

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

THE TRUSTEES OF THE UNIVERSITY
OF PENNSYLVANIA and REGENXBIO
INC.,

Plaintiff,

v.

SAREPTA THERAPEUTICS, INC. and
SAREPTA THERAPEUTICS THREE, LLC,

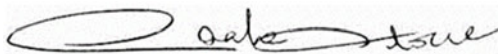
Defendant.

C.A. No. 20-1226 (RGA)

JURY TRIAL DEMAND

EXPERT REBUTTAL REPORT OF PAOLA LEONE

Dated: May 26, 2023

By: 

Paola Leone

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At the request of counsel for REGENXBIO, Inc. and The Trustees of the University of Pennsylvania, I submit the following report.

I. SUMMARY OF OPINIONS AND EXPECTED TESTIMONY

1. I have been asked by counsel for REGENXBIO, Inc. and The Trustees of the University of Pennsylvania to respond to the expert reports of Drs. Kay, Quackenbush, and Rubanyi, which I understand were all served by Sarepta on April 28, 2023. Based on my review of those reports, I understand that Drs. Quackenbush and Rubanyi opine that the '617 patent is invalid for indefiniteness, while Dr. Kay opines that the '617 patent is invalid because it covers subject matter that is not patentable, because the claims are obvious, and because it does not contain adequate written description and does not enable a person of ordinary skill in the art to make and use the patented inventions. I disagree with all of these opinions, as I discuss in detail in this report.

2. In my opinion, the claims of the '617 patent do not cover naturally occurring subject matter, and Dr. Kay's opinions to the contrary do not focus on the language of the claims as a whole. The claims of the '617 patent require a cultured host cell containing a recombinant nucleic acid molecule with a particular sequence, and a heterologous non-AAV sequence, among other things. Such a cultured host cell is not and cannot be naturally occurring.

3. I also disagree with Dr. Kay that the claims of the '617 patent are obvious. Like with his analysis of patentable subject matter, Dr. Kay's obviousness analysis does not focus on the claims, and instead, looks generally at whether the techniques used by the inventors had previously been used. I have reviewed the prior art that Dr. Kay cites, and it does not disclose many of the claim elements of the asserted claims of the '617 patent. For that reason and the reasons I describe below, the inventions described in the claims of the '617 patent would not have been obvious to a person of ordinary skill in the art.

cannot form a capsid on their own (and therefore cannot have any of the functions of an intact capsid), the '617 patent's claims should not be read as limited to any functional requirements beyond encoding for a protein that if expressed, may be used to form an AAV capsid.

C. Patentable Subject Matter

66. I have reviewed Dr. Kay's expert report and his opinions that the asserted claims of the '617 patent are invalid because they claim naturally occurring, non-patentable subject matter. I disagree.

67. There are two types of asserted claims of the '617 patent. Claims 1, 3, and 5 (which are printed in full above at ¶ 51), and the claims that depend from them, claim "cultured host cells" containing a recombinant nucleic acid molecule that (1) encodes a vp1, vp2, or vp3 capsid protein comprising a sequence of certain amino acids of SEQ ID NO: 81 or a sequence at least 95% identical to the full length of that sequence, and (2) contains a heterologous non-AAV sequence. The dependent claims contain additional limitations.

68. Claim 7 (which is printed in full above at ¶ 51), and the claims that depend from it, claims "cultured host cells" containing a recombinant nucleic acid molecule that includes (1) specified nucleotide sequences from SEQ ID NO: 59 or sequences at least 95% identical to those specified sequences, and (2) a heterologous non-AAV sequence. Again, the dependent claims contain additional limitations.

69. According to Dr. Kay, "[a]t the most fundamental level, the claims are directed to amino acid and nucleic acid sequences encoding the capsid protein of the naturally occurring variant rh.10 and other naturally occurring AAVs." (Kay Opening Report at ¶ 127.) Dr. Kay also states that "[c]laim 1 is expressly directed to the AAV rh.10 vp1 capsid protein sequence predicted from the rh.10 nucleotide sequence." (Kay Opening Report at ¶ 130.) He characterizes claim 7 similarly, stating that it "recites portions of the rh.10 DNA sequence, SEQ

ID NO: 59 that was actually cloned from the rhesus monkey liver tissue.” (Kay Opening Report at ¶ 133.) I do not agree with these characterizations.

70. None of the asserted claims claim the amino acid and nucleic acid sequences that encode the capsid protein for AAVrh10 or other AAVs alone. Instead, they claim “cultured host cells” that contain recombinant nucleic acid molecules that encode capsid proteins (or, in the case of claim 7, include particular nucleic acid sequences) along with heterologous non-AAV sequences.

71. These cultured host cells do not occur in nature. And Dr. Kay never says that the *cultured host cells*, which are the thing that the asserted claims cover, occur in nature. Instead, his report focuses only on the sequences themselves, which is not what the asserted claims cover. I understand that the analysis for whether a claim is directed to a natural product is supposed to look at the claim as a whole, not just to one part of the claim.

72. In my opinion, there are multiple parts of the asserted claims that show that the claimed cultured host cells are not naturally occurring.

73. First, the fact that the asserted claims require the cultured host cells to contain a “recombinant nucleic acid molecule” means that they are not naturally occurring.

74. “Recombinant” is generally understood in the field to refer to a cell or organism with a combination of generic material from multiple sources. For example, *Taber’s Cyclopedic Medical Dictionary* defines “recombinant” as follows: “In genetics and molecular biology, pert. to genetic material combined from different sources.”² And it defines “recombinant DNA” as “Segments of DNA from one organism artificially manipulated or inserted into the DNA of

² Taber’s Online, “Recombinant”, <https://www.tabers.com/tabersonline/view/Tabers-Dictionary/762007/all/recombinant>.

another organism through gene splicing.”³ The reference to “artificially” in the definition suggests that those in the field understand that “recombinant” nucleic acids or “recombinant” DNA refers to something that does not occur naturally.

75. I understand that Christopher Campbell, a biologist who is an employee of Sarepta, testified in his deposition that a “recombinant” mammalian cell line means a cell line that has been “genetically altered to produce the biological therapeutic.” (Campbell Depo. Tr. at 26-29.) He also agreed that recombinant mammalian cell lines are not naturally occurring and that it is “accurate” that those cell lines “are created by scientists in a laboratory and don’t exist in nature before the scientist created it.” (Campbell Depo. Tr. at 27-28.) This testimony is consistent with my understanding.

76. Second, the fact that the asserted claims require the recombinant nucleic acid in the cultured host cells to contain a “heterologous non-AAV sequence” means that they are not naturally occurring.

77. The asserted claims all require that the cultured host cell contain a recombinant nucleic acid molecule encoding the specified AAV capsid protein and a “heterologous non-AAV sequence.” “Heterologous” is generally understood to mean coming from a different species. So the inclusion of a “heterologous non-AAV” sequence as part of the recombinant nucleic acid molecule in the cultured host cells required in the claims again means those cells are not and cannot be naturally occurring—they must include a recombinant nucleic acid that encodes an AAV capsid as well as a sequence from something other than AAV. This is not a combination that occurs in nature; it is and must be created in a laboratory.

³ Taber’s Online, “Recombinant DNA”, <https://www.tabers.com/tabersonline/view/Tabers-Dictionary/735699/all/DNA>.

78. For example, [REDACTED] that Sarepta uses to make its plasmids contain recombinant nucleic acid molecules that include the sequences in the '617 patent's claims, a heterologous non-AAV sequence, as well as the nucleic acid sequences encoding the AAV2 rep protein, among other sequences. (Opening Report, ¶¶ 79-304; Campbell Depo Tr. at 148:4-21, 150:18-151:4.)

79. Third, the "cultured host cell" requirement also shows that the asserted claims are not claiming a naturally occurring product. The "cultured host cells" are created in a laboratory, using non-naturally occurring materials such as cell culture media. These are not and cannot be cells that are simply isolated from a natural source.

80. In addition to the cultured host cells covered by the asserted claims not being something that occurs in nature, they also have entirely different characteristics, function, and use than the amino acid and nucleotide sequences that encode AAVrh10 (or sequences at least 95% identical to it). The amino acid and nucleotide sequences on their own may be used for sequence analysis or potentially as primers, but they cannot be used on their own, without additional components, to manufacture gene therapy vectors.

81. As I described in detail in my opening report, the cultured host cells covered by the asserted claims are used as part of the triple transfection process to prepare rAAV vectors for gene therapy. (Opening Report at ¶¶ 48-57.) The AAVrh10 sequences are part of the rep/cap plasmids that are incorporated into those cultured host cells, but they are far from the only part of the host cell. The use of the cultured host cells as part of the triple transfection process is not a function that naturally occurring amino acid or nucleotide sequences of AAVrh10 can do on their own.

82. I have also reviewed the specification of the '617 patent in my analysis. Dr. Kay appears to believe that the way the invention is characterized in the specification supports that the asserted claims cover a natural product and are not patentable. I disagree.

83. While the specification does rightly discuss the methods used by the inventors to detect and isolate new AAV sequences, which were new and innovative, the specification is not limited to those discussions. I understand that patent specifications can describe different aspects of an invention and even multiple different inventions. And the specification here does so. In addition to the new methods of identifying new AAV sequences, the specification describes uses for those new sequences being part of the invention.

84. For example, it explains that “each of these [AAV] fragments may be readily utilized in a variety of vector systems and host cells. Such fragments may be used alone, in combination with other AAV sequences or fragments, or in combination with elements from other AAV or non-AAV viral sequences. In one particularly desirable embodiment, a vector contains the AAV cap and/or rep sequences of the invention.” ('617 patent at 3:49-56.) It goes on to further discuss that host cells and vectors that are part of the invention and to explain the advantages they provide: “The invention further provides nucleic acid molecules, gene delivery vectors, and host cells which contain the AAV sequences of the invention. As described herein, the vectors of the invention containing the AAV capsid proteins of the invention are particularly well suited for use in applications in which the neutralizing antibodies diminish the effectiveness of other AAV serotype based vectors, as well as other viral vectors. The rAAV vectors of the invention are particularly advantageous in rAAV readministration and repeat gene therapy.” ('617 patent at 4:56-67.)

85. Other portions of the specification, including at columns 22 to 24, also discuss the use of the rep/cap sequences in a cultured host cell. And it states that “[i]n a preferred embodiment, the host cell is one that has rep and cap stably transfected in the cell.” (’617 patent at 25:25-26.) In my opinion, the specification makes clear that cultured host cells that incorporate the new AAV sequences, including AAVrh10, are part of the invention.

86. I have also reviewed portions of the prosecution histories for the ’617 patent and earlier, related patents, and those also support that the cultured host cells that are claimed in the asserted claims are not naturally occurring.

87. During prosecution of the ’617 patent (U.S. Application No. 15/782,980), the examiner at one point rejected earlier versions of the claims that recited “host cells,” arguing that those claims were directed to natural products. (REGENX0006540-6549 at REGENX0006543.) The claims were amended to require “cultured host cells,” and the examiner dropped that rejection. (REGENX0006613-6620 at REGENX0006614.)

88. Also during prosecution of the ’617 patent, the examiner rejected earlier versions of the claims that did not claim cultured host cells and required that “wherein recombinant nucleic acid molecule does not contain AAV inverted terminal repeats” as naturally occurring subject matter. (REGENX0006540-6549 at REGENX0006544-6545.) After the claims were amended to specify that the recombinant nucleic acid molecule was a “plasmid,” that rejection was not made again. (REGENX0006690-6696 at REGENX0006691-6692.) And such a rejection was never made at all once the claims were amended to include a “heterologous non-AAV sequence,” such as the plasmids specified in dependent claims 22-25.

89. For all those reasons, I disagree with Dr. Kay that the asserted claims are claiming something that is a natural product. In my opinion, the cultured host cells covered by the asserted claims are not something that occurs in nature.

D. Obviousness

90. I have reviewed Dr. Kay's opinions that the asserted claims of the '617 patent are obvious. I disagree.

91. Dr. Kay cites prior art references, (a) through (r), in his report. I understand from his report and the Appendices A through R (corresponding to references (a) through (r)) that this is the primary prior art Dr. Kay relies on for his obviousness opinions. I address these prior art references below. Dr. Kay also cites other prior art references, which I also address below.

92. I understand from reading Dr. Kay's report that in his opinion, it would have been obvious, based on the prior art he cites, for persons of ordinary skill in the art to identify previously unknown AAV strains and genetically engineer constructs with them, using PCR and genetic engineering methods similar to the ones the inventors used and described in the '617 patent and their depositions. Dr. Kay states that based on the prior art, persons of ordinary skill in the art would have been motivated to do what the inventors did to make the inventions claimed in the '617 patent, and would have expected success in doing so. I do not agree.

93. In paragraphs 373 and 375 in his report, Dr. Kay summarizes his opinions, saying:

it would have been obvious ... to apply known PCR methods to identify nucleic acid sequences encoding the capsid protein of at least one variant of AAV that falls within the scope of each of the Asserted Claims, and to use conventional genetic engineering and recombinant engineering techniques to prepare cultured host cells containing a nucleic acid molecule encoding an AAV capsid protein for that variant, as set forth in the Asserted Claims

and that persons of ordinary skill in the art:

seeking to construct an AAV gene therapy vector would have been motivated to apply these methods to AAV, both to identify AAV strains of different serologies

various parts of the actual AAVrh10 reference sequences disclosed in the '617 patent. Dr. Metzker then discusses how Dr. Quackenbush runs sequence alignments in seven different programs, many of which use the length of Dr. Quackenbush's test sequences as the denominator in calculating percent identity. This results in large artificial differences in percent identity between programs, even where the alignment and number of matches identified by those programs is the same or highly similar, solely based on whether the programs use the denominator of the test sequence or the reference sequence to calculate percent identity. Dr. Metzker explains, consistent with how a person of ordinary skill in the art would approach these alignments, and consistent with the Court's claim construction, that if the correct denominator is used to calculate the percent identity in any of the programs Dr. Quackenbush used, the percent identities across the programs are consistent, even without altering the alignments that Dr. Quackenbush did. Dr. Metzker also identifies a large number of issues throughout Dr. Quackenbush's calculations, including numerous instances where Dr. Quackenbush conducts alignments in multiple ranges but then ignores portions of the results, skewing the percent identities significantly. I agree with Dr. Metzker's analysis and corrections of Dr. Quackenbush's alignments, and Dr. Metzker's opinions are consistent with mine discussed in this Report.

d. Sarepta's Experts' Patents and Cited Articles Support Definiteness

287. I note that both Dr. Kay and Sarepta have obtained patents claiming amino acid or nucleotide sequences with the same or similar language as the claims of the '617 patent, which Drs. Quackenbush and Rubanyi now state is indefinite. Some of these patents are also in the field of AAVs, while others concern adjacent technologies.

288. I understand that Dr. Kay is an inventor on patent 8,067,014 that has a priority date in 2006, several years after the priority date of the '617 patent. I note, for example, claim 1 of this patent claims a “nucleotide sequence” which includes “sequences having at least 95% sequence identity over the entire length of SEQ ID NO:2” specified in the patent.

289. I understand that Dr. Kay is an inventor on patent 7,588,772 that has a priority date in 2006, several years after the priority date of the '617 patent. I note, for example, claim 1 of this patent claims an “amino acid sequence” which includes “sequences having at least 95% sequence identity over the entire length of SEQ ID NO:1” specified in the patent.

290. I understand that Dr. Kay is an inventor on patent 8,906,387 that has a priority date in 2006, several years after the priority date of the '617 patent. I note, for example, claim 1 of this patent claims a “capsid protein having an amino acid sequence” which includes “sequences having at least 95% sequence identity over the entire length of SEQ ID NO:1” specified in the patent.

291. I understand that Dr. Kay is an inventor on patent 9,255,300 that has a priority date in 2008, several years after the priority date of the '617 patent. I note, for example, claim 1 of this patent claims a “nucleic acid sequence” which includes sequences having a “sequence identity of 70% or more to the nucleotide sequences set forth in any of SEQ ID Nos: 1, 35, 36, and 37” specified in the patent.

292. I understand that Dr. Kay is an inventor on patent 11,015,189 that has a priority date in 2011, several years after the priority date of the '617 patent. I note, for example, claims 1 and 5 of this patent claim a “capsid protein” which has “at least 97% sequence identity to SEQ ID NO: 29” specified in the patent.

293. I understand that Dr. Kay is an inventor on patent 9,856,469 that has a priority date in 2011, several years after the priority date of the '617 patent. I note, for example, claim 1 of this patent claims a “nucleotide sequence encoding a capsid protein” wherein “the capsid protein has at least 97% sequence identity to SEQ ID NO:29” specified in the patent.

294. I understand that Dr. Kay is an inventor on patent 11,091,774 that has a priority date in 2015, several years after the priority date of the '617 patent. I note, for example, claim 1 of this patent claims a “nucleotide sequence” which “has 88% or more nucleotide sequence identity with the sequence set forth in SEQ ID NO: 13” specified in the patent.

295. I understand that patent 8,618,270 is assigned to Sarepta and has a priority date in 2003, after the priority date of the '617 patent. I note, for example, claim 4 of this patent claims a “sequence with at least 90% sequence homology to the sequence identified as SEQ ID NO:25” specified in the patent.

296. I understand that patent 8,703,735 is assigned to Sarepta and has a priority date in 2010, several years after the priority date of the '617 patent. I note, for example, claim 1 of this patent claims a “sequence having at least 95% sequence homology to the sequence set forth in SEQ ID NO:77” specified in the patent. Claim 3 of this patent claims a “sequence having at least 90% sequence homology to the sequence set forth in SEQ ID NO:77” specified in the patent.

297. I understand that patent 10,849,917 is assigned to Sarepta and has a priority date in 2015, over ten years after the priority date of the '617 patent. I note, for example, claim 4 of this patent claims a “variant having at least 90% sequence identity to a targeting sequence selected from SEQ ID NOS: 2, 3, 4 or 6” specified in the patent.

298. I also understand that Dr. Louise Rodino-Klapac, Sarepta's current Executive VP, Head of R&D, Chief Scientific Officer, is a named inventor of patent 11,358,993, which has a priority date in 2016, a number of years after the priority date of the '617 patent. I note, for example, claim 1 of this patent claims a "polynucleotide sequence" which comprises "a nucleotide sequence at least 95% identical to SEQ ID NO: 1" specified in the patent.

299. In some of these patents, I note that the percent identity language is nearly exactly the same as what is in the '617 patent's claims. While a number of these patents claim 95% sequence identity just like in the '617 patent claims, some of these patents claim even lower sequence identity percentages, 90%, and even 70%.

300. In addition, in several of the articles cited by Dr. Kay (discussed above in Section IV.D.1), the researchers used sequence alignments to determine sequence identity. For example, the researchers in Green performed sequences alignments between the nucleic acid sequences of parvovirus B19, SPV, and several previously known parvovirus sequences to determine sequence similarity. (Green at 106-110.) As Green explains, the alignments were performed using publicly available alignment programs with settings adjusted to account for gap penalties and deletion penalties. (Green at 112.) Like Green, the researchers in Ganesh performed sequences alignments between the nucleic acid sequences and amino acid sequences of the HHS sample with several previously known FAV sequences to determine sequence similarity. (Ganesh at 4-7.) As Ganesh explains, the alignments were performed using publicly available alignment programs such as Clustal W. (Ganesh at 3, 6-7.) Other articles suggest that the term "'percentage identity' between two sequences is often offered as a universal means of describing the mutual degree of 'homology' between them," meaning that one would readily understand the term. David T. Jones *et al.*, "The rapid generation of mutation data matrices from

protein sequences,” 8 CABIOS 275, 275 (1992). This provides additional evidence that persons of skill in the art were capable of using alignment tools to determine sequence identity, and cuts against Dr. Rubanyi’s and Dr. Quackenbush’s assertions of indefiniteness.

2. “AAV . . . capsid protein”

301. I understand in claim construction, the Court ruled that the term “AAV capsid protein” has its plain and ordinary meaning, and did not agree with Sarepta’s argument that this term is indefinite or that it has a functionality requirement. (Dec. 30, 2022 Claim Construction Order.) I disagreed with Dr. Rubanyi’s opinions during claim construction and I continue to disagree with them in his report.

302. In my opinion, both the claims and specification of the ’617 patent use the term “AAV capsid protein” consistently with how a person of ordinary skill in the art would have used the term in 2001-2002, and even today. I see nothing in the claims or specification that indicate that the inventors used a different definition of “AAV capsid protein.” I also see nothing in the claims or specification to suggest that the inventors intended “AAV capsid protein” to have any specific functionality, as Dr. Rubanyi alleges in his report. Just that the sequences in the patent encode capsid proteins that, if expressed, may be used to form an AAV capsid.

303. **First**, Dr. Rubanyi puts forth the same arguments he presented during claim construction without taking into account the Court’s discussion and order concerning this term. I understand that the Court already considered Dr. Rubanyi’s opinions on this term and declined to read a “functional” requirement into this claim term in the ’617 patent. In his report, however, Dr. Rubanyi attempts to import functionality requirements into the ’617 patent’s claims. (Rubanyi Opening Report Section VIII.B.)

304. **Second**, Dr. Rubanyi’s opinions conflate the concept of a “capsid protein,” the term in the claims of the ’617 patent, with the functions of a whole AAV capsid, or of an AAV viral vector (which would include a whole AAV capsid). For example, Dr. Rubanyi states that the ’617 patent specification discusses various aspects of capsid functionality, including examples of how vectors can be used in different applications. (Rubanyi Opening Report at ¶¶ 98.) Dr. Rubanyi also cites to a number of publications from the time of the ’617 patent which discuss applications of an AAV capsid and/or a viral vector. (Rubanyi Opening Report at ¶¶ 105-107.) But the functional applications Dr. Rubanyi points to and discusses are each associated with the AAV capsid, or the actual AAV viral vector, not the AAV capsid proteins that are part of the claims in the ’617 patent. For example, the Wu 2000 publication Dr. Rubanyi cites addressed AAV2 vectors and altered tropisms of wholly formed capsids. In my opinion, this is not instructive or applicable to the “AAV . . . capsid protein” term in the ’617 patent’s claims.

305. Contrary to Dr. Rubanyi’s opinions, the claims of the ’617 patent specify recombinant cultured host cells containing nucleic acids that encode for AAV capsid proteins (e.g. vp1, vp2, vp3), which if expressed, may be used to form an AAV capsid. The AAV capsid proteins are building blocks for AAV capsids. Capsids can be used, by encapsidating a gene of interest, to make a complete viral vector which can be used as a gene therapy product. Dr. Rubanyi attempts to characterize applications of an AAV viral vector discussed in the ’617 patent as functionality associated with an AAV capsid protein. In my opinion, this is incorrect.

306. Like he did during claim construction, Dr. Rubanyi cites Dr. Wilson’s declaration from January 30, 2013 to support his opinion that a functionality requirement is present in the claims. (Rubanyi Opening Report at ¶¶ 99-100.) Dr. Rubanyi also cites to testimony from Dr.

Gao discussing the applications of an AAV capsid to state that the term “AAV capsid protein” in the ’617 patent’s claims requires functionality. (Rubanyi Opening Report at ¶¶ 101-102.) I disagree with Dr. Rubanyi’s opinions and reliance on statements from inventors Wilson and Gao. In my opinion, it is clear from Dr. Gao’s testimony that he was referring to a wholly formed capsid when describing various applications, such as, for example, “be able to package, be able to transduce that many tissues.” (Rubanyi Opening Report at ¶ 103.) In my opinion, this testimony does not indicate that the AAV capsid protein, as specified in the claims of the ’617 patent, has a functional requirement.

307. Dr. Rubanyi’s reliance on the Wilson Declaration from 2013 is similarly off base in my opinion. The Wilson declaration that Dr. Rubanyi cites discusses whole AAV capsids and their functions. (Rubanyi Opening Report at ¶ 100.) But in his deposition, Dr. Wilson at made a distinction between an AAV capsid protein and a wholly formed AAV capsid, or AAV viral vector, concerning functionality. (Wilson Dep. Tr. At 210:23 – 211:13 (“Q: I’m asking you in terms of the meaning of AAV vp1 capsid protein, in order to be a capsid protein the amino acid sequence has to have the functional characteristics of a capsid protein; is that right? A: I mean, there are situations just because you have a vp1 sequence doesn’t mean you have an AAV vector.”) Dr. Wilson also recognized that the claims of the ’617 patent did not explicitly include any “functional” language. (Wilson Dep. Tr. At 210:5–22 (“Q: So when Claim 1 using the term, ‘AAV vp1 capsid protein,’ that also has implicit functional characteristics, correct? A: I don’t agree with you on that. Q. And why not? A: Because . . . if you look at the claim, the claim is a cell with the vp1 capsid sequence. . . . I’m just looking at the claim, and the claim is a host cell with a vp1 sequence nucleic acid with a heterologous non-AAV sequence, so that it doesn’t say anything more than that.”) Nothing in Dr. Wilson’s Declaration indicates to me that

the term “AAV capsid protein” in the ’617 patent was intended to have a special meaning or a specific functionality. It is my opinion that Dr. Wilson used the same plain and ordinary meaning of AAV capsid protein that a person of ordinary skill in the art would have understood in 2001-2002. Again, in my opinion, a person of ordinary skill in the art would readily understand the plain and ordinary meaning of this term.

F. Written Description

308. I have reviewed Dr. Kay’s opinions that the asserted claims are invalid because they do not meet the “written description” requirement. I understand that, in short, having an adequate “written description” means that a patent’s specification shows that the inventors were “in possession” of the inventions described in the patent’s claims at the priority date (June 2002 for the ’617 patent). As I explain below, I do not agree with Dr. Kay that the asserted claims are invalid for failing to meet the written description requirement.

1. Dr. Kay’s Calculations

309. On pages 61-72 of his report, Dr. Kay begins his written description analysis with calculations about how many possible sequences are within 95% of the AAVrh10 sequences in the ’617 patent’s claims. In my opinion, these calculations are irrelevant because they are out of context and are inconsistent with how a person of ordinary skill in the art would have viewed the ’617 patent.

310. Dr. Kay explains in paragraph 206 that his “calculations take into account the random distribution of substitutions within the” sequences in the ’617 patent’s claims. However, as I explain below, the ’617 patent does not guide persons of ordinary skill in the art to make random changes to the sequences in the patent’s claims. Persons of ordinary skill would have known not to do that, both with respect to (a) the regions in AAVrh10 that can be changed, and

(b) within those regions, which specific amino and nucleic acids should be substituted for ones in the sequences encoding AAVrh10.

311. In paragraph 203 of his report, Dr. Kay discusses comments that I understand were made by a patent office examiner for a patent application for a different patent, although it was an application that I understand is in the same family of patent applications that led to the '617 patent. Like Dr. Kay's calculations, in my opinion the patent office examiner's comments lack context. The inventors' response to the patent office examiner's comments explains this:

The specification describes and the claims recite the "relevant identifying characteristics" of the claimed AAVs. The invention relates to the discovery and recombinant engineering of a new isolate - - AAV7. Claim 12 specifies that the recombinant AAV has a capsid with vp1, vp2 and vp3 proteins, defined by the "signature region" of the AAV7 vp1 protein. As described in this specification, the signature region is a hypervariable region of the capsid protein that is unique to each known AAV, and which is flanked by conserved sequences (see the specification as filed at p. 48, lines 13-17). PCR amplification of this "signature region" permits the positive identification of a sequence as an AAV capsid coding region (see the specification as filed at p. 7, lines 20-31). Moreover, the specification provides the structure of an AAV capsid, including the highly variable regions located within the vp3 splice variant, which contains the amino acids encoded by the signature region (see the specification as filed at p. 21, lines 4-13; Figure 2). The larger vp proteins, vp1 and vp2, also contain all of the vp3 sequences and thus, also include the signature region (see the specification as filed at p. 18, lines 3 to 6; p. 21, lines 4-13 and Figure 2). Thus, the claims recite and the specification teaches the requisite identifying characteristics, including structure, physical properties, and functional characteristics of the new isolate.

(REGENX0002780-2791 at REGENX0002786-2787; REGENX0002916-2927 at

REGENX0002922-2923.) The conserved and highly variable regions the inventors discussed above, and the sequences in Figure 2 in the '617 patent along with the discussion in the '617 patent's specification, provide important information to persons of ordinary skill in the art. This information would have guided persons of ordinary skill in the art as to where amino and nucleic

acids in the AAVrh10 sequences in the patent's claims should and should not be changed, and for the ones that can be changed, what the changes should be.

312. I understand that the patent office ultimately granted a patent on this patent application, that contained the claim language "at least 95% identical" to an identified sequence. (REGENX0003064-3080; REGENX0003092-3096; REGENX0003099-3103.) In other words, the patent office granted a patent based on the patent application that Dr. Kay discusses, despite the earlier comments made by the patent office examiner.

2. The '617 Patent Guides Persons of Ordinary Skill in the Art as to Where Changes in the AAVrh10 Capsid Protein Sequences Should and Should Not be Made, and What Amino Acids Should be Substituted

313. The specification of the '617 patent teaches persons of ordinary skill in the art where changes in the AAVrh10 capsid protein sequences should and should not be made, and for the regions where changes may be made, provides guidance on what amino and nucleic acids should be substituted.

314. Figure 2 in the '617 patent shows an alignment of 56 AAV vp1 amino acid sequences (and therefore vp2 and vp3 sequences also). Figure 2 includes the vp1 amino acid sequences for the previously known AAVs, AAV1-AAV6; the vp1 amino acid sequence for AAVrh10 (labeled 44_2 in Figure 2); and the vp1 amino acid sequences for the other previously unidentified AAVs.

315. One important aspect of Figure 2 is that it shows the 56 AAV capsid protein amino acid sequences in alignment. From the alignments, it is apparent that there are regions in the amino acid sequences that are highly conserved, where all the sequences in Figure 2 have identical or nearly identical amino acids. It is also apparent that there are other regions that are not conserved, where there are different amino acids.

316. Below I have highlighted the vp3 amino acids in Figure 2 that are conserved across the sequences shown in Figure 2⁴:

⁴ I have not included AAV5 in this analysis because it differs significantly from the other AAV sequences, as a person of ordinary skill in the art would have known and been able to see from Figure 2. (Kay Ex. 33 (Vandenberghe) at 1417, 1418.)

	190	200	210	220	230	240
C1\VP1	MRAAP	CGNAVDAGQ	GS	DGVGNA	SGDWHCDS	TWSEGEK
C2\VP1	MRAAP	CGNAVDAGQ	GS	DGVGNA	SGDWHCDS	TWSEGEK
C5\VP1@2	MRAAP	CGNAVDAGQ	GS	DGVGNA	SGDWHCDS	TWSEGEK
AAV4\VP1	MRAAA	GAAVEGGQ	GADGVGNA	SGDWHCDS	TWSEGEH	
AAV1	MASGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
AAV6\VP1	MASGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
A3_3	MASGG	GAPMADNNE	GADGVGNS	SGNWHCDS	TWMGDR	
A3_7	MASGG	GAPMADNNE	GADGVGNS	SGNWHCDS	TWMGDR	
A3_4	MASGG	GAPMADNNE	GADGVGNS	SGNWHCDS	TWMGDR	
A3_5	MASGG	GAPMADNNE	GADGVGNS	SGNWHCDS	TWMGDR	
AAV2	MATGS	GAPMADNNE	GADGVGNS	SGNWHCDS	TWMGDR	
AAV3	MASGG	GAPMADNNE	GADGVGNS	SGNWHCDS	QWLGR	
13.3b\VP1	VAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
AAV7	VAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
223_4	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TRLGR	
223_5	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TRLGR	
223_10	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
223_2	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
223_7	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
223_6	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
44_1	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
44_5	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
44_2	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
29.3\VP1	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
29.5\VP1	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
42_15	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
42_8	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
42_13	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
42_3A	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
42_4	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
42_5A	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
42_1B	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
42_5B	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
43_1	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
43_12	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
43_5	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
AAV8	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
43_21	MASGG	GAPMADNNE	GADGVGNS	SGNWHCDS	TWLGDR	
43_25	MASGG	GAPMADNNE	GADGVGNS	SGNWHCDS	TWLGDR	
43_23	MASGG	GAPMADNNE	GADGVGNS	SGNWHCDS	TWLGDR	
43_20	MASGG	GAPMADNNE	GADGVGNS	SGNWHCDS	TWLGDR	
AAV_9	MASGG	GAPMADNNE	GADGVGNS	SGNWHCDS	TWLGDR	
24_1	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
42.2REAL	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
7.2\VP1	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
27.3\VP1	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
16.3\VP1	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
42_10	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
42_3B	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
42_11	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
F1\VP1	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
F5\VP1@3	MAAGG	GAPTADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
F3\VP1	MAAGG	GAPMADNNE	GADGVGNA	SGNWHCDS	TWLGDR	
42_6B	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	
42_12	MAAGG	GAPMADNNE	GADGVGSS	SGNWHCDS	TWLGDR	

	250	260	270	280	290	300
C1\VP1	VTTTSTRTWV	LPTYNH	LYLRLG----	TTSNSN	TYNGF	STPWGYFDENRFCHFS
C2\VP1	VTTTSTRTWV	LPTYNH	LYLRLG----	TTSNSN	TYNGF	STPWGYFDENRFCHFS
C5\VP1@2	VTTTSTRTWV	LPTYNH	LYLRLG----	TTSNSN	TYNGF	STPWGYFDENRFCHFS
AAV4\VP1	VTTTSTRTWV	LPTYNH	LYLRLG----	ESLQSN	TYNGF	STPWGYFDENRFCHFS
AAV1	VITTSTRTWAL	PTYNNH	LYKQIS--SAST	GASNDN	HYFGY	STPWGYFDENRFCHFS
AAV6\VP1	VITTSTRTWAL	PTYNNH	LYKQIS--SAST	GASNDN	HYFGY	STPWGYFDENRFCHFS
A3_3	VITTSTRTWAL	PTYNNH	LYKQIS--SESG	ATNDN	HYFGY	STPWGYFDENRFCHFS
A3_7	VITTSTRTWAL	PTYNNH	LYKQIS--SESG	ATNDN	HYFGY	STPWGYFDENRFCHFS
A3_4	VITTSTRTWAL	PTYNNH	LYKQIS--SESG	ATNDN	HYFGY	STPWGYFDENRFCHFS
A3_5	VITTSTRTWAL	PTYNNH	LYKQIS--SESG	ATNDN	HYFGY	STPWGYFDENRFCHFS
AAV2	VITTSTRTWAL	PTYNNH	LYKQIS--SQSG	ASNDN	HYFGY	STPWGYFDENRFCHFS
AAV3	VITTSTRTWAL	PTYNNH	LYKQIS--SQSG	ASNDN	HYFGY	STPWGYFDENRFCHFS
13.3b\VP1	VITTSTRTWAL	PTYNNH	LYEQIS--SETA	GSTNDN	TYFGY	STPWGYFDENRFCHFS
AAV7	VITTSTRTWAL	PTYNNH	LYKQIS--SETA	GSTNDN	TYFGY	STPWGYFDENRFCHFS
223_4	VITTSTRTWAL	PTYNNH	LYKQIS--SQSA	GSTNDN	VYFGY	STPWGYFDENRFCHFS
223_5	VITTSTRTWAL	PTYNNH	LYKQIS--SQSA	GSTNDN	VYFGY	STPWGYFDENRFCHFS
223_10	VITTSTRTWAL	PTYNNH	LYKQIS--SQSA	GSTNDN	VYFGY	STPWGYFDENRFCHFS
223_2	VITTSTRTWAL	PTYNNH	LYKQIS--SQSA	GSTNDN	VYFGY	STPWGYFDENRFCHFS
223_7	VITTSTRTWAL	PTYNNH	LYKQIS--SQSA	GSTNDN	VYFGY	STPWGYFDENRFCHFS
223_6	VITTSTRTWAL	PTYNNH	LYKQIS--SQSA	GSTNDN	VYFGY	STPWGYFDENRFCHFS
44_1	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
44_5	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
44_2	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
29.3\VP1	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
29.5\VP1	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
42_15	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
42_8	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
42_13	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
42_3A	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
42_4	VITTSTRTWAL	PTYNNH	LYKQIS--SQSG	ATNDN	HFFGY	STPWGYFDENRFCHFS
42_5A	VITTSTRTWAL	PTYNNH	LYKQIS--SQSG	ATNDN	HFFGY	STPWGYFDENRFCHFS
42_1B	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
42_5B	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
43_1	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
43_12	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
43_5	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
AAV8	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	ATNDN	TYFGY	STPWGYFDENRFCHFS
43_21	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
43_25	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
43_23	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
43_20	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
AAV_9	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
24_1	VITTSTRTWAL	PTYNNH	LYKQIS--SQS-	GATNDN	HFFSY	STPWGYFDENRFCHFS
42.2REAL	VITTSTRTWAL	PTYNNH	LYKQIS--SQS-	GATNDN	HFFGY	STPWGYFDENRFCHFS
7.2\VP1	VITTSTRTWAL	PTYNNH	LYKQIS--SQS-	GATNDN	HFFGY	STPWGYFDENRFCHFS
27.3\VP1	VITTSTRTWAL	PTYNNH	LYKQIS--SQS-	GATNDN	HFFGY	STPWGYFDENRFCHFS
16.3\VP1	VITTSTRTWAL	PTYNNH	LYKQIS--SQS-	GATNDN	HFFGY	STPWGYFDENRFCHFS
42_10	VITTSTRTWAL	PTYNNH	LYKQIS--SQS-	GATNDN	HFFGY	STPWGYFDENRFCHFS
42_3B	VITTSTRTWAL	PTYNNH	LYKQIS--SQS-	GATNDN	HFFGY	STPWGYFDENRFCHFS
42_11	VITTSTRTWAL	PTYNNH	LYKQIS--SQS-	GATNDN	HFFGY	STPWGYFDENRFCHFS
F1\VP1	VITTSTRTWAL	PTYNNH	LYKQIS--SSSG	ATNDN	HYFGY	STPWGYFDENRFCHFS
F5\VP1@3	VITTSTRTWAL	PTYNNH	LYKQIS--SSSG	ATNDN	HYFGY	STPWGYFDENRFCHFS
F3\VP1	VITTSTRTWAL	PTYNNH	LYKQIS--SSSG	ATNDN	HYFGY	STPWGYFDENRFCHFS
42_6B	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS
42_12	VITTSTRTWAL	PTYNNH	LYKQISNGTSGG	STNDN	TYFGY	STPWGYFDENRFCHFS

	310	320	330	340	350	360
C1\VP1	QRLINNNWGLR	KAMRVKIFNIQVKEV	TTSNGETT	VANNLTSTVQI	FADSSYELPY	MDA
C2\VP1	QRLINNNWGLR	KAMRVKIFNIQVKEV	TTSNGETT	VANNLTSTVQI	FADSSYELPY	MDA
C5\VP1@2	QRLINNNWGLR	KAMRVKIFNIQVKEV	TTSNGETT	VANNLTSTVQI	FADSSYELPY	MDA
AAV4\VP1	QRLINNNWGMRE	KAMRVKIFNIQVKEV	TTSNGETT	VANNLTSTVQI	FADSSYELPY	MDA
AAV1	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
AAV6\VP1	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
A3_3	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSAVQV	FSDSEYQLPY	VLGS
A3_7	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
A3_4	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
A3_5	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
AAV2	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
AAV3	QRLINNNWGFRE	KRLSFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
13.3b\VP1	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
AAV7	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
223_4	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
223_5	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
223_10	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
223_2	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
223_7	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
223_6	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
44_1	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
44_5	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
44_2	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
29.3\VP1	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
29.5\VP1	QRLINNNWGFRE	KSLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_15	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_8	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_13	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_3A	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_4	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_5A	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_1B	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_5B	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
43_1	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
43_12	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
43_5	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
AAV8	QRLINNNWGFRE	KRLSFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
43_21	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
43_25	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
43_23	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
43_20	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
AAV_9	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
24_1	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42.2REAL	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
7.2\VP1	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
27.3\VP1	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
16.3\VP1	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_10	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_3B	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_11	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
F1\VP1	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
F5\VP1@3	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
F3\VP1	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTVQV	FSDSEYQLPY	VLGS
42_6B	QRLINNNWGFRE	KRLRFLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS
42_12	QRLINNNWGFRE	KRLNFKLFNIQVKEV	TNDGVTTI	ANNLTSTIQV	FSDSEYQLPY	VLGS

	370	380	390	400	410	420
C1\VP1	GQEGSLSPFFNDVFMV	PQYGYCGIVTG	-ENQNQTD	RNAFY	CLEYFPSQML	RTGNNFEMAY
C2\VP1	GQEGSLSPFFNDVFMV	PQYGYCGIVTG	-ENQNQTD	RNAFY	CLEYFPSQML	RTGNNFEMAY
C5\VP1@2	GQEGSLSPFFNDVFMV	PQYGYCGIVTG	-ENQNQTD	RNAFY	CLEYFPSQML	RTGNNFETAY
AAV4\VP1	GQEGSLSPFFNDVFMV	PQYGYCGLVTG	NTSQQQTD	RNAFY	CLEYFPSQML	RTGNNFEITY
AAV1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFTFSY
AAV6\VP1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFTFSY
A3_3	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFTFSY
A3_7	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFTFSY
A3_4	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFTFSY
A3_5	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFTFSY
AAV2	AHQGCLPFFPADVEMV	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFTFSY
AAV3	AHQGCLPFFPADVEMV	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFQFSY
13.3b\VP1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
AAV7	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
223_4	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFTFSY
223_5	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFTFSY
223_10	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFTFSY
223_2	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFTFSY
223_7	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFTFSY
223_6	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFTFSY
44_1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
44_5	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
44_2	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
29.3\VP1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
29.5\VP1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_15	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_8	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_13	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_3A	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_4	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_5A	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_1B	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_5B	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
43_1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
43_12	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
43_5	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY
AAV8	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFQFTY
43_21	AHQGCLPFFPADVEMV	PQYGYLTLNNG	---	SQALGRSSFY	CLEYFPSQML	RTGNNFQFSY
43_25	AHQGCLPFFPADVEMV	PQYGYLTLNNG	---	SQALGRSSFY	CLEYFPSQML	RTGNNFQFSY
43_23	AHQGCLPFFPADVEMV	PQYGYLTLNNG	---	SQALGRSSFY	CLEYFPSQML	RTGNNFQFSY
43_20	AHQGCLPFFPADVETV	PQYGYLTLNNG	---	SQALGRSSFY	CLEYFPSQML	RTGNNFQFSY
AAV_9	AHQGCLPFFPADVEMV	PQYGYLTLNNG	---	SQALGRSSFY	CLEYFPSQML	RTGNNFQFSY
24.1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42.2REAL	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
7.2\VP1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
27.3\VP1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
16.3\VP1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSMGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_10	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_3B	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_11	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
F1\VP1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
F5\VP1@3	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
F3\VP1	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_6B	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQSVGRSSFY	CLEYFPSQML	RTGNNFEFSY
42_12	AHQGCLPFFPADVEMI	PQYGYLTLNNG	---	SQAVGRSSFY	CLEYFPSQML	RTGNNFEFSY

	430	440	450	460	470	480
C1\VP1	NFGKVPFHSMYAH	SQSPDRIMNPLLDQYLWHLQST	TSGETLNQGNAAATT	FGKIRSGDFAF		
C2\VP1	NFEKVPFHSMYAH	SQSLDRIMNPLLDQYLWHLQST	TSGETLNQGNAAATT	FGKIRSGDFAF		
C5\VP102	NFEKVPFHSMYAH	SQSLDGLMNPLLDQYLWHLQST	TSGETLNQGNAAATT	FGKIRSGDFAF		
AAV4\VP1	SFEKVPFHSMYAH	SQSLDRIMNPLLDQYLWHLQST	TTGTTLNAGTATTN	FTKLRPNTNFSN		
AAV1	TFEEVPFHSMYAH	SQSLDRIMNPLLDQYLYYLNRT	QNQSG-SAQNKDLL	FSRGSFAGMSV		
AAV6\VP1	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLNRT	QNQSG-SAQNKDLL	FSRGSFAGMSV		
A3_3	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSKTQ	-GTSGETTQQSRLQ	FSQAGPSSMAQ		
A3_7	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSKTQ	-GTSGETTQQSRLQ	FSQAGPSSMAQ		
A3_4	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSKTQ	-GTSGETTQQSRLQ	FSQAGPSSMAQ		
A3_5	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSKTQ	-GTSGETTQQSRLQ	FNQAGPSSMAQ		
AAV2	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRTN	-TPSGTTTQQSRLQ	FSQAGASDIRD		
AAV3	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLNRT	QGTTSGETTNQSRLL	FSQAGPQMSL		
13.3b\VP1	SFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QSDPGGTAGNRELQ	FYQGGPSTMAE		
AAV7	SFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QSNPGGTAGNRELQ	FYQGGPSTMAE		
223_4	TFEDVPFHSMYAH	SQSLGRIMNPLLDQYLYYLART	QSNAGGTAGNRELQ	FYQGGPSTMAE		
223_5	TFEDVPFHSMYAH	SQSLGRIMNPLLDQYLYYLART	QSNAGGTAGNRELQ	FYQGGPSTMAE		
223_10	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QSNAGGTAGNRELQ	FYQGGPSTMAE		
223_2	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QSNAGGTAGNRELQ	FYQGGPSTMAE		
223_7	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QSNAGGTAGNRELQ	FYQGGPSTMAE		
223_6	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QSNAGGTAGNRELQ	FYQGGPSTMAE		
44_1	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
44_5	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
44_2	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
29.3\VP1	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
29.5\VP1	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
42_15	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
42_8	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
42_13	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
42_3A	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
42_4	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
42_5A	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
42_1B	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
42_5B	QFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TAGTQQLL	FSQAGPNNMSA		
43_1	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TQGTQQLL	FSQAGPANMSA		
43_12	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TQGTQQLL	FSQAGPANMSA		
43_5	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QSTGG-TQGTQQLL	FSQAGPANMSA		
AAV8	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLSRT	QTTGG-TANTQTLG	FSQGGPNTMAN		
43_21	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLVRT	QTTG--TGGTQTLA	FSQAGPSSMAN		
43_25	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLVRT	QTTG--TGGTQTLA	FSQAGPSSMAN		
43_23	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLVRT	QTTG--TGGTQTLA	FSQAGPSSMAN		
43_20	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLVRT	QTTG--TGGTQTLA	FSQAGPSSMAN		
AAV_9	TFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLVRT	QTTG--TGGTQTLA	FSQAGPSSMAN		
24_1	TFEEVPFHSMYVH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTMAE		
42.2REAL	TFEEVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTMAE		
7.2\VP1	TFEEVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTMAE		
27.3\VP1	TFEEVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTVAE		
16.3\VP1	TFEEVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTMAE		
42_10	TFEEVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTMAE		
42_3B	TFEEVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTMAE		
42_11	TFEEVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTMAE		
F1\VP1	SFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTMAE		
F5\VP103	SFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTMAE		
F3\VP1	SFEDVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTMAE		
42_6B	TFEEVPFHSMYAH	SQSLDRIMNPLLDQYLYYLART	QST---TGSTRELQ	FHQAGPNTMAE		
42_12	QFEDVPFHSMYAH	SQSLDRITNPLLDQYLYYLART	QST---TGSTRGLQ	FHQAGPNTMAE		

	490	500	510	520	530	540
C1\VP1	YRKNWLPGPCVKQ	QRLSKTASQN	YKIPASGGNALLKYD	THYTLNKRWSNIA	PGPPMATAG	
C2\VP1	YRKNWLPGPCVKQ	QRFSTASQN	YKIPASGGNALLKYD	THYTLNKRWSNIA	PGPPMATAG	
C5\VP1@2	YRKNWLPGPCVKQ	QRFSTASQN	YKIPASGGNALLKYD	THYTLNKRWSNIA	PGPPMATAG	
AAV4\VP1	FKKNWLPGPSIKQ	QGFSTANQN	YKIPATGSDSLIKYETH	STLDGRWSALT	PGPPMATAG	
AAV1	QPKNWLPGPCYRQ	QRVSKTKTDN	-----NNSNFTWTG	ASKYNLNGRESI	INPGTAMASHK	
AAV6\VP1	QPKNWLPGPCYRQ	QRVSKTKTDN	-----NNSNFTWTG	ASKYNLNGRESI	INPGTAMASHK	
A3_3	QAKNWLPGPSYRQ	QRMSTANDN	-----NNSEFAWTAAT	KYYLNGRNSLVN	PGPPVASEK	
A3_7	QAKNWLPGPSYRQ	QRMSTANDN	-----NNSEFAWTAAT	KYYLNGRNSLVN	PGPPVASEK	
A3_4	QAKNWLPGPSYRQ	QRMSTANDN	-----NNSEFAWTAAT	KYYLNGRNSLVN	PGPPVASEK	
A3_5	QAKNWLPGPSYRQ	QRMSTANDN	-----NNSEFAWTAAT	KYYLNGRNSLVN	PGPPVASEK	
AAV2	QSRNWLPGPCYRQ	QRVSKTSADN	-----NNSEYSWTGAT	KYHLNGRDSLVN	PGPAMASHK	
AAV3	QARNWLPGPCYRQ	QRLSKTANDN	-----NNSNFPWTAAS	KYHLNGRDSLVN	PGPAMASHK	
13.3b\VP1	QAKNWLPGPCFRQ	QRVSKTLDQN	-----NNSNFAWTGAT	KYHLNGRNSLVN	PGVAMATHK	
AAV7	QAKNWLPGPCFRQ	QRVSKTLDQN	-----NNSNFAWTGAT	KYHLNGRNSLVN	PGVAMATHK	
223_4	QAKNWLPGPCFRQ	QRVSKTLDQN	-----NNSNFAWTGAT	KYHLNGRNSLVN	PGVAMATHK	
223_5	QAKNWLPGPCFRQ	QRVSKTLDQN	-----NNSNFAWTGAT	KYHLNGRNSLVN	PGVAMATHK	
223_10	QAKNWLPGPCFRQ	QRVSKTLDQN	-----NNSNFAWTGAT	KYHLNGRNSLVN	PGVAMATHK	
223_2	QAKNWLPGPCFRQ	QRVSKTLDQN	-----NNSNFAWTGAT	KYHLNGRNSLVN	PGVAMATHK	
223_7	QAKNWLPGPCFRQ	QRVSKTLDQN	-----NNSNFAWTGAT	KYHLNGRNSLVN	PGVAMATHK	
223_6	QAKNWLPGPCFRQ	QRVSKTLDQN	-----NNSNFAWTGAT	KYHLNGRNSLVN	PGVAMATHK	
44_1	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATHK	
44_5	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
44_2	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
29.3\VP1	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
29.5\VP1	QAKNWLPGPCYRQ	QRVSTTLSQN	-----DNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
42_15	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
42_8	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
42_13	QAKNWLPGPCYRQ	QRVSTTVSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
42_3A	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
42_4	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
42_5A	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
42_1B	QAKNWLPGPCYRQ	QRVSTTVSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
42_5B	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
43_1	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
43_12	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
43_5	QAKNWLPGPCYRQ	QRVSTTLSQN	-----NNSNFAWTGAT	KYHLNGRDSLVN	PGVAMATEK	
AAV8	QAKNWLPGPCYRQ	QRVSTTTGQN	-----NNSNFAWTAGT	KYHLNGRNSLAN	PGIAMATEK	
43_21	QARNWVPGPCYRQ	QRVSTTTNQS	-----NNSNFAWTGAA	KFKLNGRDSLMN	PGVAMASHK	
43_25	QARNWVPGPCYRQ	QRVSTTTNQN	-----NNSNFAWTGAA	KFKLNGRDSLMN	PGVAMASHK	
43_23	QARNWVPGPCYRQ	QRVSTTTNQN	-----NNSNFAWTGAA	KFKLNGRDSLMN	PGVAMASHK	
43_20	QARNWVPGPCYRQ	QRVSTTTNQN	-----NNSNFAWTGAA	KFKLNGRDSLMN	PGVAMASEK	
AAV_9	QARNWVPGPCYRQ	QRVSTTTNQN	-----NNSNFAWTGAA	KFKLNGRDSLMN	PGVAMASEK	
24_1	QSKNWLPGPCYRQ	QRLSKNIDSN	-----NNSNFAWTGAT	KYHLNGRNSLTN	PGVAMATNK	
42.2REAL	QSKNWLPGPCYRQ	QRLSKNIDSN	-----NNSNFAWTGAT	KYHLNGRNSLTN	PGVAMATNK	
7.2\VP1	QSKNWLPGPCYRQ	QRLSKNIDSN	-----NNSNFAWTGAT	KYHLNGRNSLTN	PGVAMATNK	
27.3\VP1	QSKNWLPGPCYRQ	QRLSKNIDSN	-----NNSNFAWTGAT	KYHLNGRNSLTN	PGVAMATNK	
16.3\VP1	QSKNWLPGPCYRQ	QRLSKNIDSN	-----NNSNFAWTGAT	KYHLNGRNSLTN	PGVAMATNK	
42_10	QSKNWLPGPCYRQ	QRLSKNIDSN	-----NNSNFAWTGAT	KYHLNGRNSLTN	PGVAMATNK	
42_3B	QSKNWLPGPCYRQ	QRLSKNIDSN	-----NTSNFAWTGAT	KYHLNGRNSLTN	PGVAMATNK	
42_11	QSKNWLPGPCYRQ	QRLSKDIDSN	-----NNSNFAWTGAT	KYHLNGRNSLTN	PGVAMATNK	
F1\VP1	QSKNWLPGPCYRQ	QGLSKNLDFN	-----NNSNFAWTAAT	KYHLNGRNSLTN	PGIPMATNK	
F5\VP1@3	QSKNWLPGPCYRQ	QRLSKNLDFN	-----NNSNFAWTAAT	KYHLNGRNSLTN	PGIPMATNK	
F3\VP1	QSKNWLPGPCYRQ	QRLSKNLDFN	-----NNSNFAWTAAT	KYHLNGRNSLTN	PGIPMATNK	
42_6B	QSKNWLPGPCYRQ	QRLSKNIDSN	-----NNSNFAWTGAT	KYHLNGRNSLTN	PGVAMATNK	
42_12	QSKNWLPGPCYRQ	QRLSKNIDSN	-----NNSNFAWTGAT	KYHLNGRNSLTN	PGVAMATNK	

	550	560	570	580	590	600
C1\VP1	PSDGD	DFS-NAQLIF	GPS	VTGNT	TTTSAN	NLLFTS
C2\VP1	PSDGD	DFS-NAQLIF	GPS	VTGNT	TTTSAN	NLLFTS
C5\VP102	PSDGD	DFS-NAQLIF	GPS	VTGNT	TTTSAN	NLLFTS
AAV4\VP1	PADSK	FSS-NSQLIF	AGPK	QNGNT	TATVPG	TLIFT
AAV1	DDEDK	FFPMSGV	MIFGKE	SAGAS	NTALD	NVMIT
AAV6\VP1	DDKDK	FFPMSGV	MIFGKE	SAGAS	NTALD	NVMIT
A3_3	DDEEK	YFFPMHGN	LIFGKQ	GTGTT	NVDIE	SVLIT
A3_7	DDEEK	YFFPMHGN	LIFGKQ	GTGTT	NVDIE	SVLIT
A3_4	DDEEK	YFFPMHGN	LIFGKQ	GTGTT	NVDIE	SVLIT
A3_5	DDEEK	YFFPMHGN	LIFGKQ	GTGTT	NVDIE	SVLIT
AAV2	DDEEK	FFPQSGV	LIFGKQ	GSEKT	NVDIE	KVMIT
AAV3	DDEEK	FFPMHGN	LIFGKE	GTTAS	NAELD	NVMIT
13.3b\VP1	DDEDR	FFPSSGV	LIFGKT	GATN	-KTTL	NVLMT
AAV7	DDEDR	FFPSSGV	LIFGKT	GATN	-KTTL	NVLMT
223_4	DDEER	FFPSSGV	LIFGKT	GAAN	-KTTL	NVLMT
223_5	DDEER	FFPSSGV	LIFGKT	GAAN	-KTTL	NVLMT
223_10	DDEER	FFPSSGV	LIFGKT	GAAN	-KTTL	NVLMT
223_2	DDEER	FSPSSGV	LIFGKT	GAAN	-KTTL	NVLMT
223_7	DDEER	FFPSSGV	LIFGKT	GAAN	-KTTL	NVLMT
223_6	DDEER	FFPSSGV	LIFGKT	GAAN	-KTTL	NVLMT
44_1	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
44_5	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
44_2	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
29.3\VP1	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
29.5\VP1	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
42_15	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
42_8	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
42_13	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
42_3A	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
42_4	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
42_5A	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
42_1B	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
42_5B	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
43_1	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
43_12	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
43_5	DDEER	FFPSSGV	LIFGKT	GAGKN	NVDYS	SVMLT
AAV8	DDEER	FFPSSGN	LIFGKT	NAARD	NADYS	DVMLT
43_21	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
43_25	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
43_23	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
43_20	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
AAV_9	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
24.1	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
42.2REAL	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
7.2\VP1	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
27.3\VP1	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
16.3\VP1	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
42_10	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
42_3B	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
42_11	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
F1\VP1	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
F5\VP103	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
F3\VP1	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
42_6B	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT
42_12	DDDDR	FFPSSGV	LIFGKT	GAGND	GVDYS	QVLIT

	610	620	630	640	650	660
C1\VP1	NATTAPITGNVTAM	GVLPGMVWQNRDIYY	QGPIWAKI	PHADGHFHPSPLIG	GFGLKHEPPP	
C2\VP1	NATTAPITGNVTAM	GVLPGMVWQNRDIYY	QGPIWAKI	PHADGHFHPSPLIG	GFGLKHEPPP	
C5\VP1@2	NATTAPITGNVTAM	GVLPGMVWQNRDIYY	QGPIWAKI	PHADGHFHPSPLIG	GFGLKHEPPP	
AAV4\VP1	SNSNLFTVDRLTAL	GAVPGMVWQNRDIYY	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
AAV1	SSSTDPATGDVHAM	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
AAV6\VP1	SSSTDPATGDVHVM	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
A3_3	SQNTTASYGSVDSQ	GILPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
A3_7	SQNTTASYGSVDSQ	GILPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
A3_4	SQDTTASYGSVDSQ	GILPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
A3_5	SQNTTASYGSVDSQ	GILPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
AAV2	RGNRQAATADVNTQ	GVLPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
AAV3	SSNTAPTGTGVNHQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
13.3b\VP1	AANTAAQTQVVNNQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
AAV7	AANTAAQTQVVNNQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
223_4	AASTAAQTQVVNNQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
223_5	AASTAAQTQVVNNQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
223_10	AASTAAQTQVVNNQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
223_2	AASTAAQTQVVNNQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
223_7	AASTAAQTQVVNNQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
223_6	AASTAAQTQVVNNQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
44_1	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
44_5	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
44_2	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
29.3\VP1	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
29.5\VP1	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_15	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_8	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_13	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_3A	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_4	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_5A	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_1B	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_5B	QQNAAPIVGAVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
43_1	QTNGAPIVGTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
43_12	QTNGAPIVGTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
43_5	QTNGAPIVGTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
AAV8	QCNTAPQIGTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
43_21	AANTQAQTGLVHNQ	GVI PGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
43_25	AANTQAQTGLVHNQ	GVI PGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
43_23	AANTQAQTGLVHNQ	GVI PGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
43_20	AANTQAQTGLVHNQ	GVI PGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
AAV_9	AANTQAQTGLVHNQ	GVI PGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
24_1	SSTAGPQTQTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42.2REAL	SSTAGPQTQTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
7.2\VP1	SSTAGPQTQTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
27.3\VP1	SSTAGPRTQTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
16.3\VP1	SSTAGPQTQTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_10	SSTAGPQTQTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_3B	SSTAGPQTQTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_11	SSTAGPQTQTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
F1\VP1	PSTAGPQSQTINSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
F5\VP1@3	SSTAGPQSQTINSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
F3\VP1	SSTAGPQSQTINSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_6B	SSTAGPQTQTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	
42_12	SSTAGPQTQTVNSQ	GALPGMVWQNRDVYL	QGPIWAKI	PHTDGHFHPSPLIG	GFGLKHEPPP	

	670	680	690	700	710	720
C1\VP1	QIFIKNTVPAN	PATTE	TAARVD	SFITQYSTGQVA	QIEWEIE	KERSKRWN
C2\VP1	QIFIKNTVPAN	PATTE	TAARVD	SFITQYSTGQVA	QIEWEIE	KERSKRWN
C5\VP1@2	QIFIKNTVPAN	PATTE	TAARVD	SFITQYSTGQVA	QIEWEIE	KERSKRWN
AAV4\VP1	QIFIKNTVPAN	PATTE	SSTPVNS	SFITQYSTGQVS	VOIDWEI	QKERSKRWN
AAV1	QILIKNTVPAN	PAEFS	SATKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
AAV6\VP1	QILIKNTVPAN	PAEFS	SATKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
A3_3	QILIKNTVPAN	PATTE	TPGKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
A3_7	QILIKNTVPAN	PATTE	TPGKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
A3_4	QILIKNTVPAN	PATTE	TPGKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
A3_5	QILIKNTVPAN	PATTE	TPGKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
AAV2	QILIKNTVPAN	PTTES	SAAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
AAV3	QIMIKNTVPAN	PTTES	SPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
13.3b\VP1	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
AAV7	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
223_4	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
223_5	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
223_10	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
223_2	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
223_7	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
223_6	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
44_1	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
44_5	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
44_2	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
29.3\VP1	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
29.5\VP1	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_15	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_8	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_13	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_3A	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_4	QILIKNTVPAN	PTTES	SQAKPAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_5A	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_1B	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_5B	QILIKNTVPAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
43_1	QILVKNTPVAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
43_12	QILVKNTPVAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
43_5	QILVKNTPVAN	PTTES	SQAKLAS	SFITQYSTGQVS	VEIEWEL	LQKENS
AAV8	QILIKNTVPAN	PTTES	NQSKLNS	SFITQYSTGQVS	VEIEWEL	LQKENS
43_21	QILIKNTVPAN	PLTEN	NQAKLNS	SFITQYSTGQVS	VEIEWEL	LQKENS
43_25	QILIKNTVPAN	PLTEN	NQAKLNS	SFITQYSTGQVS	VEIEWEL	LQKENS
43_23	QILIKNTVPAN	PLTEN	NQAKLNS	SFITQYSTGQVS	VEIEWEL	LQKENS
43_20	QILIKNTVPAN	PLTEN	NQAKLNS	SFITQYSTGQVS	VEIEWEL	LQKENS
AAV_9	QILIKNTVPAN	PLTEN	NQAKLNS	SFITQYSTGQVS	VEIEWEL	LQKENS
24_1	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42.2REAL	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
7.2\VP1	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
27.3\VP1	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
16.3\VP1	QILIKNTVPAN	PEVET	TPALFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_10	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_3B	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_11	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
F1\VP1	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
F5\VP1@3	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
F3\VP1	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_6B	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS
42_12	QILIKNTVPAN	PEVET	TPAKFAS	SFITQYSTGQVS	VEIEWEL	LQKENS

	730	740	750
			
C1\VP1	GNQSSMLWAPD	TTGKYTEPRV	IGSRYLTNHL
C2\VP1	GNQSSMLWAPD	TTGKYTEPRV	IGSRYLTNHL
C5\VP1@2	GNQSSMLWAPD	TTGKYTEPRV	IGSRYLTNHL
AAV4\VP1	GQNSLLWAPDA	AGKYTEFRA	IGTRYLTHHL
AAV1	AKSANVDFTVD	NNGLYTEPR	PIGTRYLTRPL
AAV6\VP1	AKSANVDFTVD	NNGLYTEPR	PIGTRYLTRPL
A3_3	NKSVNVEFTVD	ANGVYSEPR	PIGTRYLTRNL
A3_7	NKSVNVEFTVD	ANGVYSEPR	PIGTRYLTRNL
A3_4	NKSVNVEFTVD	ANGVYSEPR	PIGTRYLTRNL
A3_5	NKSVNVEFTVD	ANGVYSEPR	PIGTRYLTRNL
AAV2	NKSVNVDFTV	DNGVYSEPR	PIGTRYLTRNL
AAV3	NKSVNVDFTV	DNGVYSEPR	PIGTRYLTRNL
13.3b\VP1	EKQTGVDFAV	DSSQGVYSEPR	PIGTRYLTRNL
AAV7	EKQTGVDFAV	DSSQGVYSEPR	PIGTRYLTRNL
223_4	DKQTGVDFAV	DSSQGVYSEPR	PIGTRYLTRNL
223_5	DKQTGVDFAV	DSSQGVYSEPR	PIGTRYLTRNL
223_10	DKQTGVDFAV	DSSQGVYSEPR	PIGTRYLTRNL
223_2	DKQTGVDFAV	DSSQGVYSEPR	PIGTRYLTRNL
223_7	DKQTGVDFAV	DSSQGVYSEPR	PIGTRYLTRNL
223_6	DKQTGVDFAV	DSSQGVYSEPR	PIGTRYLTRNL
44_1	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
44_5	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
44_2	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
29.3\VP1	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
29.5\VP1	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
42_15	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
42_8	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
42_13	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
42_3A	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
42_4	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
42_5A	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
42_1B	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
42_5B	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
43_1	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
43_12	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
43_5	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
AAV8	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
43_21	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
43_25	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
43_23	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
43_20	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
AAV_9	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL
24.1	AKSNNVEFAV	NNEGVYTEPR	PIGTRYLTRNL
42.2REAL	AKSNNVEFAV	NNEGVYTEPR	PIGTRYLTRNL
7.2\VP1	AKSNNVEFAV	NNEGVYTEPR	PIGTRYLTRNL
27.3\VP1	AKSNNVEFAV	NNEGVYTEPR	PIGTRYLTRNL
16.3\VP1	AKSNNVEFAV	NNEGVYTEPR	PIGTRYLTRNL
42_10	AKSNNVEFAV	NNEGVYTEPR	PIGTRYLTRNL
42_3B	AKSNNVEFAV	NNEGVYTEPR	PIGTRYLTRNL
42_11	AKSNNVEFAV	NNEGVYTEPR	PIGTRYLTRNL
F1\VP1	AKSNNVEFAV	NPBGVYTEPR	PIGTRYLTRNL
F5\VP1@3	AKSNNVEFAV	NPBGVYTEPR	PIGTRYLTRNL
F3\VP1	AKSNNVEFAV	NPBGVYTEPR	PIGTRYLTRNL
42_6B	AKSNNVEFAV	NNEGVYTEPR	PIGTRYLTRNL
42_12	YKSTNVDFAV	NTDGTYS	SEPRPIGTRYLTRNL

317. As the highlighted version of Figure 2 shows, a person of ordinary skill in the art would have understood several things from Figure 2 of the '617 patent.

318. First, Figure 2 would have guided a person of ordinary skill in the art as to where changes should and should not be made in the AAVrh10 sequence. Persons of ordinary skill in the art would have understood that changes should be avoided in the red regions, and that changes should be concentrated in the regions that are not highlighted in red.

319. Second, persons of ordinary skill in the art would have been guided by Figure 2 as to substitutions in the non-highlighted regions that can be made. For example, in positions 609 and 610, which are within a region that is not highlighted red, 44_2 (AAVrh10) has the amino acids "G" (glycine) at position 609 and "A" (alanine) at position 610. Other vp3 sequences in Figure 2 have D (aspartic acid), A (alanine) or Q (glutamine) at position 609; and N (asparagine), R (arginine), D (aspartic acid), S (serine), T (threonine), V (valine) or L (leucine) at position 610. A person of ordinary skill in the art would have reasonably expected that changing the G or A in positions 609 and 610 in sequence 44_2 to one of the amino acids present in other sequences in Figure 2 would result in a sequence that corresponds to, for example a vp3 protein, that may be used to form an AAV capsid.

320. Persons of ordinary skill in the art would have been further guided by the information Dr. Kay discusses in paragraph 298 of his report regarding amino acids that can be substituted at certain positions in the variable regions. As Dr. Kay explains, the 1991 Altschul paper, (Kay Ex. 31), "Amino Acid Substitution Matrices from an Information Theoretic Perspective," has a matrix in Table 4 "setting out the degree to which amino acid substitutions are conservative, with larger values indicating increasingly conservative substitutions."

321. The 1991 Altschul paper was from more than ten years before the 2002 priority date of the '617 patent, and the information in Table 4 would have been well known to persons of ordinary skill in the art. Also, it discusses the PAM substitution model, as discussed further in the 1992 paper by Steven Henikoff and Jorja G. Henikoff, "Amino acid substitution matrices from protein blocks," 89 Proc. Natl. Acad. Sci. USA at 10915 (Nov. 1992). This paper described the BLOSUM metric, an improvement to the PAM substitution model. Before the '617 patent's 2002 priority date, other researchers developed matrices as well, for example, as described in Gaston H. Gonnet *et al.*, "Exhaustive Matching of the Entire Protein Sequence Database," 256 Science 1443 (June 5, 1992) and David T. Jones *et al.*, "The rapid generation of mutation data matrices from protein sequences," 8 CABIOS 275, 279 table 2, 280 (1992). From these and other substitution matrices, persons of ordinary skill would have been further guided regarding amino acid substitutions.

322. Dr. Kay explains in paragraph 288 of his report that the sequences disclosed in the '617 patent "are naturally occurring variants cloned from the various tissues specified, for example, in Table 1" of the patent. Table 1 identifies the "Source Species" of the strains. The '617 patent also explains that Figure 1 "provides the non-human primate (NHP) AAV nucleic acid sequences of the invention." ('617 patent at 11:46-47.) Figure 1 includes, for example, AAV7, AAV8 and AAV9 that are also in Figure 2. Since the sequences in Figure 2 correspond to naturally occurring AAV capsid proteins, persons of ordinary skill in the art would have understood that the newly identified amino acid sequences in Figure 2 correspond to proteins that may be used to form an AAV capsid.

323. In summary, persons of ordinary skill in the art would have understood from Figure 2 in the '617 patent and the other information I discuss above where changes to the amino

acid sequence for AAVrh10 should and should not be made, and for the amino acids that may be changed, what substitutions to make. Also, persons of ordinary skill in the art would have understood that the fewer amino acids that were changed, the more likely the sequence would correspond to proteins that may be used to form an AAV capsid, and would have been able to determine with a reasonable degree of probability whether a particular sequence that is 95% identical to the claimed sequences would be capable of forming a capsid.

324. The '617 patent specification discusses these same concepts, and provides guidance to a person of ordinary skill in the art regarding where changes in the sequence can be made. The '617 patent describes that AAV capsid proteins have different regions – some that are constant, or conserved (like those highlighted in red above), some that are variable, and some that are hypervariable. ('617 patent at 15:58-16:21.) The patent explains that previous studies had found that AAV2 had 12 hypervariable regions, and specifically describes where those regions can be found in the AAV2 sequence (which the patent provides as SEQ ID NO:70). ('617 patent at 16:1-7 (“For example, with respect to the number of the AAV2 vp11 [SEQ ID NO:70], the HVR are located as follows: HVR1, aa 146-152; HVR2, aa 182-186; HVR3, aa 262-264; HVR4, aa 381-383; HVR5, aa 450-474; HVR6, aa 490-495; HVR7, aa500-504; HVR8, aa 514-522; HVR9, aa 534-555; HVR10, aa 581-594; HVR11, aa 658-667; and HVR12, aa 705-719.”).)

325. The '617 patent further explains that “the HVR of the novel AAV serotypes of the invention are determined,” and states that a person of ordinary skill can utilize Figure 2 of the patent and conventional alignment techniques in order to make that determination. ('617 patent at 15:66-16:1, 16:7-21; 16:54-59; 13:66-14:31.) In particular, the '617 patent says that “using

the information provided herein, the HVRs for the other novel serotypes of the invention can be readily determined.” (’617 patent at 16:19-21.)

326. The ’617 patent also explains that “substantial homology” and “substantial similarity” mean “when referring to amino acids or fragments thereof ... when optimally aligned with appropriate amino acid insertions or deletions with another amino acid, there is amino acid sequence identity in at least about 95 to 99% of the aligned sequences.” (’617 patent at 4:24-33.) The patent explains these same concepts similarly with respect to nucleic acid sequences. (’617 patent at 4:14-23.)

327. The patent further explains that “included in this invention are nucleic acid sequences which are greater than 85%, preferably at least about 90%, more preferably at least about 95%, and most preferably at least about 98 to 99% identical or homologous to the sequences that the invention, including FIG. 1 and the Sequence Listing [SEQ ID NO: 1, 9-59, 117-120].” (’617 patent at 12:66-13:5.) As noted above, SEQ ID NO:59 is for AAVrh10.

328. Dr. Kay’s report discusses the variable and conserved regions in the sequences in Figure 2 of the ’617 patent, although he focuses on the sequences in Figure 2 that are at least 95% identical to the AAVrh10 amino acid sequences in the patent’s claims.

329. In paragraph 275 of his report, Dr. Kay states that he “analyzed the protein and DNA sequences for the 50 clones disclosed in the ’617 patent” and “aligned amino acids 1 to 738 of SEQ ID NO: 81 against the other capsid protein sequences” to “calculate percent identity.” In paragraph 281, Dr. Kay shows in a table how many of the 50 clones “disclosed in the ’617 patent” are at least 95% identical to the AAVrh10 sequences in the patent’s claims. For example, Dr. Kay’s table shows that there are 15 amino acid sequences that are at least 95% identical to the AAVrh10 vp3 amino acid sequence.

330. Paragraph 292 of Dr. Kay's report includes a table showing where the amino acid sequences in Figure 2 that are at least 95% identical to AAVrh10 differ from AAVrh10's sequence, and what the substitutions are.⁵ Dr. Kay states in paragraph 289 that this table shows "limited variations when compared to the rh.10 amino acid sequence" and that there are a "concentrated set of modifications." In paragraph 293 he similarly states that "the disclosed sequences are very similar to rh.10, having at most a handful of substitutions and/or deletions" that are "concentrated in only 66 out of 738 residues, or about 9% of the total length of the 738 amino acid sequence of rh.10." In paragraph 297 he states that it is "apparent from the rows of the table, where more than one of the example sequences is substituted at a particular position, the substitution is identical." He further explains in paragraph 298 that "many of the substitutions are conservative substitutions."

331. Dr. Kay's statements are generally consistent with my opinions. Dr. Kay's analysis shows that the '617 patent does not guide persons of ordinary skill in the art to make a "random distribution of substitutions within the" AAVrh10 sequences, as he implies in paragraph 206 of his report. The '617 patent teaches persons of ordinary skill in the art that "limited variations" (or a "concentrated set of modifications") should be made, and guides persons of ordinary skill in the art to what the substitutions should be.

332. It is also my opinion that persons of ordinary skill in the art could have easily done the same analysis Dr. Kay did. Dr. Kay's analysis is based on sequence alignments that were well within the capability of persons of ordinary skill in the art in 2002, and are described in the '617 patent, for example, at 16:7-21, 16:54-59, and 13:66-14:31, among other places.

⁵ In paragraph 302 of his report, Dr. Kay presents similar information for the nucleic acid sequences. My statements above apply equally to Dr. Kay's analysis of the nucleic acid sequences.

333. In addition to looking to where amino acid substitutions were in the sequences in Figure 2 that are at least 95% identical to the claimed AAVrh10 sequences, a person of ordinary skill in the art would have looked more broadly to Figure 2 regarding where substitutions could be made that would still result in a nucleotide sequence that, if expressed, would reasonably be expected to form a capsid. Similarly, a person of ordinary skill in the art would have identified what kind of substitutions to make, along these same lines, using the information in my annotated Figure 2 above, as well as generally known concepts about amino acid substitutions, such as the information described in paragraph 298 of Dr. Kay's report. Using these methods, a person of ordinary skill in the art would be taught quite a lot about sequences that could be made that would share 95% identity to the patented sequence.

334. For the reasons I have explained above, it is my opinion that the '617 patent does not guide persons of ordinary skill in the art to make "random" changes to the AAVrh10 sequences in the patent's claims. It is my opinion that the '617 patent guides persons of ordinary skill in the art as to where changes to the AAVrh10 sequences in the patent's claims can be made, and what the substitutions should be. Also, persons of ordinary skill in the art would have understood from the patent's specification that the fewer amino or nucleic acids that were changed, the more likely the sequences would encode proteins that, if expressed, may be used to form an AAV capsid, and would have been able to determine with a reasonable degree of probability whether a particular sequence that is 95% identical to the claimed sequences would be capable of forming a capsid.

3. The '617 Patent Describes Structural Features Common to the Members of the Genus so that Persons of Ordinary Skill in the Art Could Visualize or Recognize the Members of the Genus

335. For the reasons I have explained above, I do not agree with Dr. Kay's opinion that the sequences disclosed "in the '617 Patent Are Not Representative of the Claimed Genera."

(Kay Opening Report at page 76.) As I have explained above, the sequences in Figure 2 of the '617 patent include AAVrh10, and guide persons of ordinary skill in the art as to where changes should and should not be made to the AAVrh10 sequence and what the substitutions should be.

336. The '617 patent also explains that “substantial homology” and “substantial similarity” mean “... when optimally aligned with appropriate amino acid insertions or deletions with another amino acid, there is amino acid sequence identity in at least about 95 to 99% of the aligned sequences,” and explains these same concepts similarly with respect to nucleic acid sequences. ('617 patent at 4:14-33.) The patent then explains “included in this invention are nucleic acid sequences which are greater than 85%, preferably at least about 90%, more preferably at least about 95%, and most preferably at least about 98 to 99% identical or homologous to the sequences that the invention, including FIG. 1 and the Sequence Listing [SEQ ID NO: 1, 9-59, 117-120].” ('617 patent at 12:66-13:5.) As noted above, SEQ ID NO:59 is for AAVrh10.

337. In my opinion, this language in the specification is consistent with the percent identity language in the '617 patent's claims, and would have taught a person of ordinary skill in the art that the sequences within the genera in the patent's claims have relatively few changes from the AAVrh10 sequences.

338. For the same reasons, in my opinion, persons of ordinary skill in the art would have been able to recognize the “structural features common to the members of the genus.” The '617 shows, for example in Figure 2, the amino acid sequence for AAVrh10 capsid proteins vp1, vp2, and vp3. Persons of ordinary skill in the art would have understood that amino acids (and nucleic acids) are physical structures, and that the sequences of amino acids in Figure 2 correspond to and represent physical structures, as do the nucleic acid sequences in the patent.

339. As I have explained above, persons of ordinary skill in the art would also understand from Figure 2 and other information in the '617 patent where in the structure of the AAVrh10 amino acid sequence changes should be made and should not be made. As I have also explained above, persons of ordinary skill in the art would also understand what structures (what amino or nucleic acids) can be substituted at the locations where changes can be made. These structural features are in my opinion “common to the members of the genus.”

340. In my opinion, for the reasons I explain above, persons of ordinary skill in the art would have been able to “visualize or recognize” the “structural features common to the members of the” groups of sequences in the asserted claims of the '617 patent: ones that are at least 95% identical to the AAVrh10 sequences in patent’s claims, with the differences at the structural locations I have discussed above (as shown, for example, in the sections that are not highlighted in my annotated Figure 2), and with the substituted amino acids I have discussed above (which are physical structures)—resulting in sequences that encode proteins that, if expressed, may be used to form an AAV capsid.

341. In paragraphs 311, 315 and elsewhere in his report, Dr. Kay refers to forming “a functional capsid,” “the functional characteristics of the rh.10 variant” and similar. I do not understand what function or functions he is referring to, for example, when he says there is a “lack of correlation between structure and function in the specification.” (Kay Opening Report at ¶ 311.) As I explained above, I do not agree with Dr. Kay’s suggestions that the '617 patent’s claims require or are limited to a capsid protein that has the functions of a gene therapy product, for example when he says in paragraph 309 of his report that the '617 patent’s “disclosure is not sufficient to permit a person of ordinary skill in the art to recognize or visualize those AAV capsid sequences ... that are capable of carrying out the most basic functions of an AAV capsid

protein, such as capsid formation or the packaging and delivery of nucleic acid molecules to target host cells.”

342. I also do not agree with Dr. Kay’s statements regarding function in paragraph 312 of his report. Dr. Gao’s deposition testimony that Dr. Kay cites in that paragraph appears to be related to the functions of the conserved and variable regions in, or fragments of, the sequences disclosed in the ’617 patent, and not whether the sequences encode proteins that, if expressed, may be used to form an AAV capsid. Dr. Kay’s statements in paragraphs 313, 314 and 317 of his report regarding a “function associated” with the “signature region,” and his comments in paragraph 314 regarding functions for the “the constant and/or variable regions” are similar. These statements miss the point in my opinion, which again, is whether the sequences encode proteins that, if expressed, may be used to form an AAV capsid.

343. For the reasons explained above, I disagree with Dr. Kay’s statement in paragraph 310 of his report that the “’617 patent does not identify a correlation between structure and function that would allow a person of ordinary skill in the art to recognize or visualize the amino acid or nucleic acid sequences within the broad genera recited in the Asserted Claims” and that the “specification does not identify any regions of the claimed sequences that must be preserved.” As I have explained, based on the ’617 patent’s disclosure, persons of ordinary skill in the art would have reasonably expected that if the structural modifications to the AAVrh10 sequence are made at the locations described above, with the substitutions described above, and relatively few changes are made, that will result in structures (sequences) that encode proteins that, if expressed, may be used to form an AAV capsid.

4. Other Information Supporting My Opinions Written Description

344. It was well understood by those of ordinary skill in the art as of June 2002 to use sequence alignment information similar to that provided in Figures 1A through 1AAAR and 2A

through 2M of the '617 patent to make rational and reasonable modifications to a sequence.

There is a large body of literature that makes clear that those working in the field understood that it was not sensible to make random changes, and that changes could be guided by looking at comparisons with other sequences.

345. A chapter authored by Davidson in the book *Protein Design: Methods and Applications*, which was published in 2006, provides a review of some of the literature and teachings concerning the use of sequence alignments and comparisons to select where to make modifications to a sequence that was known in the art as of the time of the invention. The Davidson chapter, titled “Multiple Sequence Alignment as a Guideline for Protein Engineering Strategies,” teaches that using sequence alignments allows those of skill in the art to limit the number of sequences they try and test:

Many proteins lack the thermodynamic stability and/or solubility that is required for their use in a desired application. For this reason, it can be advantageous to improve these qualities through rational protein engineering. An effective means for achieving this goal is to use sequence alignment analysis to select amino acid substitutions that are likely to increase the thermodynamic stability or solubility of a protein. Advantages of using this approach are that generally only a small number of substitutions need to be tested, these substitutions are rarely debilitating to protein function, and knowledge of the three-dimensional structure of the protein of interest is not required. This chapter will describe approaches that have been used to exploit the information contained in sequence alignments for the engineering of improved protein properties.

(Davidson at 171.)

346. Davidson also cites examples of situations in the years preceding its publication where sequence alignments were used to guide the use of substitutions in modified protein sequences. Davidson explains that the “advantages of sequence alignment-based methods are that they are simple to carry out, they do not require knowledge of the three dimensional structure of the protein under investigation, and the resulting mutants generally maintain their

biological function. Furthermore, the method has been shown to work with alignments ranging from thirteen to thousands of sequences.” (Davidson at 172.)

347. One of the papers cited in Davidson is Steipe *et al.*, published in the *Journal of Molecular Biology* in 1994. (Steipe *et al.*, “Sequence statistics reliably predict stabilizing mutations in a protein domain,” 240 J. Mol. Biol. 188 (1994).) Steipe warns against the use of random mutations, which can be harmful for protein stability, and teaches that the use of the sequence statistics (looking at non-consensus versus consensus amino acids from a database of sequences) could reliably predict stabilizing modifications. Steipe teaches that this technique has broad applicability, explaining that this concept has “far reaching implications for antibody engineering.” (Steipe at 188.)

348. Davidson also cites to Lehmann, published in *Protein Engineering* in 2000. (Lehmann *et al.*, “From DNA sequence to improved functionality: using protein sequence comparisons to rapidly design a thermostable consensus phytase,” 13(1) Protein Engineering 49 (2000).) The researchers in Lehmann used protein sequence comparisons to make sequence modifications to design more stable phytases. Specifically, they used computer alignment tools to align the 13 known fungal phytase amino acid sequences and used that to create a consensus phytase sequence. They found that the consensus phytase has significantly improved stability. They concluded that their “approach allowed the rapid design of a fully functional phytase with drastically increased thermostability based only on a comparison of primary protein sequences.” (Lehmann at 56.) They also stated that they “expected” this approach to be applicable to other protein families. (Lehmann at 56.)

349. Like Steipe, Lehmann shows that those of skill in the art were very familiar, as of June 2002, with using protein sequence comparisons to design and modify sequences. The

sequence comparison information provided in the '617 patent would have allowed those of skill in the art to use that knowledge to guide them in making modifications to the disclosed sequences, including the sequence of AAVrh10, that would retain similar properties.

350. The Mountz comment, which I discussed elsewhere in this report, further supports my opinion that the specification adequately describes the inventions of the '617 patent. (Mountz, "Monkey see, monkey do," 10 Gene Therapy 194 (2003).) Mountz, which reviewed the work of the Wilson lab that led to the '617 patent, stated that the techniques described in the '617 patent could be used to identify additional serotypes. (Mountz at 195 ("There is no reason why further AAV serotypes cannot be isolated in the same way.").)

351. A 1999 Nature Medicine article by Girod, cited by Dr. Quackenbush in his report, further supports my opinion that a person of ordinary skill in the art would use the information in the patent specification and known alignment tools to determine where substitutions may be made. Girod describes a study generating six different AAV capsid mutants where a 14-amino acid tag was inserted in order to attempt to change the tropism of AAV2. (Girod *et al.*, "Genetic capsid modifications allow efficient re-targeting of adeno-associated virus type 2," 5(9) Nature Medicine, 1052 (September 1999) (Quackenbush Ex. 58).) In order to determine the best sites to make those insertions, the authors aligned the AAV2 capsid protein and with canine parvovirus, which were natural viruses known to form capsids. (Girod at 1052.) Based on that alignment, the authors selected six sites in the AAV2 capsid protein to make those insertions, and all six AAV2 capsid mutants were capable of forming a viral capsid. (Girod at 1052.)

352. I also note that Dr. Kay has several patents with claims that are similar to the '617 patent's claims, claiming sequences that are "at least 95% identical" to AAV vp1 capsid protein sequences.

353. Dr. Kay's 7,588,772 patent states that its SEQ ID NO:1 "is an amino acid sequence of a novel recombinant VP1 capsid protein, referred to herein as AAV-DJ." (7,588,772 patent at 5:16-30.) The patent also explains that AAV-DJ "has an amino acid sequence comprising a first region that is derived from ... AAV-2), a second region that is derived from ... AAV-8), and a third region that is derived from ... AAV-9)"; and that SEQ ID NO:2 is the nucleic acid sequence corresponding to the amino acid SEQ ID NO:1. (7,588,772 patent at 7:11-16, 25-27.)

354. Figure 2 of the '617 patent (and for example, claim 1) shows that the AAVrh10 vp1 capsid protein has approximately 738 amino acids. Dr. Kay's 7,588,772 patent shows that, similarly, there are 737 amino acids in the vp1 capsid protein in SEQ ID NO:1 in that patent. (7,588,772 patent at the bottom of column 19.)

355. Dr. Kay's 7,588,772 patent's claim 1 covers:

An amino acid sequence selected from the group of sequences consisting of (i) sequences having at least 95% sequence identity over the entire length of SEQ ID NO:1 and (ii) SEQ ID NO:1

356. Like claim 1 in the '617 patent, claim 1 in Dr. Kay's 7,588,772 patent addresses amino acid sequences that are at least 95% identical to a vp1 capsid protein amino acid sequence disclosed in the specification. However, unlike the '617 patent claim 1, Dr. Kay's claim 1 appears to only address the sequences, and does not include other elements required by the '617 patent's claims, like cultured host cells and a heterologous non-AAV sequence.

357. Dr. Kay's 8,067,014 patent is similar to his 7,588,772 patent. It discloses the same 15 sequences disclosed in the 7,588,772 patent. Claim 1 in Dr. Kay's 8,067,014 patent covers SEQ ID NO:2:

A nucleotide sequence selected from the group of sequences consisting of (i) sequences having at least 95% sequence identity over the entire length of SEQ ID NO:2 and (ii) SEQ ID NO:2.

358. As explained above, SEQ ID NO:2 is the nucleic acid sequence for the vp1 capsid protein AAV-DJ that corresponds to the amino acid sequence in SEQ ID NO:1. SEQ ID NO:2 has 2215 nucleotides. (8,067,014 patent at bottom of column 23.) This is similar to the AAVrh10 vp1 nucleic acid sequence referred to in claim 7(a) of the '617 patent, which has 2213 nucleotides.

359. In summary, Dr. Kay's two claim 1's (claim 1 in his 7,588,772 patent and claim 1 in his 8,067,014 patent) are like the '617 patent's claims 1 and 7(a) in that all address sequences that are at least 95% identical to vp1 capsid protein sequences that have approximately the same number of amino and nucleic acids.

360. That means that Dr. Kay's calculations in paragraphs 222-235 and 254-260 of his report show the number of possible sequences in his claims if a "random distribution of substitutions" is made "within the recited sequences." (Kay Opening Report at ¶ 206.) As Dr. Kay's calculations show, there are approximately 7.8×10^{109} sequences within claim 1 of his 7,588,772 patent and approximately 1.2×10^{241} sequences within claim 1 of his 8,067,014 patent.

361. In Dr. Kay's 7,588,772 and 8,067,014 patents, there are no sequences disclosed that are at least 95% identical to SEQ ID NO:1 and SEQ ID NO:2. As explained in Dr. Kay's patents and shown below, SEQ ID NO:1 is an amino acid sequence and SEQ ID NO:2 is a nucleic acid sequence, so it is obvious these sequences are not at least 95% identical to each other even though they relate to the same AAV-DJ vp1 capsid protein. SEQ ID NO:3, SEQ ID NO:4 and SEQ ID NO:5 in Dr. Kay's patents are amino acid sequences for AAV2, AAV8 and AAV9 capsid proteins, respectively. It is also obvious that these sequences are not at least 95%

identical to the AAV-DJ SEQ ID NO:1 or AAV-DJ SEQ ID NO:2 because as Dr. Kay's patents explain, AAV-DJ "has an amino acid sequence comprising a first region that is derived from ... AAV-2), a second region that is derived from ... AAV-8), and a third region that is derived from ... AAV-9)."⁶ (7,588,772 patent at 7:11-16.) Finally, as shown in columns 37-39 of Dr. Kay's 7,588,772 patent, SEQ ID NOS:6-15 are for primers, are much shorter than SEQ ID NO:1 and SEQ ID NO:2, and it is also therefore obvious the primer sequences are not at least 95% identical to SEQ ID NO:1 or SEQ ID NO:2.

BRIEF DESCRIPTION OF THE SEQUENCES

SEQ ID NO:1 is an amino acid sequence of a novel recombinant VP1 capsid protein, referred to herein as AAV-DJ.

SEQ ID NO:2 is a nucleotide sequence encoding the protein AAV-DJ.

SEQ ID NO:3 is the amino acid sequence of the capsid protein of AAV-2.

SEQ ID NO:4 is the amino acid sequence of the capsid protein of AAV-8.

SEQ ID NO:5 is the amino acid sequence of the capsid protein of AAV-9.

SEQ ID NOS:6-15 are artificial primers.

(7,588,772 patent at 5:16-30.)

362. As explained above, there are 56 AAV vp1 capsid protein amino acid sequences disclosed in Figure 2 of the '617 patent. As Dr. Kay explains in the right most column of the table in paragraph 281 of his report, several of those sequences are at least 95% identical to the AAVrh10 amino acid sequences in the '617 patent's claims 1, 3, 5 and others.

⁶ I also understand that Dr. Kay's 7,588,772 and 8,067,014 patents both have priority dates no earlier than 2006, years after AAV2, AAV8 and AAV9 were identified, and therefore AAV2, AAV8 and AAV9 are prior art to those patents. Since Dr. Kay's two claim 1's only address sequences with no other structures or requirements, I understand that if the sequences of AAV2, AAV8 and AAV9 were at least 95% identical to SEQ ID NO:1 or SEQ ID NO:2, those claims would be invalid.

363. In paragraph 286 of his report, Dr. Kay states that the table in paragraph 281 of his report shows “the vast genera of sequences recited in the Asserted Claims are not supported by the miniscule number of example sequences that are actually disclosed ... In my opinion, the stark disparity between the broad scope of what is claimed and the disclosure of only a handful of examples strongly supports a conclusion that the Asserted Claims lack written description.”

364. In my opinion, it is inconsistent for Dr. Kay to argue that for the '617 patent, “the stark disparity between the broad scope of what is claimed and the disclosure of only a handful of examples strongly supports a conclusion that the Asserted Claims lack written description,” when, on the other hand, his own patents also address sequences that are at least 95% identical to AAV capsid protein sequences, and his patents disclose zero additional sequences that are at least 95% identical to the sequences in his claims.

365. I understand that Sarepta’s chief scientific officer, Louise Rodino-Klapac, also has a patent that contains the term “95% identical.” In particular, I understand that Dr. Rodino-Klapac is an inventor on patent 11,358,993, which relates to a potential treatment for limb-girdle muscular dystrophy. Claim 1 of patent 11,358,993 requires “A recombinant AAV vector comprising a polynucleotide sequence encoding β -sarcoglycan, wherein the polynucleotide sequence comprises a nucleotide sequence at least 95% identical to SEQ ID NO:1.” All the other claims in patent 11,358,993 refer back to claim 1.

366. I note that there is no discussion in patent 11,358,993 of how to calculate whether a sequence is 95% identical to SEQ ID NO:1 or any other sequence. No alignment programs or parameters are discussed.

367. The specification of patent 11,358,993 discloses the nucleic acid sequence of β -sarcoglycan at SEQ ID NO:1 and the amino acid sequence at SEQ ID NO:2. (11,358,993 patent

at 3:51-4:6.) While other sequences are disclosed, none of those other sequences encode β -sarcoglycan, and none have 95% identity to SEQ ID NO:1. All of the remaining sequences disclosed in patent 11,358,993 (SEQ ID NO:3 through SEQ ID NO:18) are primers rather than a sequence of the invention. (11,358,993 patent at column 39-55.) SEQ ID NO:10-18 are all short sequences of between 19-39 nucleotides, while SEQ ID NO:1 contains 957 nucleotides. (11,358,993 patent at column 37, 51-55.) The only sequence disclosed in the 11,358,993 patent that is within 95% of SEQ ID NO:1 is SEQ ID NO:1 itself. No other sequences within the claims are disclosed.

5. Responses to Other Statements Regarding Written Description in Dr. Kay's Report

368. In paragraph 288 of his report, Dr. Kay states that the sequences in the patent “are naturally occurring variants” and the sequences in the patent “do not show all the different types of modifications encompassed by the Asserted Claims ... the disclosed sequences do not show examples of substitutions, deletions, or modifications at each point in the claimed sequences that meet the ‘at least 95%’ identity limitation.” As I have explained, because the sequences in the patent were isolated from primates, persons of ordinary skill in the art would have understood that the disclosed sequences encode proteins that, if expressed, may be used to form an AAV capsid.

369. Regarding “substitutions, deletions, or modifications,” Dr. Kay states, and I agree that “it would have been a routine matter for a person of ordinary skill to make modifications to the naturally occurring nucleic acid sequence encoding the AAVrh10 capsid protein. Methods for modifying nucleic acid sequences were conventional and well known to those skilled in the art at the time of the ‘617 patent.” (Kay Opening Report at ¶ 181.) Since the advent of PCR in the 1980s, it was known how to make substitutions, deletions and modifications to nucleic acid

sequences. This is described, for example, in the 1986 article, K. Mullis *et al.*, “Specific Enzymatic Amplification of DNA In Vitro: The Polymerase Chain Reaction,” 51 Cold Spring Harb. Symp. Quant. Biol., 263 (1986). In my opinion, as Dr. Kay states, “it would have been a routine matter for a person of ordinary skill to” makes such changes in the sequences disclosed in the ’617 patent. For the same reasons, in my opinion Dr. Kay’s comments in paragraphs 315-316 of his report about the inventors not making “changes or modifications to the rh.10 nucleic acid or amino acid sequences” are not particularly relevant.

370. In paragraphs 321-323 of his report, Dr. Kay appears to criticize the “95% identity term in the claims” [REDACTED] [REDACTED] because “Dr. Gao also did not recall any scientific reason for the identification of the 95% identity limitation” and based on other testimony of the ’617 patent’s inventors. I do not agree with Dr. Kay’s criticisms or his summaries of the inventors’ deposition testimony.

371. Dr. Gao said that “we also identify sequences -- sequences that they are close to each other, but they are not exactly the same. And then based on those sequence information we have, we found -- I don’t remember exactly criteria how we generate that, but we found use this 95 percent rule enabled us to differentiate a large category of sequences.” (Gao Deposition at 178:19-179:3.) Dr. Gao then explained that he and inventor Mauricio Alvira did an analysis “to come up with this 95 percent sequence identity that’s recited in the claims of the ’617 patent.” (Gao Deposition at 180:20-181:2.) Dr. Gao also said the analysis was “recorded in the notebooks and in the computers,” which he no longer has access to “20 years” later. (Gao Deposition at 181:3-182:1.)

372. In my opinion, Dr. Gao's testimony is consistent with the '617 patent's discussion of "substantial homology" that I have discussed above. ('617 patent at 4:14-34, 13:66-14:5.)

The '617 patent also explains that:

the method of the invention facilitated analysis of cloned AAV sequences by the inventors, which revealed heterogeneity of proviral sequences between cloned fragments from different animals, all of which were distinct from the known six AAV serotypes, with the majority of the variation localized to hypervariable regions of the capsid protein. Surprising divergence of AAV sequences was noted in clones isolated from single tissue sources, such as lymph node, from an individual rhesus monkey. This heterogeneity is best explained by apparent evolution of AAV sequence within individual animals due in part, to extensive homologous recombination between a limited number of co-infected parenteral viruses. These studies suggest sequence evolution of widely disseminated virus during the course of a natural AAV infection that presumably leads to the formation of swarms of quasispecies which differ from one another in the array of capsid hyper-variable regions.

('617 patent at 10:61-11:11.)

373. In my opinion, this language in the '617 patent is also consistent with Dr. Gao's testimony that "we also identify sequences -- sequences that they are close to each other, but they are not exactly the same" and that "we found use this 95 percent rule enabled us to differentiate a large category of sequences." (Gao Deposition at 178:19-179:3.)

374. I am not an attorney, but it appears to me that the "at least 95% identical" language in the '617 patent's asserted claims refers to what Dr. Gao explained: it is used to "identify sequences -- sequences that they are close to each other, but they are not exactly the same." For example, as Dr. Kay explains, there are several sequences in the '617 patent that are at least 95% identical to the AAVrh10 sequence. (Kay Opening Report at ¶ 281 (table).)

375. In paragraph 325 of his report, Dr. Kay discusses two papers that were published after the 2002 priority date of the '617 patent, where Dr. Gao is listed as an author. Dr. Kay says that these papers identify "additional, naturally occurring AAV variants" and that the papers

“report these variants as new discoveries, without regard to whether” their “amino acid and nucleic acid sequences ... fall within the scope of the earlier claims in the ’617 patent to all sequences that are ‘at least 95% identical’ to rh.10.” As I have explained before, the “claims in the ’617 patent” require more than just “sequences that are at least 95% identical’ to rh.10.” Also, as far as I can see, Dr. Kay did not do any alignments or analysis to show if any of the “additional, naturally occurring AAV variants” are “at least 95% identical to rh.10.” Regarding the papers themselves, the only “discovery” mentioned in Exhibit 32 that Dr. Kay cites is “the discovery of two novel AAV serotypes, called AAV7 and AAV8,” for which the authors cite reference (10). (Kay Ex. 32, 6381.) Reference (10) is a 2002 paper by the ’617 patent’s three inventors and others. (Kay Ex. 32, 6388.) I do not see the word “discovery” in Exhibit 33 Dr. Kay cites.

376. In paragraphs 326 and 327 of his report, Dr. Kay discusses patents where “Dr. Gao is the first named inventor ... filed by the University of Pennsylvania directed to the AAV9 variant,” and later work done by Dr. Gao’s at the University of Massachusetts where he “discovered” an “AAV9.HR variant, having just two amino acid differences from AAV9.” Dr. Kay does not identify the University of Pennsylvania patents he is referring to or what is required by their claims. It does not seem to me that Dr. Kay is referring to the ’617 patent. Also, the claims in the ’617 are not just to “discoveries” of amino or nucleic acid sequences, as I have explained. If Dr. Kay explains his comments more clearly later, I can respond then.

6. The Inventors Were in Possession of the Asserted Claims of the ’617 Patent at the June 2002 Priority Date and the Written Description Requirements are Met

377. Dr. Kay states in paragraph 311 of his report that “it is my opinion that the inventors were not in possession of the full range of sequences that fall within the vast scope of the Asserted Claims.” I do not agree.

378. Dr. Kay's written description opinions, and opinions that the inventors were not in possession of the inventions, appear to be based only on the limitations in the '617 patent's claims that require amino or nucleic acid sequences that are at least 95% identical to an AAVrh10 capsid protein sequence—and his opinion that those limitations gave “vast scope.” Dr. Kay does not seem to dispute that the inventors were in possession of the other limitations in the claims of the '617 patent.

379. I do not agree that the claims of the '617 patent have “vast scope,” as Dr. Kay states. This conclusion appears to be based on Dr. Kay's calculations on pages of 61-72 of his report, which I have explained are irrelevant in my opinion and are not consistent with what the '617 patent teaches.

380. Dr. Kay's conclusion from his calculations, that the '617 patent's claims have “vast scope,” is the basis of many of his arguments. As I have explained, I do not agree with that conclusion. I also disagree, as I have explained above, that the asserted claims of the '617 patent pertain to or are limited to gene therapy products that include “capsid formation or the packaging and delivery of nucleic molecules to target host cells.” (Kay Opening Report at ¶ 309.)

381. I understand that to have an adequate written description, a patent's specification should have sufficient “blaze marks,” or directions, that guide persons of ordinary skill as to what structures or features are within and are not within the inventions in the patent's claims.

382. As I have explained above, in my opinion there are “blaze marks” in the '617 patent guiding persons of ordinary skill in the art as to where changes in the AAVrh10 sequences should and should not be made, and what the substitutions should be. As I have also explained, in my opinion the '617 patent's specification guides persons of ordinary skill in the art that the sequences covered by the patent's claims (consistent with the claim language) should be “greater

than 85%, preferably at least about 90%, more preferably at least about 95%, and most preferably at least about 98 to 99% identical or homologous” the reference sequences. (’617 patent at 12:66-13:5.) This would have taught a person of ordinary skill in the art that the sequences within the groups in the patent’s claims have relatively few changes from the AAVrh10 sequences.

383. In my opinion, there are “blaze marks” in the ’617 patent—that would have led persons of ordinary skill in the art to the inventions in the patent’s claims—in Figure 2 in the patent, but as I have also explained, in the other figures, the specification and the claims, and within the knowledge that persons of ordinary skill in the art would have had. In Figure 2, 56 AAV capsid protein amino acid sequences are provided and aligned, including AAVrh10. As Dr. Kay has explained in his report, for each of the AAVrh10 amino acid sequences in claims 1, 3, 5 and others in the ’617 patent, there are several sequences in Figure 2 that are at least 95% identical.

384. By following the ’617 patent’s “blaze marks,” or directions in the patent, persons of ordinary skill in the art would have had a reasonable expectation that the resulting sequences would encode proteins that, if expressed, may be used to form an AAV capsid. Related, and as I have also explained, I disagree with Dr. Kay’s opinion that the ’617 patent does not identify a correlation between structure and function that would allow a person of ordinary skill in the art to recognize or visualize the amino acid or nucleic acid sequences within the scope of the ’617 patent’s claims. As I have explained, based on the ’617 patent’s teachings, a persons of ordinary skill in the art would reasonably expect that if the modifications to the AAVrh10 sequence are made at the locations I have described above, with the substitutions (amino or nucleic acid structures) I have described above, and relatively few changes are made, that will result in

structures (sequences) that encode proteins that, if expressed, may be used to form an AAV capsid.

385. Also related, in my opinion there are common structural features that would have allowed persons of ordinary skill in the art to “visualize or recognize” the members of the genera in the asserted claims of the ’617 patent—namely, sequences at least 95% identical to the AAVrh10 sequences in the ’617 patent’s claims, where the differences are in the sequence positions I have described above, and where the substitutions are as I described above.

386. I understand that patent claims are presumed to be valid, that clear and convincing evidence (in other words, significant evidence) must be present to find claims invalid, and that Sarepta and Dr. Kay have the burden of showing there is such evidence.

387. For the reasons I have explained above, it is my opinion that the inventors were in possession of the inventions in the claims in the ’617 patent at the priority date in June 2002, and that the claims have the required written description in the ’617 patent’s disclosure.

G. Enablement

388. I have reviewed Dr. Kay’s opinions that the asserted claims are invalid because they are not enabled. I disagree. I understand that enablement requires that a person of ordinary skill in the art have sufficient information, from the specification and the knowledge in the art, to make and use the full scope of the claimed invention without undue experimentation. The basis of Dr. Kay’s opinions as I understand them are his statements in paragraphs 332 and 333 of his expert report that (i) the claims of the ’617 patent require the formation of a “functional AAV capsid,” and (ii) that the ’617 patent does not teach a person of ordinary skill how to select capsid sequences “that will possess any particular functional characteristic, even the fundamental ability to form part of a functional viral capsid.”

389. As I discussed above, and as I understand is supported by the Court's claim construction, I disagree that the claims require the functionality laid out by Dr. Kay. Dr. Kay's analysis conflates the "AAV . . . capsid protein" required by the claims with a fully-functional viral capsid that is capable of delivering a gene to a patient. The '617 patent's claims do not require a fully-functional viral capsid, and Dr. Kay's analysis in my opinion does not properly focus on the language of the claims.

1. The '617 Patent Does Not Claim an AAV Capsid

390. Claims 1, 3, and 5 of the '617 patent require a "cultured host cell containing a recombinant nucleic acid molecule encoding an AAV" vp1, vp2, or vp3 "capsid protein," with a particular amino acid sequence, along with a "heterologous non-AAV sequence." Claim 7 requires a "cultured host cell containing a recombinant nucleic acid molecule" that encodes particular nucleic acid sequences, along with a heterologous non-AAV sequence.

391. None of the asserted claims require a fully-functional capsid, as opposed to a capsid protein encoded by a recombinant nucleic acid molecule. As I explained elsewhere in this report, and as Dr. Wilson explained in his deposition, the "capsid protein" required by the claims does not have the same functions as a viral capsid. (For example, Wilson Deposition at 210:5-217:8.) Instead, the claims require only recombinant nucleic acid sequences or amino acid sequences that encode proteins that, if expressed, may be used to form an AAV capsid. In my reading of the claims and in my opinion, nothing more is required as a matter of "function."

392. Taking a step back, as I explained above and in my opening report, an AAV capsid is comprised of three different capsid proteins, vp1, vp2, and vp3. The vp1 protein is a full-length protein, while vp2 and vp3 are smaller proteins, produced through alternative splicing of the mRNA transcript. The AAV capsid itself is comprised of a specific molar ratio of the different vp proteins to create an icosahedral structure that can package, or hold, the transgene of

interest, having the ratio 10:10:80 of vp1:vp2:vp3. ('617 patent at 13:32-37.) The gene therapy that is ultimately administered to patients is the AAV viral vector, that is, the AAV capsid containing the packaged transgene.

393. On their own, individual vp1, vp2 and vp3 capsid proteins do not form a capsid. They can, however, be used for purposes other than forming functional AAV capsids. For example, as I discuss above, empty capsids—that is, capsids not containing a transgene—may be used for things like prophylactic vaccination or used as commercial reference materials. Additionally, empty capsids can be used to test patients for seropositivity, meaning whether a patient has antibodies to a given AAV type. Boris Gorovits, *Evaluation of the Humoral Response to Adeno-Associated Virus-Based Gene Therapy Modalities Using Total Antibody Assays*, 23 The AAPS Journal 108, page 4 (September 16, 2021). Further, the individual capsid proteins can also be useful apart from being in an actual capsid. For example, isolated protein sequences can be utilized as reference materials for molar ratio analysis in electrophoresis, dot blot, SDS PAGE, and Western blotting techniques. This is explained in, for example, [e3c0abba637d45398087431712575e65 \(progen.com\)](https://pubmed.ncbi.nlm.nih.gov/33000000/). Individual capsid proteins, along with capsid protein fragments, which cannot form capsids, can also be used in antibody quantification by using the fragments as a product for antigenic simulation. Sihong Song *et al.*, “Sustained secretion of human alpha-1 antitrypsin from murine muscle transduced with adeno-associated virus vectors,” 95 Biological Sciences 14384 (November 1998).

394. As Dr. Wilson, one of the inventors of the '617 patent, explained in his deposition, a capsid protein that happens to be defective (i.e. a capsid protein not capable of forming a capsid or else of performing certain functions) is nevertheless still a capsid protein. (Wilson Deposition at 217:1-8 (“there are -- there are many ways -- many ways that I or a

graduate student could introduce variations in an AAV capsid protein, in which it is virtually incapable of forming a -- a vector, but I wouldn't then call it not an AAV capsid protein. It's just a deviant mutant dysfunctional capsid protein.”.)

395. Therefore, I do not understand the claims of the '617 patent to require anything more than that the amino acid or nucleic acid sequences encode proteins that, if expressed, may be used to form an AAV capsid. Whether the AAV capsid is actually formed or, once formed, has particular functionality or not is unrelated to the claims of the '617 patent.

396. In my opinion, once the claims are properly viewed, and the focus is on the claim language rather than on the improper requirement that the claims require a fully “functional” viral capsid or AAV gene therapy vector, much of Dr. Kay's argument falls away.

2. A Person of Ordinary Skill in the Art Would Understand How to Make and Use the Full Scope of the Asserted Claims

397. As I discussed in the previous section, Dr. Kay vastly overestimates the number of amino acid and nucleic acid sequences that would fall within the scope of the asserted claims. A person of ordinary skill in the art would have understood where changes to the AAVrh10 capsid protein could be made without substantially compromising the ability to form a capsid, if expressed, and I disagree with Dr. Kay's suggestion that persons of ordinary skill in the art would begin by inserting random mutations at random points in the sequence. As explained above, the '617 patent contains numerous examples that a person of ordinary skill in the art would use to understand where mutations could be made in the sequence without substantially affecting the structural properties of the capsid protein.

398. It is my opinion that a person of ordinary skill in the art in June 2002 would have understood from the specification of the '617 patent that at least one way recombinant nucleic acids encoding capsid proteins that are within the scope of the claims (i.e. having at least 95%

identity to the claimed nucleic or amino acid sequences) could be made was by substituting one or more of the non-conserved amino acid positions in the capsid protein. Figure 2 discloses amino acids that could be substituted for an alternate amino acid recruited from the corresponding position in any one of the other AAV capsids aligned in Figure 2. Having selected an alternate amino acid, a person of ordinary skill in the art would then make the appropriate substitution(s) to the nucleic acid sequence shown in Figure 1 to execute the substitution.

399. Additionally, a person of ordinary skill in the art would understand that additional substitutions could be made without affecting capsid formation, so long as the substitution replaced the amino acid in SEQ ID NO:81 with a conservative substitution. A conservative substitution is a substitution that is not expected to affect protein structure or function. Examples of conservative substitutions are set forth in Exhibit 31 to Dr. Kay's opening report, Altschul, "Amino Acid Substitution Matrices from an Information Theoretic Perspective," 219 J. Mol. Biol. 555-565 (1991) at Table 4 (reporting a matrix setting out the degree to which amino acid substitutions are conservative, with larger values indicating increasingly conservative substitutions). Other substitution matrices were also known to persons of ordinary skill in the art, and I discuss these above in Section VI.F. A conservative substitution in the context of Figure 2 could be an amino acid disclosed in another of the AAV capsid protein sequences given in Figure 2 or an amino acid with a higher score in the matrix in Table 4 of Altschul. A person of ordinary skill in the art would understand that the fact that a particular amino acid was used in the same position in another AAV capsid protein means it does not disrupt capsid formation, if expressed.

400. Having identified the scope of the changes that could be made to the AAVrh10 capsid protein and still fall within the asserted claims—which demonstrates possession (see above)—it would have been routine for a person of ordinary skill in the art to then make and use cultured host cells encoding proteins with the full scope of those identified nucleic or amino acid sequences.

401. As Dr. Kay acknowledges, researchers have been creating rAAV vectors since at least the early 1980's, and had developed various capsid engineering strategies. (Kay Opening Report at ¶¶ 90-91, 95.) In fact, I agree with a number of Dr. Kay's statements⁷ characterizing knowledge of a person of ordinary skill in the art at the time of the invention, including:

- “A person of ordinary skill in the art as of the priority date would have been very familiar with the use of cultured host cells to produce viruses from recombinant vectors and would have viewed those techniques as routine.” (Kay Opening Report at ¶ 164.)
- “Methods were known in the art for making recombinant AAVs using cultured host cells – such as triple transfection methods and the use of genetically modified host cells.” (Kay Opening Report at ¶ 167.)
- “methods for manufacturing recombinant AAVs using cultured host cells – such as methods based on transient transfection – were well known before the '617 patent.” (Kay Opening Report at ¶ 170.)
- “Ordinary molecular biology methods would, as a matter of routine, involve making recombinant nucleic acid molecules.” (Kay Opening Report at ¶ 171.)
- “it would have been a routine matter for a person of ordinary skill to make modifications to the naturally occurring nucleic acid sequence encoding the AAV rh.10 capsid protein. Methods for modifying nucleic acid sequences were

⁷ In my opinion, Dr. Kay's statements when discussing obviousness and what was known in the art with respect to patentable subject matter are inconsistent with his statements on what a person of ordinary skill would have known to be able to make and use the claimed invention. Once a person of ordinary skill in the art obtained the claimed, previously unknown, sequences taught in the '617 patent, they would have known how to make and use variations of the sequences that are 95% identical to the claimed sequences.

conventional and well known to those skilled in the art at the time of the '617 patent.” (Kay Opening Report at ¶ 181.)

- “techniques for site directed mutagenesis were well known in the art as of the priority date.” (Kay Opening Report at ¶ 182.)
- “a person of ordinary skill in the art knew how to carry out site directed mutagenesis of DNA, cloning of that DNA into a vector such as a plasmid, combining DNA sequences from different strains of AAV to create recombinant viral genomes, and inserting these constructs into host cells.” (Kay Opening Report at ¶ 197.)
- “conventional genetic engineering and recombinant engineering techniques were available to prepare cultured host cells containing a nucleic acid molecule encoding an AAV capsid protein.” (Kay Opening Report at ¶ 447.)
- “It would then have been routine for the person of ordinary skill in the art to apply known genetic engineering and recombinant engineering techniques to prepare cultured host cells – for example, by inserting the identified AAV sequence into a plasmid and inserting that plasmid into a bacterial host cell.” (Kay Opening Report at ¶ 471.)

402. I note that the inventors similarly described the knowledge of a person of ordinary skill in the art at the time of the invention, in their depositions in this case and in comments I understand they made to the patent office while the applications for the '617 patent and related patents were pending:

- “Methods of generating recombinant adeno-associated viruses in packaging host cells were well known as of November 2001.” (1/30/13 Wilson Declaration at ¶ 3(d).)
- “Packaging host cells for producing AAV were known to those of ordinary skill in the art at the time this invention was made. Also known were a variety of methods for generating such packaging host cells.” (1/30/13 Wilson Declaration at ¶ 5(b).)
- “Q. And, in 2001, methods for making recombinant AAVs using cultured host cells were known? A. Correct” (Wilson Deposition at 168:6-11.)

403. I note that the '617 patent itself identifies a similar state of the art at the time of the invention:

- “The preparation of a host cell according to this invention involves techniques such as assembly of selected DNA sequences. This assembly may be accomplished utilizing conventional techniques. Such techniques include cDNA and genomic cloning, which are well known.” ('617 patent at 25:37-47.)
- “The methods used to construct any embodiment of this invention are known to those with skill in nucleic acid manipulation and include genetic engineering, recombinant engineering, and synthetic techniques.” ('617 patent at 17:30-33; 18:57-61.)
- “The methods employed for constructing embodiments of this invention are conventional genetic engineering or recombinant engineering techniques such as those described in the references above.” ('617 patent at 24:3-6.)

404. In summary, Dr. Kay and I appear to generally agree about the state of the art at the time of the priority date of the '617 patent, in 2002. A person of ordinary skill in the art would have had all the tools needed to make and use cultured host cells containing nucleic acids encoding the full scope of the claimed capsid proteins.

405. I disagree with Dr. Kay's statement in paragraph 334 of his report that “it is not possible to determine the functional characteristics of an AAV capsid protein simply by inspection of the one dimensional sequence.” As an initial matter, as I have noted several times, I disagree that the asserted claims of the '617 patent require and are limited to AAV capsid proteins with the “functional characteristics” suggested by Dr. Kay. Rather, the sequences need only encode proteins that, if expressed, may be used to form an AAV capsid. With that understanding in mind, in my opinion, it would have been a routine task for a person of ordinary skill in the art to first, align a given AAV capsid protein sequence with AAVrh10 and determine the percent identity of the two sequences. If the percent identity was greater than 95%, then the person of ordinary skill in the art could go on to identify the amino acid substitutions different

from AAVrh10. It would have been a routine matter for the person of ordinary skill in the art to (i) assess the location of each substitution to determine if it was in a conserved region or a hypervariable region, (ii) identify whether each substitution was conservative or not, and (iii) compare the substitution against other substitutions in sequences that were known to result in a capsid protein, if expressed, namely those shown in Figure 2 of the '617 patent. In this manner a person of ordinary skill in the art could have reasonably determined whether the sequence would likely form a capsid protein, if expressed.

406. In my opinion, a person of ordinary skill in the art at the time of the invention would have been able to determine with a reasonable degree of probability whether a particular sequence that is 95% identical to the claimed sequences would be capable of forming a capsid, and the number of such sequences that fall within the asserted claims would not be “incomprehensibly large,” as I explained with respect to written description above.

3. The Inventors' Statements Further Show That the Asserted Claims Are Enabled

407. I do not agree with Dr. Kay's summaries of the deposition testimony of the '617 patent's inventors or the conclusions he reaches from that testimony.

408. Dr. Kay states that Dr. Wilson “testified that an amino acid sequence must function as an AAV capsid protein to form a functional AAV capsid.” (Kay Opening Report at ¶ 336, citing Wilson Deposition at 201:11-15.) Not only is this irrelevant in my opinion, as the claims do not require a “functional AAV capsid,” but it also does not accurately reflect what Dr. Wilson said. Dr. Wilson was asked “So an AAV -- an amino acid sequence that doesn't function as an amino -- as an AAV capsid protein can't form a functional AAV capsid, right?,” and he answered “Correct.” In my opinion, all Dr. Wilson was saying was that an amino acid sequence that is not a capsid protein is not capable of forming a functional AAV capsid. That does not

mean that the opposite is true – that in order to be a capsid protein, an amino acid sequence must be capable of forming a capsid. Dr. Wilson appears to agree with me, as he was asked just a few pages later: “If an amino acid sequence isn’t able to function to form an AAV capsid, then would you consider that AAV -- that amino acid sequence to be an AAV capsid protein?” and he answered “It still could. It just may not do its job well.” (Wilson Deposition at 214:21-215:2.)

409. Dr. Kay next states that “For an AAV vector, implicit functional properties of the AAV capsid protein include tropism – targeting of the recipient cell – and delivery of the nucleic acid,” citing Dr. Wilson’s deposition testimony and declarations that I understand were submitted to the patent office (while patent applications were pending that I understand are related to, but are not, the application that led to the ’617 patent and that claim different subject matter). (Kay Opening Report at ¶ 336, citing Wilson Deposition at 201:16-202:16, 203:21-204:16, 207:22-208:2; ¶ 343, citing Wilson Deposition at 191:21-192:15, 194:17-195:8, 195:9-196:14, 197:10-198:23, 199:8-24, 200:1-20.)

410. I have reviewed Dr. Wilson’s deposition testimony that Dr. Kay cites and Dr. Wilson’s declarations that Dr. Kay cites. I understand that the claims that Dr. Wilson discussed in his declarations were directed to an AAV capsid, not to cultured host cells encoding sequences of AAV capsid proteins. In my opinion therefore, all of Dr. Wilson’s statements in his declarations are irrelevant to the requirements of the asserted claims of the ’617 patent, as Dr. Wilson explained in his deposition. (Wilson Deposition at 194:9-12 (“Q. So they’re different functionalities of an AAV capsid, correct? A. They’re different functionalities of an AAV vector.”).)

411. In other words, the capsid protein encoded by the cultured host cells in the ’617 patent’s claims does not—and in fact, cannot—deliver nucleic acid or target a recipient cell on

its own. For example, in bacterial cells, the encoded protein is not expressed, and cannot have any of these functions. Dr. Wilson explained this in his deposition, stating that if you look at the claims of the '617 patent, "the claim is a cell with the vp1 capsid -- sequence -- it -- it -- I'm just looking at the claim, and the claim is a host cell with a vp1 sequence nucleic acid with a heterologous non-AAV sequence, so that -- it doesn't say anything more than that," and "there are many situations where -- I mean, there are situations just because you have a vp1 sequence doesn't mean you have an AAV vector." (Wilson Deposition at 210:5-211:15.) Dr. Wilson's characterization of the claims in the '617 patent is consistent with my opinions. For this reason, none of the "different degrees of functionality for each characteristic of an AAV capsid protein" that Dr. Kay identifies in paragraph 343 are required by the asserted claims. Instead, the asserted claims of the '617 patent require only that the sequence encode a protein that, if it is expressed, may be used to form an AAV capsid.

412. Dr. Gao's deposition testimony that Dr. Kay cites does not change my opinions. (Kay Opening Report at ¶¶ 335, 337, 338.) As I discuss above, in his deposition both Dr. Gao and Sarepta's attorney seemed to interchange the specific, narrow, invention in the '617 patent's claims and the AAV vector itself, which I understand is described in the '617 patent but is not claimed. Dr. Gao's testimony, therefore, does not change my opinion on the scope of the asserted claims or what would be required for a person of ordinary skill in the art to make and use the full scope of the asserted claims.

413. Mr. Alvira's testimony that Dr. Kay cites does not change my opinions either. Dr. Kay cites a section of Mr. Alvira's testimony where Mr. Alvira was being asked about the work leading up to the invention described in the '617 patent. (Kay Opening Report at ¶¶ 339-340,

citing Alvira Deposition at 124:21-125:25, 126:11-127:4, 127:5-132:22, 144:6-145:25.) Mr.

Alvira described how, in the process of arriving at the invention:

whenever I would make these discoveries, all I had to go by was the DNA sequence, which tells you nothing. It could be anything. It could be a piece of the -- you know, the tissue -- tissue host -- host tissue DNA, right? And so, in order for us to characterize it to find out if it actually can code for a protein sequence that is a capsid protein and that would make a virus, you know, all of that goes into the process of concluding that what I discovered is -- is this a real AAV sequence.

(Alvira Deposition at 124:9-19.) Mr. Alvira's testimony simply explains that determining that what he had discovered was a real AAV sequence required additional experimentation and analysis, including testing to determine whether the AAV sequence would result in a functional AAV capsid. In my opinion, that is a different question than whether, once discovered, and then described in the '617 specification, a person of ordinary skill in the art would be able to make and use the full scope of the claimed inventions. The same analysis applies to Dr. Kay's statement in paragraph 342 that "Dr. Wilson testified that in 2001, to understand the functional characteristics of AAV capsid proteins, he and his colleagues made and tested them" and that "At the time of the '617 patent, they would not have relied on just the amino acid sequence or nucleic acid sequence to determine the functional characteristics of an AAV capsid protein." (Kay Opening Report at ¶ 342, citing Wilson Deposition at 164:13-18, 165:11-22, 165:23-166:4.) For all of the reasons I discuss here, a person of ordinary skill in the art would have been able to make and use the full scope of the claims by following the guidance in the '617 patent and applying nothing more than routine analysis and experimentation.

4. The Scientific Literature Dr. Kay Cites Does Not Support Lack of Enablement

414. Dr. Kay cites the Wu 2000 paper, and states that "it has been demonstrated in the scientific literature that even small changes in an AAV capsid protein can have significant

deleterious effects on capsid structure and function,” and in particular “a single amino acid mutation wiped out a core function of the capsid protein.” (Kay Opening Report at ¶ 345, discussing Kay Ex. 13.) Specifically, Dr. Kay identifies a single point mutation that “completely destroyed the ability of the capsid to package the viral DNA.” (Kay Opening Report at ¶ 345.) But in my opinion, Dr. Kay misses a key point. While the capsid may not have been able to package viral DNA, it was able to form a stable capsid. (Wu 2000 at 8639, identifying *mut31* as an arginine to alanine substitution at residue 432 that resulted in “ni, empty particle,” meaning a noninfectious empty capsid.) Therefore, if a mutation like Wu’s single point mutation was made in the AAVrh10 sequence, the sequence would still be within the scope of the asserted claims of the ’617 patent because it was still capable of forming a capsid. Instead, mutations that resulted in “no capsid” in Wu required much more disruptive mutations, either of multiple residues over a short span, or through larger insertions, such as insertions of the highly serpin receptor ligand (FVFLI) or the FLAG antibody epitope (DYKDDDDKYK)—both of which were expected to disrupt the capsid structure. (Wu 2000 at 8638, identifying these as class 4 mutations; at 8640, stating “As expected, substitutions at class 2 (partially defective) or class 4 (nonviable) positions did not produce infectious virus.”)

415. Further, I note that Wu 2000 is an excellent example of conducting routine experimentation to easily determine whether capsids are formed in a variety of different sequences. Wu 2000 tested 93 different sequences using high throughput assays such as the A20 ELISA kit, in which crude (i.e. not purified) rAAV stocks harvested from individual cell cultures are serially diluted and tested for the presence of particles (i.e. capsids)—both full and empty. (Wu 2000 at 8636.) I have used similar ELISA kits, and they generally consist of 96 well plates that allow a researcher to easily analyze a multitude of samples at one time. That was also the

case in 2002. After making modifications to the sequences of the type that are disclosed and described in the specification, it would be trivial to test numerous samples simultaneously for the presence or absence of capsid.

416. Dr. Kay also cites a 2009 paper by Vandenberghe and states that “even a single mutation in a capsid protein can destroy one or more core functions.” (Kay Opening Report at ¶ 346, citing Kay Ex. 33.) As Dr. Kay acknowledges, Vandenberghe “describes certain point mutations with the term ‘singleton,’ which they define as a point mutation that occurs at an otherwise apparently conserved site in the protein.” (Kay Opening Report at ¶ 347, citing Vandenberghe at 1417.) Interestingly, these singletons—though acting on conserved residues—are found not only in conserved domains, but can also be found in hypervariable domains too. (Vandenberghe at 1417, explaining that “Singleton sites were found throughout Cap and surprisingly located both within hypervariable domains as well as within structurally conserved domains of the capsid.”) The key is that the residue the singleton acts upon is a conserved residue. That is why a person of ordinary skill in the art would generally avoid substituting residues known to be conserved through multiple stable capsid proteins, as I explained above. Additionally, the mutations described in Vandenberghe did not destroy all functions, as Dr. Kay appears to imply. Instead, the authors found that the singleton mutations reduced certain functions of the AAV viral vectors, including a reduced ability to produce a vector in the first place or to transduce. (Vandenberghe at 1417.) There is no suggestion in the paper that these singleton mutants fail to form a capsid at all. Just like I described above with respect to the Wu paper, if the singleton mutations in Vandenberghe were made in the AAVrh10 sequence, they could fall within the scope of the asserted claims (assuming they meet the “at least 95% identical” limitation) because a capsid would still be expected to form.

417. In my opinion, Vandenberghe supports that a person of ordinary skill in the art identifying whether a given sequence meets the at least 95% identity limitation of the asserted claims in the '617 patent would know to avoid substituting conservative residues, or else would know how to test the resulting capsid protein to determine whether it, when expressed, creates a capsid. This testing would be nothing more than routine experimentation, conducted because a persons of ordinary skill in the art would have understood it was changing a typically conserved residue. For this reason, I disagree with Dr. Kay's statement that Vandenberghe "confirms that the art of the '617 patent is highly unpredictable" such that a "person of ordinary skill in the art would have no way of selecting amino acid or nucleic acid sequences with any desired functionality from the enormous genera encompassed in the Asserted Claims without undue experimentation."⁸ (Kay Opening Report at ¶ 348.)

418. I also do not agree that any of the remaining materials that Dr. Kay cites support lack of enablement. Dr. Kay references a 2004 paper by Dr. Gao that Dr. Kay says supports his opinion "that the specification of the '617 patent does not enable a person of ordinary skill in the art to practice the full scope of the Asserted Claims without undue experimentation." (Kay Opening Report at ¶ 350, referring to Kay Ex. 32.) But I note that Dr. Kay only says, without citing anything, that "many" of the identified AAV isolates "potentially fall within the scope of the Asserted Claims." (Kay Opening Report at ¶ 350.) In my opinion, whether these additional isolates were discovered experimentally or through sequence prediction is irrelevant to whether

⁸ I also note that Dr. Kay cites Dr. Gao's testimony in interpreting Vandenberghe. (Kay Opening Report at ¶ 349.) Dr. Gao testified that his only contribution to Vandenberghe "likely...was [to] provide those sequences for them to do analysis," (Gao Deposition at 225:19-24), and that Vandenberghe "has nothing to do with rhesus 10 [rh10] sequence" (Gao Deposition at 231:10-13). Further, while Dr. Gao testified that one would use an "error and trial process," I understand that Dr. Gao was never asked if the amount of experimentation required to do so would be undue. (Gao Deposition at 232:9-15.)

the asserted claims are enabled. Similarly, in my opinion, Dr. Kay's statement that other researchers "discovered and characterized additional AAV strains after the priority date of the '617 patent" is also irrelevant. (Kay Opening Report at ¶ 351.) Additional strains identified after the '617 patent's 2002 priority date have nothing to do with whether a person of ordinary skill in the art was able to make and use the full scope of the asserted claims of the '617 patent.

419. In my opinion, Dr. Kay's statement that the "degeneracy of the genetic code provides further evidence that the applicants did not enable a person of ordinary skill in the art to practice the Asserted Claims without undue experimentation" is equally irrelevant, as is his statement that as "late as 2017, researchers continued to publish original research articles describing codon optimization strategies they were employing to improve the functioning of gene therapy vectors." (Kay Opening Report at ¶¶ 352-353.)

420. As I explain above, the claims of the '617 patent require cultured host cells containing recombinant nucleic acid sequences that encode particular sequences. In my opinion, potential effects of codon usage on protein expression (particularly those not discovered until 2017) are not relevant to the asserted claims or whether they were enabled. And just because researchers continued to find additional strategies does not suggest that the knowledge and tools available in the art as of June 2002, along with the information provided in the '617 patent specification, was insufficient to enable the claims.

5. The Wands Factors Demonstrate That Any Experimentation to Practice the Full Scope of the Asserted Claims Was Routine

421. As I have previously said, I am not a lawyer, but I understand that certain factors referred to as the "Wands factors" are considered when determining whether a person of ordinary skill may be able to practice the full scope of the claims without undue experimentation. I address each Wands factor and Dr. Kay's position as to each below.

a. Factor 1: The Quantity of Experimentation Necessary to Make or Use the Invention

422. Based on the significant guidance provided in the '617 patent, coupled with the knowledge of a person of ordinary skill in the art, in my opinion relatively minimal experimentation would be necessary to make or use the inventions in the claims of the '617 patent. As discussed above, a person of ordinary skill in the art in 2002 would have been able to readily determine sequences that were at least 95% identical the claimed sequences, and would have further understood from the specification (including Figure 2), from the knowledge of conserved and variable regions in the '617 patent, and from knowledge in the art about which types of substitutions could be made to AAVrh10 such that the sequence could, if expressed, be part of an AAV capsid. Because the techniques used to make and use recombinant AAV vectors were well known to persons of ordinary skill in the art at the time of the invention in 2002, in my opinion it would have required little experimentation for a person of ordinary skill in the art to make and use the full scope of the inventions in the '617 patent's claims. I note, for example, that papers Dr. Kay cited, such as the Wu 2000 reference, describe testing nearly 100 different mutations in just one study, demonstrating that some experimentation is routine in the art, and not undue.

423. As discussed above, I disagree with Dr. Kay's calculations and assertion that the scope of the invention "is unimaginably large – on the order of 10^{100} amino acid sequences, and 10^{200} nucleotide sequences." (Kay Opening Report at ¶ 357.) Dr. Kay ignores both the teachings in the '617 patent and what a person of ordinary skill in the art would know about the effects of making substitutions in different domains of the sequences that are disclosed and described in the specification, for example the conserved domain as opposed to the hypervariable domain. Specifically, a person of ordinary skill in the art would have known that substituting

residues in a conserved domain (particularly if the substitution itself is not conservative) would have been significantly more likely to affect the AAV capsid protein structure than, for example, a conservative substitution in a hypervariable domain.

424. I further disagree with Dr. Kay’s statement that “the function of the viral capsid protein produced by each such cell would have to be characterized, to determine if it could even form a functional capsid.” (Kay Opening Report at ¶ 358.) Depending on the particular substitutions being made to the sequences that are disclosed and described in the specification and the location of those substitutions, testing may not even be necessary to reasonably predict whether the sequence will yield an AAV capsid protein within the scope of the asserted claims of the ’617 patent. Where a substitution is less conservative, or made in a conserved domain, then a simple test like the ELISA assay described in Wu 2000 could be used to determine if the expressed protein may form a capsid (regardless of whether filled or empty). In my opinion, the other testing⁹ that Dr. Kay suggests is required to determine if a sequence falls within the scope of the claims is not needed to determine whether a sequence falls within the asserted claims because that testing is all directed to functions that go beyond what the claims require. (Kay Opening Report at ¶ 358, describing testing of “other basic functions of an AAV virion, such as viral genome packaging capability, serology, tissue tropism, and transduction efficiency.”)

b. Factor 2: The Amount of Direction or Guidance the Patent Provides

425. As I discuss above, the ’617 patent provides significant guidance to the person of ordinary skill in the art as to how to select particular sequences falling within the scope of the

⁹ Dr. Kay cites Mr. Alvira’s testimony that “it would have taken an ‘army of scientists’ years to fully characterize just the naturally occurring variants,” (Kay Opening Report at ¶ 358), which again in my opinion confuses the development of the invention with the proper inquiry here—which is whether persons of ordinary skill in the art were able to make and use the inventions in the ’617 patent’s claims without undue experimentation.

asserted claims. I note that, when discussing written description, Dr. Kay acknowledges that the '617 patent provides 10-15 sequences "plausibly within the claimed genus." (Kay Opening Report at ¶ 281.) Dr. Kay acknowledges that within those sequences, specific substitutions can be identified that are within the scope of the asserted claims. (Kay Opening Report at ¶ 292.) Specifically, Dr. Kay identifies from the example sequences that the "variations in the disclosed amino acid sequences that appear to meet the limitations of the asserted claims are concentrated in only 66 out of 738 residues, or about 9% of the total length of the 738 amino acid sequence of rh.10." (Kay Opening Report at ¶ 293.) While I do not believe the scope of the asserted claims of the '617 patent are limited to substitutions in those 66 residues, it is my opinion that the location and nature of those substitutions does inform a person of ordinary skill in the art about the type of substitutions that can be made within the scope of the asserted claims.

426. In addition to the sequences that the '617 patent discloses that are within the scope of the asserted claims, the other sequences identified by the '617 patent in Figure 2 are other AAV capsid proteins. A comparison of the amino acids in each of these residues provides significant additional guidance to a person of ordinary skill in the art as to what additional substitutions can be made to the sequence of the AAVrh10 capsid protein without compromising the sequence's ability to form a capsid, if expressed.

427. By focusing on whether the '617 patent provides guidance for how to "obtain particular functional characteristics," Dr. Kay does not focus his analysis on the language of the claims of the '617 patent. (Kay Opening Report at ¶¶ 359-360.) This analysis is incorrect, as I explain above.

c. Factor 3: The Presence or Absence of Working Examples in the Patent

428. As I discuss above, Dr. Kay’s table in paragraph 281 of his report shows there are 15 amino acid sequences and 10-12 examples of nucleic acid sequences disclosed in the ’617 patent that have “at least 95% sequence identity” to the sequences in the asserted claims of the ’617 patent. In my opinion, a person of ordinary skill in the art would have understood these sequences to be examples in the ’617 patent of proteins that, when expressed, form capsids and meet the asserted claims. Coupled with the other AAV capsid protein sequences disclosed in Figure 2, these implemented examples provide significant guidance to a person of ordinary skill in the art.

429. I note that Dr. Kay’s statements in paragraph 363 of his report about “actual testing” of only two sequences (other than AAVrh10 itself) “to determine their functional characteristics” are misplaced, because as I have described above, the claims of the ’617 patent do not require any functional characteristics.

d. Factor 4: The Nature of the Invention

430. As I have discussed above, the ’617 patent discloses a number of examples of sequences that are within the asserted claims, in addition to other examples of working capsid proteins, from which a person of ordinary skill in the art would be able to discern the types of substitutions that could be made to a sequence and still be within the scope of the asserted claims. In my opinion, Dr. Kay’s assertion in paragraph 365 that the “relationship of the linear, one dimensional sequences of these variants to their possible functions as part of an AAV capsid is a scientific area that is extremely complicated and unpredictable” is largely irrelevant to the asserted claims (which require no specific function) and also ignores the many teachings in the

prior art that mutations that can be made to an AAV vector without affecting the AAV vector's ability to form a capsid, if expressed.

e. Factor 5: The State of the Prior Art

431. In my opinion, the prior art at the time of the priority date of the '617 patent was not nearly as stunted as Dr. Kay describes in paragraph 366. I note that the references Dr. Kay cites, such as Wu 2000, contain significant information and guidance regarding the types of substitutions that could be made in AAV vectors without compromising a sequence's ability to encode for a protein, that, if expressed, can be used to form a capsid.

432. In my opinion, Dr. Kay's characterizations of the disclosures of the '617 patent are inconsistent with Dr. Kay's own patents in the same field. As I discussed above, Dr. Kay has several patents claiming sequences that are "at least 95% identical" to AAV vp1 capsid protein sequences and contain even less examples or guidance than the '617 patent. I therefore do not agree with Dr. Kay's comment that the "extremely limited number of '617 patent examples" (compared against even fewer examples in his own patents) would be insufficient to permit a person of ordinary skill in the art to practice the full scope of the claims, even today, falls short. (Kay Opening Report at ¶ 366, stating "Even today, such an undertaking would not be possible".)

f. Factor 6: The Skill Level Possessed by a Person of Ordinary Skill in the Art

433. While I agree with Dr. Kay that "A person of ordinary skill in the art of the '617 patent would have technical training," I disagree that "such training would not be sufficient to reduce the unpredictability of the field." (Kay Opening Report at ¶ 367.) For all the reasons described above, in my opinion, the '617 patent and the knowledge in the art at the time provided sufficient predictability to enable a person of ordinary skill in the art to identify, make, and use,

the full scope of the inventions claimed in the '617 patent, without undue experimentation. In my opinion, whether a person of ordinary skill in the art could “predict the functional characteristics of an AAV capsid protein from the one dimensional amino acid sequence alone” is irrelevant to this inquiry. (Kay Opening Report at ¶ 367.)

g. Factor 7: The Predictability or Unpredictability of the Art

434. Dr. Kay’s analysis of Factor 7 again focuses on making “functional predictions” and he repeats his comment that a single amino acid change “can destroy the ability of an AAV capsid protein to carry out its core functions.” (Kay Opening Report at ¶ 368.) As I discuss above, the Wu 2000 and Vandenberghe papers that Dr. Kay cites show that a single amino acid substitution change does not actually prevent an AAV capsid protein from forming. In my opinion, a person of ordinary skill in the art could use the guidance in the '617 patent to make and use cultured host cells that have sequences that could be reasonably predicted to form AAV capsids if expressed.

h. Factor 8: The Breadth of the Claims

435. As I have addressed above, the asserted claims are not as broad as Dr. Kay states. I understand the asserted claims are limited by the Court’s definition of “at least 95% identical,” which I understand specifies that the sequences must be aligned for maximum correspondence and considered over the full length of the referenced sequence. That step alone reduces the potential scope of the claims. Further, as I discuss in the written description section above, Dr. Kay’s calculations of “on the order of 10^{100} amino acid sequences, and 10^{200} nucleotide sequences” are not consistent with how a person of ordinary skill in the art would have understood the '617 patent and the asserted claims and does not take into account the understanding of a person of ordinary skill in the art about where and how to make sequence alterations.

436. For all of the reasons I explain above, in my opinion a person of ordinary skill in the art could have made and used the inventions in the asserted claims of the '617 patent without undue experimentation.