sarepta numbering of Jans and Jans,
2 Jans and Jans describes the mutations that are made in
3 that table; right?

4 A. The first column and then the subsequent
5 sequence in the central column describe mutations that
6 are made to a putative sequence.

7 Q. So the first three sequences in Table 1, those
8 are all the wild-type sequences, just different lengths
9 of the wild-type sequence; right?

10 A. And just to clarify, by "wild-type sequence,"
11 you're referring to the nuclear localization sequence?

12 Q. Yes. I'm referring to the nuclear
13 localization sequence of the SV40 T antigen.

14 A. I agree with that, yes. The first three rows
15 that are listed show the nuclear localization sequence
16 of the T antigen in a peptide with different lengths.

17 Q. Okay. And then the fourth row shows a single
18 mutation of a serine at position 111 to a glycine;
19 right?

20 A. That's correct.

21 Q. The fifth mutation, which I think is one --
22 the one you were referring to, substitutes two aspartic

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1 acids for asparagine and a glutamate for a glutamine?

2 A. That's correct.

3 Q. Or glutamic acid for glutamine?

4 A. Glutamic.

5 So and then "Q," which would be two
6 asparagines and then one glutamine. The "Q" would stand
7 for glutamine.

8 Q. Mm-hmm. And in the wild-type sequence, it
9 would be "DDE"?

10 A. Correct.

11 Q. So the aspartic acids are substituted for
12 asparagines; right?

13 A. That's correct. It's a DDE-to-an-NNQ swap.

14 Q. And just to be clear, the "E" is a glutamic
15 acid in the wild-type sequence?

16 A. Yes. It's an aspartic acid, aspartic acid,
17 glutamic acid to a asparagine, asparagine, glutamine
18 swap.

19 Q. Okay. And then in the -- that was the fifth
20 one.

21 In the sixth mutant that's made, the serines
22 are changed to an alanine and a glycine; right?

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1 A. That's correct.

2 Q. And then the final one, the serines are
3 changed to a glycine and an aspartic acid; right?

4 A. That's correct.

5 Q. Okay. And so Jans and Jans at the -- at
6 pages 5 -- starting at page 5 and going over on to
7 page 6, Jans and Jans concludes that mutating the serine
8 at 112 to an aspartic acid to mimic phosphorylation,
9 that that improved nuclear transport, or at least it
10 kept it close to the wild-type level; right?

11 A. Just to refresh, can you refer to which of the
12 columns in D you're referring to. I anticipate you're
13 talking about B or perhaps 4B or else figure 2. That
14 would be -- sorry. Go ahead.

15 Q. Yeah, let's look at figure 2 first just to
16 ground ourselves.

17 A. Okay.

18 Q. So figure 2 graphs the infectivity or the
19 nuclear import of the T antigen protein -- all the ones
20 we just looked at in the Table 1; right?

21 A. That's correct.

22 Q. And the wild-type is graphed at the -- the

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1 wild-type is shown close to the top of figure 2?

2 A. That's correct.

3 Q. And the mutation where the only mutant is that
4 the serine at 111 is changed to a glycine is equivalent
5 essentially, to wild-type; right?

6 A. That's correct.

7 Q. The next best mutant is where the serine at
8 111 is changed a glycine and the serine at 112 is
9 changed to a aspartic acid. That has some reduced
10 import, but it still is better than many of the others;
11 right?

12 A. I --

13 (Clarification inquiry by The Court Reporter.)

14 THE WITNESS: I agree with your
15 interpretation.

16 BY ATTORNEY MORRISON:

17 Q. And then finally, all of the remaining mutants
18 that were made, nuclear import was much lower.

19 Is that fair?

20 A. That is fair.

21 Q. Okay. So the conclusion of Jans and Jans is
22 that mutating the serine at 111 to glycine, which is a

81 (Pages 321 to 324)

Page 325 1 not-phosphorylatable amino acid has no impact; right? 2 ATTORNEY WILSON: Object to form. 3 THE WITNESS: As you indicated, it's imported 4 almost as well as the wild-type. Are you talking about 5 the wild-type versus the GLY 111? 6 BY ATTORNEY MORRISON: 7 Q. Yes. 8 A. Oh, I see. I was moving down to the next 9 mutants. 10 So the wild-type 111 through 135 and the 11 GLY 111 through 135 appear to be very similar to each 12 other without having done statistics on them. 13 Q. Well, sure. So changing the serine, which is 14 phosphorylatable, at position 111 to a glycine, which 15 cannot be phosphorylated, had little impact; right? 16 A. At that position 111, that's correct. 17 Q. But at position 112, the results were very 18 different; right? 19 A. That is correct. Adding the additional 20 mutation at 112 did result in a significant decrease in 21 importance. 22 Q. And mutating the serine at 112 to a glycine	Page 326 1 was a very significant decrease in import; right? 2 ATTORNEY WILSON: Object to form. 3 THE WITNESS: Could you repeat that. 4 BY ATTORNEY MORRISON: 5 Q. Sure. 6 A. Mutating the serine at -- 7 Q. At 112 to a glycine at 112 very negatively 8 impacted nuclear import. 9 A. Yes. I mean, there's a caveat here that two 10 modifications were made at the same time. It's a -- you 11 know, what one would call a double-variable experiment, 12 that that first serine is being changed to an alanine 13 and the second serine is being changed to a glycine at 14 the same time, which makes it a little bit harder to 15 determine which site is -- is most important. However, 16 with that caveat, certainly one of those two sites is 17 important. 18 Q. Mm-hmm. Well, and Jans and Jans concludes in 19 the paragraph just under that figure: 20 [As Read] Clearly, CK2 predominantly 21 phosphorylated the T antigen fusion proteins 22 at serine 112 consistent with in vivo results
Page 327 1 for T antigen and SV40 infected cells. 2 A. I see that passage. The sentence comes after 3 an interpretation of figure 5, which is 3 figures after 4 the one we just went through. So that appears to be 5 drawing some conclusions based on data that we didn't 6 just go through. 7 Q. So let's look at figure 5 because that 8 compares the mutation of the two serines at positions 9 111 and 112; right? 10 A. It appears to be quantifying phosphorylation 11 on the Y axis over time of several different potential 12 substrates by the kinase CK2 in vitro. And the mutation 13 of the serine 111 to a glycine did not substantially 14 impact the phosphorylation, but the corresponding 15 mutation of the serine 112 to glycine at that position 16 was deleterious for phosphorylation. 17 Q. So Jans and Jans shows that not all mutations 18 changing a potentially phosphorylated amino acid to one 19 than cannot be phosphorylated have an impact on actual 20 phosphorylation; right? 21 ATTORNEY WILSON: Object to form. 22 THE WITNESS: Jans and Jans shows or analyzes	Page 328 1 that, you know, two potential sites for phosphorylation, 2 and specifically serine 111 and serine 112, that 3 mutation of the serine 112 to a glycine reduced 4 phosphorylation by 80 percent in the assay. 5 BY ATTORNEY MORRISON: 6 Q. But the mutation of the serine at 111 to a 7 glycine reduced phosphorylation only a small amount; 8 right? 9 A. The mutation of serine 111 to glycine reduced 10 phosphorylation by -- well, I would have to do the 11 statistics to assess whether those are different from 12 each other, but I would say by a little. 13 Q. And based on that data, Jans and Jans 14 concludes that the CK2 kinase phosphorylates this 15 protein at serine 112? That was that sentence we read a 16 few moments ago. 17 A. Could you review or go back? 18 Q. Sure. 19 A. That's the sentence on the prior page? 20 Q. It is. 21 A. Okay. 22 Q. It starts with the word "Clearly."

Page 329 1 A. They say that CK2 predominantly 2 phosphorylated the T antigen fusion protein at sera 112. 3 Q. Jans and Jans also in the next section talks 4 about the serine-to-aspartic-acid mutation that it makes 5 in the next constitutive phosphorylation; right? 6 A. If you could highlight the -- the location of 7 the text -- 8 Q. Sure. 9 A. -- I'm happy to -- to dive in there. 10 Q. It's the same page, page 5 of Jans and Jans, 11 in the right-hand column. 12 A. Okay. 13 Q. Jans -- and in the second sentence, Jans and 14 Jans says that aspartic acid -- 15 That's -- ASP is the three-letter code; right? 16 A. Mm-hmm. 17 Q. [As Read] Closely resembles phosphoserine 18 or phosphothreonine with regard to size and 19 charge. 20 And then it goes on; right? 21 A. I see that text, yes. 22 Q. And so that serine-to-aspartic-acid mutation	Page 330 1 is intended to mimic constitutive phosphorylation; 2 right? 3 A. Let me read the surrounding text so I can 4 gather the full context. 5 So that section is referring to a mutation of 6 the position 112 to an aspartic acid to be able to mimic 7 a phosphorylation. 8 Q. Mm-hmm. And the conclusion that Jans and Jans 9 draws is that that serine at position 112 is 10 phosphorylated to -- strike that. Let me say this a 11 different way. 12 That nuclear import of this T antigen -- 13 SV40 T antigen needs that serine at 112 to be able to be 14 phosphorylated. 15 That's the conclusion that's drawn? 16 A. Well, it indicates that on figure 2, going 17 back to that figure which we discussed, it indicates 18 that a loss of potential for phosphorylation at that 19 site does correspond to a slowing down of nuclear 20 import. With the caveat in figure 2, of course, that 21 they didn't actually make the substitution of a -- just 22 the glycine 112 without affecting alanine 111 or without
Page 331 1 affecting the identity of the serine at 111. 2 Q. The "Discussion" section on page 6 in Jans and 3 Jans, the first sentence states that: 4 [As Read] This study conclusively 5 confirms our previous hypothesis that the CK2 6 phosphorylation site flanking the SV40 T 7 antigen NLS has a central role in enhancing 8 nuclear import of T antigen proteins. 9 A. That's what that sentence states. 10 Q. So the conclusion Jans and Jans is drawing is 11 that that phosphorylation site at serine at 112 has a 12 central role in enhancing import of T antigen proteins? 13 A. Yeah, I don't know how much of a stickler to 14 be or how much to quibble about the point, but if -- 15 again, I would have to sit down and reread the entire 16 publication. 17 But based on figure 2, yeah, they say: 18 [As Read] Point mutations at the site, 19 either of the -- point mutations at the site, 20 ether of the phosphorylatable serines -- 21 And then dot dot dot. Hopefully you'll 22 forgive me the ellipsis.	Page 332 1 [As Read] -- drastically reduce the 2 nuclear import rate. 3 I don't think that they showed mutation in 4 either of the serines. 5 "Dramatically reduced nuclear import" at least 6 in figure 2. Perhaps they showed that elsewhere within 7 the publication. 8 Q. Okay. 9 A. They show that mutation of both of them 10 dramatically reduced nuclear import. 11 Again, not sure how material that is. 12 Q. Okay. So I think we can agree, though, that 13 Jans and Jans is concluding that that phosphorylation 14 site needs to be there and be able to be phosphorylated 15 to get the nuclear import right. 16 Is that a fair reading? 17 ATTORNEY WILSON: Object to form. 18 THE WITNESS: It shows that the 112 site needs 19 to be serine in order to get phosphorylated because they 20 do a kinase assay in figure 5. However, I would 21 quibble with this publication as a reviewer because 22 the -- the link between phosphorylation and nuclear

Page 333 1 import is not drawn between figure and figure 5. 2 BY ATTORNEY MORRISON: 3 Q. Okay. 4 A. However, that's -- it's a reasonable -- it's 5 likely interpretation. 6 Q. And it's -- that's -- for Snowdy, though, 7 Snowdy showed that getting rid of a phosphorylation site 8 enhanced nuclear import; right? 9 A. Snowdy showed that getting rid of a 10 phosphorylation site increased infectivity of the target 11 cell. 12 Q. And so for Jans and Jans, getting rid of a 13 phosphorylation site and making it not able to be 14 phosphorylated decreased nuclear localization; right? 15 A. That is, again, with the quibble that they got 16 rid of both sites -- 17 Q. Sure. 18 A. -- both serines. But upon getting rid of both 19 serines, it significantly slowed the rate of nuclear 20 import. 21 Q. And Jans and Jans showed that when you got rid 22 of a phosphorylation site and made it not	Page 334 1 phosphorylatable it increased nuclear import; right? 2 ATTORNEY WILSON: Object to form. 3 THE WITNESS: Snowdy shows that it increased 4 infectivity of a target cell. 5 ATTORNEY MORRISON: Okay. 6 I apologize. We've been going a lot more than 7 an hour. Why don't we take a break. 8 THE WITNESS: Sounds good. Thank you. 9 (A break was taken.) 10 BY ATTORNEY MORRISON: 11 Q. Dr. Schaffer, did you talk to your counsel 12 about the substance of your testimony during the break? 13 A. I did not. 14 Q. Okay. At footnote 3 in your declaration, 15 which is at pages 69 to 70 -- 16 A. I see footnote 3 on page 69. 17 Q. -- you talk about using a program called 18 NetPhos? 19 A. Correct. The subject of the footnote covers 20 NetPhos. 21 Q. Okay. And you did -- as Exhibit 1021 to your 22 declaration, you ran or you used NetPhos to identify
Page 335 1 potential -- and I can hand it to you if that makes it 2 easier. 3 A. Okay. 4 Q. You used NetPhos -- 5 A. Thank you. 6 Q. -- to identify potential phosphorylation sites 7 and potential kinases that might phosphorylate those 8 sites in AAVrh.10. 9 A. That's correct. 10 Q. Okay. So, Dr. Schaffer, who -- did you 11 actually do this NetPhos -- did you actually run this 12 program, or did someone else do it and give it to you? 13 A. This was done under my supervision by counsel. 14 Q. Do you know the specific person who did it? 15 A. I believe it was Counsel Toker. 16 Q. Okay. Is NetPhos a program that you use in 17 your work in your lab? 18 A. I have analyzed phosphorylations. I have used 19 NetPhos. 20 Q. Okay. Is -- how often would you say you've 21 used it? 22 A. Not very often.	Page 336 1 Q. And I just want to understand what this is 2 showing. 3 A. Mm-hmm. 4 Q. So the first column says "sequence," and it 5 says "AAVrh.10" all the way down -- right? -- to the 6 end? 7 A. It enumerates AAVrh.10 all the way to the end; 8 correct. 9 Q. Okay. The second column says number -- the 10 heading says a number sign and then X; right? 11 A. That's right. In the top row? 12 Q. Mm-hmm. 13 A. Correct. 14 Q. And what that's identifying is the position 15 number in the AAVrh.10 sequence and the amino acid that 16 exists in the native AAVrh.10 sequence; right? 17 A. That's correct. The number is the amino acid 18 number using a VP1 numbering, and the "X" corresponds to 19 the identity of the amino acid at that position. 20 Q. Okay. And then the next column says context, 21 and that just gives the amino acid surrounding that 22 amino acid position that's identified in the prior

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1 **column; right?**

2 A. Correct. The amino acid shown under X is
3 placed roughly halfway through that context sequence; so
4 it's intended to show the amino acids that flank that
5 almost middle position.

6 **Q. And then the next column says score. Do you**
7 **see that?**

8 A. Yes, I do.

9 **Q. And what does the score represent?**

10 A. The score is a relative prediction by the
11 software indicating how likely it is according to the
12 software to be a substrate for a given kinase.

13 **Q. Okay. And then the next column that says**
14 **kinase identifies the kinases that might phosphorylate**
15 **that site?**

16 A. That's correct.

17 **Q. And then finally the final column says**
18 **"answer," and there's either a "Yes" or nothing in that**
19 **column; right?**

20 A. Correct.

21 **Q. And a "Yes" means that the program was able to**
22 **identify a kinase that might phosphorylate that site.**

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1 A. I am only familiar the inner workings of the
2 code but my interpretation of the column is that the
3 score, you know, exceeds some threshold in the opinion
4 of the NetPhos software to indicate it's a likely
5 phosphate site.

6 **Q. Okay. And so the "Yes" doesn't mean that that**
7 **site is phosphorylated. It just means it's a likely**
8 **kinase site?**

9 A. That's correct. It exceeds the score that as
10 a result in the opinion of the software it's a very
11 likely kinase site.

12 **Q. So for example, the position -- the first**
13 **position here is a tyrosine position 6?**

14 A. That's correct.

15 **Q. But there's no yes answers for any kinase; is**
16 **that right?**

17 A. That's correct. All four -- the last column
18 appear to be asterisks rather than a yes.

19 **Q. So the -- does that mean the program's**
20 **predicting that it's unlikely that that site is**
21 **phosphorylated by any of those kinases?**

22 A. It's indicating that the score doesn't exceed

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1 some threshold --

2 **Q. Okay?**

3 A. -- within the software; however, as I
4 mentioned I'm not as familiar the inner workings of the
5 stair and what that threshold corresponds to.

6 **Q. Okay. And then -- strike that.**

7 **That site -- that tyrosine at position 6 could**
8 **be phosphorylated by one of those kinases?**

9 A. It's conceivable that it could, yes. NetPhos
10 provides guidance about potential sites that can become
11 phosphorylated.

12 **Q. Okay. But the program based on its scoring is**
13 **not predicting that that's a likely site of**
14 **phosphorylation is that a fair interpretation of the**
15 **data?**

16 A. It says it doesn't reach its thresh hold to be
17 classified yes a very likely site for phosphorylation.

18 **Q. Okay. So then looking at the next position,**
19 **position 16 which is a serine, there are two kinases**
20 **that are identified as likely or possible to**
21 **phosphorylate that site; right?**

22 A. I see those two rows, yes, that end with a

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1 "Yes."

2 **Q. And that's the CK2 kinase and the CK1 kinase;**
3 **right?**

4 A. That's correct.

5 **Q. Okay. And so based on the algorithm of this**
6 **program, it's predicting that those two kinases at that**
7 **site exceeded whatever the program's threshold score is**
8 **that say it's possible to be phosphorylated is that**
9 **fair?**

10 A. I think that's a fair interpretation.

11 **Q. Okay. And I'm not going to go through all you**
12 **the rest of the positions, but if we counted up the yes**
13 **positions or the positioning with a yes in them I'll**
14 **represent to you that there were 82 positions within the**
15 **avenue rh.10 protein that have at least one kinase that**
16 **was a "yes" according to NetPhos.**

17 **Does that seem about right to you?**

18 ATTORNEY WILSON: Just.

19 THE WITNESS: I haven't counted the positions
20 themselves. I'll take your word if you say there are
21 82.

22 BY ATTORNEY MORRISON:

85 (Pages 337 to 340)

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1 **Q. Okay. And for several of the positions,**
 2 **position 16, for example, there's more than one kinase**
 3 **that is potentially phosphorylating at that site.**
 4 **Is that --**
 5 A. That's correct, yes. It lists CK1 and CK2.
 6 **Q. And so for some positions there's only a**
 7 **single possible kinase that's phosphorylating**
 8 **potentially phosphorylating that site like position 79,**
 9 **for example?**
 10 A. Yes. I see that.
 11 **Q. But, for example, if you turn to the second**
 12 **page at position 149 there's four possible kinases that**
 13 **the program identified as possible to phosphorylate that**
 14 **site; right?**
 15 A. That's correct.
 16 **Q. Okay. So there's 82 according to this**
 17 **document there's 82 sites that have a "yes" at the --**
 18 **that -- there's a possible kinase to phosphorylate those**
 19 **sites?**
 20 ATTORNEY WILSON: Object to form.
 21 THE WITNESS: I'll take your word for it.
 22 Again I have not counted them.

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1 BY ATTORNEY MORRISON:
 2 **Q. Okay. And one of those 82 sites is position**
 3 **665; right?**
 4 A. 665 is listed as one of the positions that's
 5 potentially phosphorylated.
 6 **Q. Okay but it's just one out of 82; right?**
 7 ATTORNEY WILSON: Object to form.
 8 THE WITNESS: If you say there are 82 I'll
 9 again take your word for it and then position 665 does
 10 have a yes so I would anticipate that's one of your 82.
 11 BY ATTORNEY MORRISON:
 12 **Q. Okay. Let's go on to your last reference that**
 13 **using your grounds that's the Fabb reference it's**
 14 **Exhibit 1010, and I'm happy to hand you a copy --**
 15 A. Sure.
 16 **Q. -- so you can continue to look at your**
 17 **declaration.**
 18 A. Thank you.
 19 **Q. Okay. Do you know Dr. Fabb or have you ever**
 20 **heard of him?**
 21 A. I don't know Dr. Fabb. Nor have I heard of
 22 him aside from this publication.

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1 **Q. So sure. And this paper, this publication, is**
 2 **about the creation of a micro-dystrophin construct;**
 3 **right?**
 4 A. The title of the paper does indicate yes the
 5 creation of 144 kill Dalton micro-dystrophin.
 6 **Q. Okay. And this paper's not about the creation**
 7 **of new AAV capsids or the modification of AAV capsid**
 8 **proteins; right?**
 9 A. It focuses on the minigene, and I'm using that
 10 phrase namely. The micro-dystrophin construct does not
 11 focus on the delivery as much.
 12 **Q. Okay. And you'd agree -- and I think the Fabb**
 13 **paper says this throughout -- that dystrophin a protein**
 14 **found in muscle and that you'd want to target dystrophin**
 15 **to the muscle; right?**
 16 ATTORNEY WILSON: Object to form.
 17 THE WITNESS: Dystrophin is expressed in many
 18 tissues including muscle.
 19 BY ATTORNEY MORRISON:
 20 **Q. Okay. Fabb, if you look at page 3 of Fabb, at**
 21 **the bottom of the right-hand column, there's a section**
 22 **talking about expression of Fabb's micro-dystrophin**

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1 **construct in skeletal muscle of nude MDX mice?**
 2 A. Expression of micro-dystrophin delta 3788 --
 3 **Q. Yes.**
 4 A. -- in the skeletal muscle?
 5 **Q. Yes.**
 6 A. Okay.
 7 **Q. So Fabb in this section is looking at the**
 8 **expression of its micro-dystrophin construct in skeletal**
 9 **muscle; right?**
 10 A. That appears to be the case yes.
 11 **Q. Okay. Fabb doesn't discuss which AAV capsid**
 12 **he uses; is that right?**
 13 A. Let me take a look at the methods.
 14 At least within the methods where one
 15 typically looks for information like that. It says "to
 16 produce rAAV particles -- I'm referring to a section
 17 calls cells in production of the rAAV delta 3788 on
 18 page 7 using Sarepta numbering.
 19 There's midway through or perhaps the second
 20 sentence to produce rAAV particles, the plasmid, and had
 21 it describes the micro-dystrophin construct. Was
 22 co-transfected with a helper plasmid PDG to 293 cells.

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Page 345 1 So I'm not seeing which serotype based on that 2 information they utilized. 3 Q. In the preceding section of the methods, it 4 talks about planking terminal repeats of AAV serotype 2. 5 Do you see that? 6 A. Are you describing generation of the -- 7 Q. Mm-hmm. 8 A. Yes. 9 Q. Yes. 10 A. It describes, yes, flanking internal -- 11 terminal repeats ITRs of AAV serotype 2. 12 Q. But that does not necessarily mean they used 13 the AAV2 capsid is that fair? 14 A. As we discussed earlier as you indicated it's 15 possible to be able to fuse together genetically a 16 capsid sequence with a -- or rather, sorry, a minigene 17 with ITRs that are used with a different capsid sequence 18 pseudotyping is how we described it. 19 Q. Okay. If we go back to the discussion section 20 of Fabb which is on prior page, page 6 of the Fabb 21 reference Exhibit 1010? 22 A. Sure yes.	Page 346 1 Q. The very end of the discussion right before 2 the materials and methods section there's another 3 mention of several AAV vectors in a sentence that starts 4 furthermore recent observations? 5 A. All right. Let me read that had paragraph. 6 Q. Mm-hmm. 7 A. I'm seeing that yes the sentence beginning 8 with furthermore. 9 Q. Right. And in that sentence, Fabb mentions 10 that recent observations have shown that AAV vectors 11 based upon alternative capsid serotypes particularly 12 Type 1 but also Types 3 and 5 can increase levels of 13 protein production by 100 to one thousandfold. 14 A. Ave yes that's what the passage reads and it 15 relies upon a reference 64 for that information. 16 Q. All right. And so Fabb doesn't -- the only 17 AAV serotypes that Fabb mentions are AAVs 1, 2, 3, and 5 18 anywhere in the publication? 19 ATTORNEY WILSON: Object to form. 20 THE WITNESS: At least within the materials 21 and methods didn't mention AAV2 and you highlighted 22 places where it mentions 1, 3, and 5. I would have to
Page 347 1 reread the rest of the publication to determine whether 2 AAV2 or serotypes other than 1, 3, and 5 are explicitly 3 mentioned. 4 BY ATTORNEY MORRISON: 5 Q. Okay. Let's talk about those four serotypes. 6 Is it fair to say that you didn't do any 7 alignment of those serotypes against rh.10 or AAV8 the 8 alignments you did are in 1008 to 1020? 9 ATTORNEY WILSON: Object to form. 10 THE WITNESS: Haven't done alignments between 11 AAV1, 3, 5, or you also brought up 2. 12 BY ATTORNEY MORRISON: 13 Q. Mm-hmm. 14 A. With AAV8 or rh.10. 15 Q. Okay. 16 A. Oh, actually, let me amend that. There's, I 17 believe, in the exhibit where I talked about the Xie 18 numbering, you know, given the unfortunate 137 amino 19 acid discrepancy between VP numbering -- VP1 numbering 20 versus VP2 numbering I did do an alignment between 21 AAV -- I can find it. Certainly between AAV2 and rh.10 22 so I could correct the numbering to Xie.	Page 348 1 Q. And we discussed already that at the position 2 that would correspond to position 8 -- excuse me 665 in 3 rh.10 that position in AAV2 is also a serine; right? 4 A. That is correct, yes. I'm looking at now 5 Exhibit 1023 which is the table of surface residues and 6 that shows that, yes, correct. Position 665 is a 7 certain in rh.10 and appears to be a certain in AAV2 at 8 the corresponding position 662. 9 Q. And did you look at what amino acid is at 10 that -- at a corresponding position in AAVs 1, 3, or 5? 11 ATTORNEY WILSON: Object to form. 12 THE WITNESS: So I -- as we mentioned a second 13 ago, I didn't do an alignment between rh.10 and R -- and 14 AAV as you mentioned 3 and 5. 15 BY ATTORNEY MORRISON: 16 Q. Okay. And Fabb does not mention AAVrh.10 or 17 AAV8; right? 18 ATTORNEY WILSON: Object to form. 19 THE WITNESS: I could take a look as we 20 mentioned or as we indicated a second ago, the only 21 three serotypes that so far I've seen are 1, 3, and 5 22 mentioned within Fabb but again I'm happy to sit down

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1 and read the publication to ski if other certificates
 2 are mention.
 3 BY ATTORNEY MORRISON:
 4 **Q. Doctor, and you don't mention that in your**
 5 **declaration either you don't say Fabb talks about**
 6 **AAVrh.10 or AAV8?**
 7 A. I don't describe Fabb, you know, talking about
 8 rh.10 or AAV8.
 9 **Q. Okay. We talked about earlier about -- and I**
 10 **want to the go back to ground one for a moment. And so**
 11 **if you could turn in your declaration to ground 1 which**
 12 **begins on page 74 of your declaration which is page 81**
 13 **in the Sarepta numbering?**
 14 A. I'm at ground 1.
 15 **Q. And we talked about where in your declaration**
 16 **you talked about targeting muscle.**
 17 **Do you recall that will discussion much, much**
 18 **earlier today?**
 19 A. There was a discussion of muscle within the
 20 '772 publication, and we spent some time going through
 21 the data within 772 and that taught the exemplary nature
 22 of rh.10 within muscle.

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1 **Q. And I think I asked you, and you said "I'd**
 2 **have to go through every paragraph," where you talked**
 3 **about that in your declaration.**
 4 **Do you remember that conversation?**
 5 A. I do.
 6 **Q. Okay. So I want to just look through your**
 7 **analysis in ground 1 and talk about where you talk about**
 8 **muscle.**
 9 **And so in -- so ground 1 starts at**
 10 **paragraph 194.**
 11 **Do you see that?**
 12 A. I'm at paragraph 194.
 13 **Q. Okay. And paragraph 194 is just a summary**
 14 **paragraph is that fair summary of your overall opinion?**
 15 A. That's correct.
 16 **Q. Okay. And paragraph 195 is just talking about**
 17 **the disclosure of a recombinant adeno-associated virus**
 18 **in the '772 publication; right?**
 19 A. That's correct.
 20 **Q. And you don't talk about targeting muscle in**
 21 **paragraph 195; right?**
 22 A. Within that particular paragraph, I don't talk

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1 about targeting muscle.
 2 **Q. And the same is true for paragraph 196; right?**
 3 A. In paragraph 196, I don't discuss muscle.
 4 **Q. And the same is true for paragraph 197? You**
 5 **don't discuss muscle?**
 6 A. In paragraph 197, muscle is not mentioned;
 7 correct.
 8 **Q. And the same is true in paragraph 198 muscle**
 9 **is not mentioned; right?**
 10 A. That is correct.
 11 **Q. And same is true in paragraph 199 muscle is**
 12 **not mentioned?**
 13 A. That's correct. Muscle is not mentioned in 9.
 14 **Q. And in 200 the same is true muscle is not**
 15 **mentioned?**
 16 A. 200 doesn't mention muscle.
 17 **Q. Nor does 201?**
 18 A. 201 doesn't mention muscle.
 19 **Q. Nor does 202 mention muscle; correct?**
 20 A. 202 does not mention muscle.
 21 **Q. And 203 does not mention muscle?**
 22 A. 203 does not discuss muscle.

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1 **Q. And 204 does not discuss muscle?**
 2 A. 204 doesn't discuss muscle.
 3 **Q. And 205 does not discuss muscle?**
 4 A. The actual content of 205 does not discuss
 5 muscle approximately but I'll mention as well that a lot
 6 of these passages refer to rh.10, refer to, you know,
 7 AAVs that earlier on within the declaration did discuss
 8 muscle.
 9 **Q. Okay. But this -- you'd great word "muscle"**
 10 **isn't in 205; right?**
 11 A. 205 doesn't discuss muscle. It does refer to,
 12 you know, for example, rh.10 and to the 772 publication
 13 wisdom discuss the performance of rh.10 within muscle.
 14 **Q. Right but in 205 you're just talking about a**
 15 **sequence alignment you did; right?**
 16 ATTORNEY WILSON: Object to form.
 17 THE WITNESS: 205 discusses rh.10 and
 18 discusses sequence alignment.
 19 BY ATTORNEY MORRISON:
 20 **Q. Okay.**
 21 A. However, you know, as I mentioned earlier it's
 22 inherent earlier throughout the entire declaration that

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1 rh.10 is a superior vector within muscle.
 2 **Q. All right. 206 the word "muscle" does not**
 3 **appear?**
 4 A. In 206 muscle is not present.
 5 **Q. The word "muscle" does not appear in**
 6 **paragraph 207?**
 7 A. Yes, muscle doesn't appear in paragraph 207.
 8 **Q. Okay. And the word "muscle" I'm going to skip**
 9 **208 because you do talk about muscle in 208; right?**
 10 A. In 208 I come back to that very strong
 11 guidance from the '772 publication that describes the
 12 performance of clone 44.2 namely rh.10 in liver and
 13 muscle directed gene transfer. Describes it as
 14 outstanding.
 15 **Q. Okay. And in 209 you don't discuss muscle?**
 16 **The word "muscle" does not appear?**
 17 A. Muscle is not in 209.
 18 **Q. And in 210 the word "muscle" doesn't appear?**
 19 A. In 210, muscle doesn't appear.
 20 **Q. Ask it doesn't appear in 211 either the word**
 21 **"muscle" does not appear?**
 22 A. That's correct 211 teaches that concept of

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1 making individual amino acids to be able to do confer a
 2 new function.
 3 **Q. Mm-hmm. And in 212 the word "muscle" doesn't**
 4 **appear.**
 5 A. Paragraph 212 doesn't mention muscle.
 6 **Q. Okay. And paragraph 213 doesn't mention**
 7 **muscle?**
 8 A. 213 discusses this concept of making single
 9 amino acid mutations based on an alignment
 10 and substitutions within nonconserved sequences of AAV8
 11 and rh.10, and following the guidance of '772 as a way
 12 to create an artificial AAV serotype.
 13 And it does not mention muscle.
 14 **Q. Okay. And then I'm going to try to group some**
 15 **of these together but you take as much time as you'd**
 16 **like took read it through them the next sex which is**
 17 **paragraphs 214 through 226 discusses Dr. Leone's expert**
 18 **report and none of those paragraphs 214 through 226**
 19 **mention muscle.**
 20 And please take all the time you'd like to
 21 read through it.
 22 A. Thank you.

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1 I've finished reading through paragraph 26,
 2 and, yes, the region I just read with your guidance did
 3 not contain muscle or discuss muscle. It discusses
 4 rh.10 which has superior tropism to muscle.
 5 **Q. Mm-hmm, but you don't mention the word**
 6 **"muscle" in any of those paragraphs fair?**
 7 ATTORNEY WILSON: Object to form.
 8 THE WITNESS: Within those paragraphs that I
 9 just read through, the word "muscle" isn't mentioned;
 10 however, that's understood to be a part of the superior
 11 properties of rh.10.
 12 BY ATTORNEY MORRISON:
 13 **Q. Okay. And in the next section which is**
 14 **paragraphs 227 through 233, you discuss reasonable**
 15 **expectation of success; is that right?**
 16 A. You said 227 through --
 17 **Q. 233.**
 18 A. 233?
 19 227 through 233 all lie under the heading of
 20 "Reasonable Expectation of Success."
 21 **Q. And the word "muscle" does not appear in any**
 22 **of paragraphs 227 through 233? And, again, take your**

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1 **time to read through them.**
 2 A. Paragraphs 27 through 233 don't describe
 3 muscle specifically, but it does recite the fact that
 4 the '772 publication states that assays for determining
 5 the suitability of various AAV vector constructs in
 6 different tissues would have been well known to a POSA
 7 and can 72 in describing such materials and discussing
 8 assays certainly very prominently mentions muscle liver
 9 as well as lung in the context of rh.10.
 10 **Q. But you agree with me that the word "muscle"**
 11 **doesn't appear in paragraphs 227 through 233; right?**
 12 ATTORNEY WILSON: Object to form.
 13 THE WITNESS: I read through 227 and 2 --
 14 through 233. I do see the word "muscle," but it does
 15 refer to the capacity of AAVs to be able to infect
 16 various tissues and inherent within that is muscle.
 17 BY ATTORNEY MORRISON:
 18 **Q. Mm-hmm. Okay. The next section of your**
 19 **declaration is -- discusses claim 3 of the 274 patent;**
 20 **right?**
 21 A. That's correct. The section B.
 22 **Q. Mm-hmm.**

89 (Pages 353 to 356)

Page 357

1 A. On page 90 at the top of it discusses claim 3.
 2 **Q. And paragraphs in and 235 discussed in claim 3**
 3 **don't include the word "muscle"; right?**
 4 A. Paragraphs in and 235 don't use the word
 5 "muscle."
 6 **Q. Okay and then next section, section C which is**
 7 **paragraphs 236 to 239 discusses claim 4 of the '274**
 8 **patent, and none of those paragraphs include the word**
 9 **"muscle"? And, again, take your time to read them.**
 10 A. Are you saying 236 through 239, for
 11 clarification?
 12 **Q. I am. I am.**
 13 A. Thank you.
 14 This section describes the concept of
 15 pseudotyping use an I it estimate R1 serotype with a
 16 capsid of a different serotype so within that discussion
 17 it doesn't refer to muscle.
 18 **Q. Okay. And section D which is paragraphs 240**
 19 **through 242 is about -- it adds the requirement of a**
 20 **physiologically compatibility carrier; is that right?**
 21 A. That's what the area yes but the language
 22 starting with the bold letter D talks about

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1 physiologically compatible carrier.
 2 **Q. And that's claim 5 of the '274 patent?**
 3 A. Yes. That's claim 5 of the '274 patent not.
 4 **Q. And the paragraphs under that Section 240**
 5 **through 242 don't discuss -- don't use the word**
 6 **"muscle"?**
 7 A. Paragraphs 240 through 224 talk about the
 8 buffers and salts that are used for storing AAV so they
 9 don't refer to muscle.
 10 **Q. Okay. And section E is -- relates to claim 6**
 11 **of the '274 patent, and that's paragraphs 243 through**
 12 **247. And, again, those do not discuss or use the word**
 13 **"muscle"; correct?**
 14 A. Those paragraphs from 243 to 247 describe a
 15 number of minigenes or a number of cDNAs that could
 16 potentially be encoded inside an AAV.
 17 So they do not discuss muscle.
 18 **Q. And then, finally, section F talks about**
 19 **secondary considerations of nonobviousness; is that**
 20 **right?**
 21 A. That's correct that's the title forgets
 22 section.

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1 **Q. And that section spans 248 -- paragraphs 248**
 2 **through 251 and none of those paragraphs use the word**
 3 **"muscle"; correct?**
 4 A. Section or 248 through 251 discussed, as you
 5 mentioned, secondary considerations that may be relevant
 6 to obviousness.
 7 And they do not mention muscle.
 8 **Q. Okay. You said earlier that dystrophin is**
 9 **expressed in many tissues including muscle or something**
 10 **to that effect? Do I have that about right?**
 11 A. Statement earlier yes.
 12 **Q. Would you agree with me that dystrophin is**
 13 **expressed primarily in muscle or predominantly in**
 14 **muscle?**
 15 ATTORNEY WILSON: Object to form.
 16 THE WITNESS: It was well known back at that
 17 time. The dystrophin is expressed throughout the entire
 18 body there's dystrophin in the brain in the cerebellum,
 19 in the retina, in muscle, in liver, throughout the
 20 entire body. So at that time -- or actually I'm unaware
 21 of whether somebody's done a quantitative analysis of
 22 where it's expressed more than other places, but it is

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1 expressed throughout the entire body.
 2 BY ATTORNEY MORRISON:
 3 **Q. Okay. So is it fair to say that you wouldn't**
 4 **agree with me that it's expressed predominantly in**
 5 **muscle?**
 6 ATTORNEY WILSON: Object to form.
 7 THE WITNESS: I would need to look on the
 8 other referenced to assess what the word predominantly
 9 means and get a little bit more specificity about that
 10 word.
 11 ATTORNEY MORRISON: Okay. Why don't we take a
 12 quick break so I can confer with my team and -- just for
 13 a few minutes.
 14 ATTORNEY WILSON: Okay. We'll step out.
 15 (A break was taken.)
 16 ATTORNEY MORRISON: So subject to any
 17 questions from your counsel, I don't have any further
 18 questions for you at this time.
 19 ATTORNEY WILSON: Okay. And I don't have any
 20 further -- I don't have any questions for you.
 21 ATTORNEY MORRISON: Okay.
 22 ATTORNEY WILSON: So we can go off the record.
 (Deposition concluded at 5:43 P.M.)

90 (Pages 357 to 360)

Page 361 1 TRANSCRIPT ORDERS 2 ATTORNEY MORRISON: Regular delivery. Yes, 3 rough. 4 ATTORNEY WILSON: Same order. Rough, regular 5 delivery. 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	Page 362 1 CERTIFICATE OF SHORTHAND REPORTER 2 3 I, Michael P. Hensley, Registered Diplomate 4 Reporter for the State of California, CSR No. 14114, the 5 officer before whom the foregoing deposition was taken, 6 do hereby certify that the foregoing transcript is a 7 true and correct record of the testimony given; that 8 said testimony was taken by me stenographically and 9 thereafter reduced to typewriting under my direction; 10 that reading and signing was not requested; and that I 11 am neither counsel for, related to, nor employed by any 12 of the parties to this case and have no interest, 13 financial or otherwise, in its outcome. 14 15 16 17 18 19 20 21 22 _____ Michael P. Hensley, CSR, RDR
Page 363 1 Dr. David V. Schaffer, c/o QUINN EMANUEL URQUHART & SULLIVAN, LLP 2 51 Madison Avenue, 22nd Floor New York, New York 10010 3 Case: Sarepta Therapeutics, Inc. v. The Trustees of the University of Pennsylvania et al. 4 Date of deposition: November 1, 2024 Deponent: Dr. David V. Schaffer 5 6 Please be advised that the transcript in the above referenced matter is now complete and ready for signature. 7 The deponent may come to this office to sign the transcript, 8 a copy may be purchased for the witness to review and sign, 9 or the deponent and/or counsel may waive the option of 10 signing. Please advise us of the option selected. 11 Please forward the errata sheet and the original signed 12 signature page to counsel noticing the deposition, noting the 13 applicable time period allowed for such by the governing 14 Rules of Procedure. If you have any questions, please do 15 not hesitate to call our office at (202)-232-0646. 16 17 18 Sincerely, 19 Digital Evidence Group 20 Copyright 2024 Digital Evidence Group 21 Copying is forbidden, including electronically, absent 22 express written consent.	Page 364 1 Digital Evidence Group, L.L.C. 1730 M Street, NW, Suite 812 2 Washington, D.C. 20036 (202) 232-0646 3 4 SIGNATURE PAGE Case: Sarepta Therapeutics, Inc. v. The Trustees of the University of Pennsylvania et al. 5 Witness Name: Dr. David V. Schaffer Deposition Date: November 1, 2024 6 I do hereby acknowledge that I have read 7 and examined the foregoing pages 8 of the transcript of my deposition and that: 9 (Check appropriate box): () The same is a true, correct and 10 complete transcription of the answers given by me to the questions therein recorded. 11 () Except for the changes noted in the attached Errata Sheet, the same is a true, 12 correct and complete transcription of the 13 answers given by me to the questions therein 14 recorded. 15 16 _____ 17 DATE WITNESS SIGNATURE 18 19 20 21 _____ 22 DATE NOTARY

Page 365

1 Digital Evidence Group, LLC
2 1730 M Street, NW, Suite 812
3 Washington, D.C. 20036
4 (202)232-0646
5

6 ERRATA SHEET
7

8 Case: Sarepta Therapeutics, Inc. v. The Trustees of the University of
Pennsylvania et al.

9 Witness Name: Dr. David V. Schaffer

10 Deposition Date: November 1, 2024

11 Page No. Line No. Change
12
13
14
15
16
17
18
19
20

21 _____
22 Signature Date

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ERRATA SHEET

Deposition of Dr. David V. Schaffer

Sarepta Therapeutics, Inc. v. The Trustees of the University of Pennsylvania et al.,
IPR2024-00580, Patent 11,680,274 B2

Deposition Date: November 1, 2024

Page : Line	Change From	Change To	Reason
15:2	in personal	no personal	mis-transcription
16:5	REGENEX	Regenx	mis-transcription
21:5	and ended up	, and it ended up	typographical error
21:6	somewhat lengthy	a somewhat lengthy	typographical error
25:15	SS.SNODI	Snowdy	mis-transcription
26:5	it was	it was the	typographical error
31:11	engineering, the	engineering the	typographical error
34:10	about definition	about the definition	mis-transcription
35:11	material. To	material – to	typographical error
42:16	Mike Metzger	Mike Metzker	typographical error
45:4	irritative	iterative	mis-transcription
46:18	rather a	rather than a	mis-transcription
53:22	antigen	an antigen	typographical error
55:5	affectivities	infectivities	mis-transcription
55:22	overt	over	typographical error
56:12	retirement	requirement	mis-transcription
57:21-22	capabilities of realm	realm of capabilities	mis-transcription
58:9	of AV9.	of AAV9.	typographical error
58:9	AV9 goes	AAV9 goes	typographical error
62:10	paragraph start	paragraph starts	typographical error
62:11	Progress-limiting	A progress-limiting	mis-transcription
63:8	saying	saying is,	typographical error
66:20	stand	stands	typographical error
67:1	inside –	inside the	typographical error

Page : Line	Change From	Change To	Reason
67:10	end terminus	N-terminus	mis-transcription
67:13	end terminus	N-terminus	mis-transcription
67:18	end terminus	N-terminus	mis-transcription
67:19-20	from 138 amino acids to 202 amino acids	from amino acid 138 to amino acid 202	mis-transcription
67:20	end terminus	N-terminus	mis-transcription
68:1	VP1, '2, and '3	VP1, 2, and 3	typographical error
68:4	1 to 10 to 10	1 to 1 to 10	typographical error
69:7	nuclear limit	nuclear lumen	mis-transcription
70:10	timing where	timing when	mis-transcription
73:1	that virus	that the virus	typographical error
73:2	confirmation	conformation	mis-transcription
73:11	confirmation	conformation	mis-transcription
73:12	confirmation	conformation	mis-transcription
73:19	by the various	by the virus	mis-transcription
73:20	under difference	under different	mis-transcription
76:17	to go	to go through	typographical error
77:2	the route of the	the route of	typographical error
77:21	be able to say	be able to – say	typographical error
77:22	earlier,	earlier –	typographical error
79:4	has go	has to go	typographical error
80:18	that's determined into	that's a determinant of	mis-transcription
81:8	determinant to	determinant of	mis-transcription
84:22	their	there are	typographical error
85:1	They're	There are	typographical error
98:21	Xie – G.	Xie.	typographical error
102:15	related total	related to	mis-transcription
102:19	presence	present	mis-transcription
103:4	In cases,	In some cases,	mis-transcription
103:5	no	into	mis-transcription

Page : Line	Change From	Change To	Reason
103:13	presence	present	mis-transcription
107:21	out of the Dr.	out of Dr.	typographical error
109:7	pretty	a pretty	mis-transcription
110:2	AAV6	six AAVs	mis-transcription
111:3	Oliveira	Alvira	typographical error
111:4	Oliveira	Alvira	typographical error
117:5	reported	repeated	mis-transcription
117:14	and the	and	typographical error
121:1	opening	open	typographical error
122:8	data that it	data that are	typographical error
125:4	that's why	that's where	typographical error
128:8	The inventors	The inventors'	typographical error
128:16	some rh.10	rh.10	typographical error
129:6	specifications	specification	typographical error
131:2	know to be	have to be	mis-transcription
131:6	AAV2s	AAVs	typographical error
137:3	reserve	preserve	mis-transcription
140:5	relatedly	repeatedly	mis-transcription
142:10	patents	patent	typographical error
142:10	specification of the patents	specification of the patent	typographical error
146:12	provided answer	provided my answer	mis-transcription
146:17	proved my answer	provided my answer	mis-transcription
153:22	MUT through	<i>mut1</i> through	typographical error
155:5	D2A	D to A	mis-transcription
155:12	for a MUT 1	for <i>mut1</i>	mis-transcription
158:12	chained	changed	mis-transcription
158:18	would a	would be a	typographical error
160:11	immunities	mutants	mis-transcription
167:4	MUT	<i>mut</i>	typographical error
167:6	MUT	<i>mut</i>	typographical error

Page : Line	Change From	Change To	Reason
169:17	B ning	Büning	typographical error
170:11	B ning	Büning	typographical error
170:12	B ning	Büning	typographical error
172:2	a view	in view	typographical error
174:13	Generic Modification	Genetic Modification	mis-transcription
181:8	engineers	engineering	mis-transcription
181:11	evolution a technology	evolution is a technology	typographical error
181:18	alternate cert	alternative	mis-transcription
183:19	years or; so I'm	years or so; I'm	typographical error
203:12	but is AAV8	but AAV8	mis-transcription
205:6	a accurate	an accurate	typographical error
208:1	on any	not any	mis-transcription
208:12	naturalized	neutralized	mis-transcription
209:22	Clarification. I said --	I said --	mis-transcription
210:11	The Example 7	Example 7	mis-transcription
216:6	is the equal	is equal	mis-transcription
232:9	deteriorate confer binding	confer binding	mis-transcription
237:2	refer	prefer	mis-transcription
237:4	a accurate	an accurate	typographical error
259:1	at a time	at that time	mis-transcription
265:6	hemology	homology	mis-transcription
265:14	hemology	homology	mis-transcription
265:15	hemology	homology	mis-transcription
265:17	hemology	homology	mis-transcription
266:12	hemology	homology	mis-transcription
267:9	hemology	homology	mis-transcription
268:14	hemology	homology	mis-transcription
268:17	hemology	homology	mis-transcription
269:1	hemology	homology	mis-transcription
269:4	hemology	homology	mis-transcription

Page : Line	Change From	Change To	Reason
269:8	hemology	homology	mis-transcription
269:11	hemology	homology	mis-transcription
269:19	hemology	homology	mis-transcription
270:11	Hemology	Homology	mis-transcription
291:10	session some point	session at some point	mis-transcription
291:22	a analysis	an analysis	typographical error
292:19	while	after	mis-transcription
306:3	transaction	transduction	mis-transcription
306:9	transaction	transduction	mis-transcription
316:18	phosphorylate residue	phosphorylate the residue	typographical error
325:21	importance	import	mis-transcription
329:2	sera	serine	mis-transcription
331:20	ether	either	mis-transcription
332:20	as assay	assay	mis-transcription
333:1	figure and figure 5	figure 2 and figure 5	mis-transcription
333:4-5	it's likely interpretation	it's a likely interpretation	mis-transcription
338:1	am only	am not	mis-transcription
338:1	familiar the	familiar with the	mis-transcription
339:4	familiar the	familiar with the	mis-transcription
339:5	stair	software	mis-transcription
339:16	thresh hold	threshold	typographical error
339:17	classified yes	classified as	mis-transcription
343:5	144 kill Dalton	144 kilo-Dalton	mis-transcription
343:10	phrase namely. The	phrase, namely, the	mis-transcription
343:10	construct does not	construct, and does not	mis-transcription
343:13	dystrophin a protein	dystrophin is a protein	mis-transcription
344:17	calls cells in production of the rAAV delta 3788	called "Cells and production of rAAV delta 3788"	mis-transcription
344:20	to produce rAAV particles, the plasmid	"To produce rAAV particles, the plasmid" --	mis-transcription

Page : Line	Change From	Change To	Reason
344:20-21	and had it	and it	mis-transcription
344:21-22	construct. Was co-transfected with a helper plasmid PDG to 293 cells.	construct "was co-transfected with a helper plasmid pDG into 293 cells."	mis-transcription
345:4	planking	flanking	mis-transcription
345:17-18	sequence pseudotyping	sequence. Pseudotyping	typographical error
346:14	Ave yes	Yes,	mis-transcription
346:21	didn't mention	it mentions	mis-transcription
348:7	certain in rh.10	serine in rh.10	mis-transcription
348:7	certain in AAV2	serine in AAV2	mis-transcription
349:1	ski	see	mis-transcription
349:1	certificates	serotypes	mis-transcription
349:2	mention	mentioned	mis-transcription
351:13	9	199	mis-transcription
352:5	muscle approximately	muscle explicitly	mis-transcription
352:9	great	agree the	mis-transcription
352:12	772	'772	typographical error
352:13	wisdom discuss	which discusses	mis-transcription
354:16	sex	section	mis-transcription
355:1	26	226	mis-transcription
356:2	27	227	mis-transcription
356:7	and can 72	and	mis-transcription
356:8-9	muscle liver as well as lung	muscle, liver, as well as lung,	typographical error
356:14	do see	do not see	mis-transcription
357:2	in and 235	234 and 235	mis-transcription
357:4	in and 235	234 and 235	mis-transcription
357:15	use an I it estimate R1 serotype	using an ITR of one serotype	mis-transcription
357:21	what the area yes but	what the area is, but	mis-transcription

Page : Line	Change From	Change To	Reason
358:3	patent not.	patent.	mis-transcription
358:7	240 through 224	240 through 242	mis-transcription
358:21-22	correct that's the title forgets section	correct; that's the title for this section.	mis-transcription
359:4	Section or 248	Section 248	mis-transcription
359:11	Statement earlier yes.	I recall that statement earlier, yes.	mis-transcription
359:17	time. The dystrophin is	time that dystrophin is	mis-transcription
359:18	body there's	body. There's	typographical error
360:7-8	on the other referenced	at the references	mis-transcription

I declare under penalty of perjury that I have reviewed the transcript of the above-described deposition, and that the same is true and accurate, save for changes and corrections indicated above, with the understanding that I offer these changes as if still under oath.

A handwritten signature in cursive script, appearing to read "Paul Schaffer", written in black ink.

December 11, 2024

DATE

SIGNATURE

A				
A.4 297:14	239:20,22	273:3 275:1,5	134:6,17	110:7 112:18
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