IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENZYME CORPORATION and AVENTIS INC., Plaintiffs v. NOVARTIS GENE THERAPIES, INC. and NOVARTIS PHARMACEUTICALS CORPORATION, Defendants.	Civil Action No. 21-1736-RGA

MEMORANDUM OPINION

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ANDREWS, U.S. DISTRICT JUDGE:

Before me is the issue of claim construction of multiple terms in U.S. Patent Nos. 6,596,535 ("the '535 patent"), 7,125,717 ("the '717 patent"), 7,785,888 ("the '888 patent"), 7,846,729 ("the '729 patent"), 8,093,054 ("the '054 patent"), and 9,051,542 ("the '542 patent"). The '535, '717, '888, '729, and '054 patents are members of the same patent family; I will refer to them as the "Carter patents." The parties submitted a Joint Claim Construction Brief (D.I. 101), and I heard oral argument on April 13, 2023 (D.I. 177, hereinafter cited as "Tr.").

I. BACKGROUND

The asserted patents concern techniques for gene therapy. The technology at issue uses recombinant vectors of adeno-associated virus ("AAV") to deliver functional copies of a gene to patients who lack them. ('535 patent at 1:21-24;[1] '542 patent at 1:15-19; D.I. 101 at 8, 11). Adeno-associated virus is a naturally occurring virus with several serotypes, or strains. (D.I. 109 at A0761). On entering a cell, it replicates its genome, creating copies of itself. ('535 patent at 1:65-2:39). An AAV's natural genome can be replaced by another gene sequence, such as the desired human sequence. When the modified virus enters the cell, it will create copies of itself as modified. (*Id.* at 3:19-3:28). A virus that has been modified to deliver a gene other than its natural genome into a cell is called a recombinant viral vector—in the case of AAV, an "rAAV vector." (*Id.* at 9:19-40).

The five Carter patents concern the making of recombinant gene therapy vectors. They disclose a structure of rAAV vector that increases the efficiency of replication of the payload gene. (*Id.* at 4:45-49). The '542 patent teaches the formulation of prepared vectors for storage without clumping. ('542 patent at 1:17-19).

[1] The Carter patents share an identical specification. Citations are to the specification of '535 patent, which is the earliest of the Carter patents (and the one cited by the parties).

II. LEGAL STANDARD

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" *SoftView LLC v. Apple Inc.*, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (alteration in original) (quoting *Phillips*, 415 F.3d at 1324). When construing patent claims, a court considers the literal language of the claim, the patent specification, and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977–80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Of these sources, "the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (internal quotation marks omitted).

"[T]he words of a claim are generally given their ordinary and customary meaning. . . . [Which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312–13 (citations and internal quotation marks omitted). "[T]he ordinary meaning of a claim term is its meaning to [an] ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted). "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314.

When a court relies solely upon the intrinsic evidence—the patent claims, the specification, and the prosecution history—the court's construction is a determination of law. *See Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 331 (2015). The court may also make factual findings based upon consideration of extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317–19 (quoting *Markman*, 52 F.3d at 980). Extrinsic evidence may assist the court in understanding the underlying technology, the meaning of terms to one skilled in the art, and how the invention works. *Id.* Extrinsic evidence, however, is less reliable and less useful in claim construction than the patent and its prosecution history. *Id.*

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). Inferring indefiniteness because a claim's scope is broad, however, is "legally incorrect: 'breadth is not indefiniteness.'" *BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1367 (Fed. Cir. 2017) (quoting *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1341 (Fed. Cir. 2005)). The party raising indefiniteness bears the burden of proving it by clear and convincing evidence. *See BASF*, 875 F.3d at 1365.

III. CONSTRUCTION OF AGREED-UPON TERMS

I adopt the parties' agreed-upon constructions as set forth in their Joint Claim Construction Brief.[2] (D.I. 101 at 3-6).

[2] I do this with some reservations. *See, e.g.*, footnote 4 *infra*. Some of the constructions include examples, which, generally-speaking, are not definitional. At some time before trial, I would like the parties to consider whether some of these constructions cannot be improved.

IV. THE CARTER PATENTS

A. Background and Representative Claims

The Carter patents disclose a molecule referred to as a "snapback molecule" that purports to speed up the process of expressing the gene delivered by an rAAV vector. (D.I. 101 at 8, 13). AAV and rAAV genomes consist of single-stranded DNA molecules, which need to be converted to double-stranded DNA molecules to be expressed and replicated in the human body. (*Id.* at 7, 12). Snapback molecules contain both sides of the double strand to be delivered, stacked into a single long strand that can bend back on itself to form a double strand. (*Id.* at 7-8, 13).

For a gene sequence to be properly replicated in the patient, certain sequences need to be present at the ends of the longer single strand. (*Id.* at 12). These are known as "inverted terminal repeat" (ITR) sequences. (*Id.*). Naturally occurring AAVs of the same serotype have the same ITR sequences. (*Id.* at 23). These naturally occurring ITR sequences are referred to as "native." Scientists have also developed modified ITR sequences that can serve the same function as native sequences. (*See generally* D.I. 101 at 8-9, 17-18). These modified sequences may also be referred to as "mutated" or "recombinant."

The parties agree for the purposes of claim construction of terms in the Carter patents that claim 2 of the '717 patent, claim 1 of the '729 patent, and claim 1 of the '054 patent are representative. Those claims read as follows.

> 2. A method for expressing a polynucleotide coding region in a cell, comprising subjecting the cell to ***conditions which allow*** expression of the coding region, whereby the coding region is expressed, wherein the polynucleotide coding region is introduced into the cell by contacting the cell essentially in the absence of an AAV helper virus with an rAAV particle comprising an ***rAAV vector***, wherein the rAAV vector comprises a single-stranded heterologous nucleotide sequence comprising the coding region which ***forms intrastrand base pairs such that expression of the coding region of the heterologous sequence is enhanced***

relative to a second rAAV vector that lacks sufficient intrastrand base pairing to enhance said expression, wherein the rAAV vector comprises one or more inverted terminal repeat (ITR) sequences flanking said heterologous sequence.

('717 Patent, 42:53-67 (disputed terms bolded and italicized)).

1. A method for preparing a recombinant adeno-associated virus (rAAV), the method comprising:
1) incubating a host cell under ***conditions that allow*** AAV replication and encapsidation, wherein said host cell comprises:
(a) a ***rAAV vector*** comprising a heterologous nucleotid sequence and one or more AAV inverted terminal repeat (ITR) sequences flanking said heterologous sequence, wherein the vector is less than about 2.5 kb, and
(b) AAV rep function, AAV cap function, and helper virus function for AAV; and
2) purifying rAAV particles produced from the host cell, wherein the rAAV particles comprise a ***rAAV genome*** which ***forms intrastrand base pairs along its length, such that expression of the coding region of the heterologous sequence is enhanced relative to a second rAAV vector that lacks sufficient intrastrand base pairing to enhance said expression***.

('729 Patent, 41:31-49 (disputed terms bolded and italicized)).

1. A composition comprising a purified recombinant adeno-associated virus (rAAV) particle comprising an AAV capsid and a single-stranded ***rAAV vector genome***, wherein the rAAV vector genome comprises in the 5′ to 3′ direction: ***a 5′ AAV inverted terminal repeat (ITR) sequence, a first heterologous nucleotide sequence, an internal AAV ITR sequence, a second heterologous nucleotide sequence, and 3′ AAV ITR sequence***, wherein the first heterologous nucleotide sequence can form intrastrand base pairs with the second nucleotide sequence ***along most or all of its length***.

('054 Patent, 41:30-40 (disputed terms bolded and italicized)).

B. Construction of Disputed Terms

I treat the first three terms together because the same issue is disputed for all three terms: whether the inverted terminal repeat (ITR) sequences in the claimed invention must be native sequences that can be found in naturally occurring AAV vectors. Based on the evidence and arguments presented, I conclude that the AAV ITR sequences in the claimed vectors must be native.

1. **"A 5′ AAV inverted terminal repeat (ITR) sequence, a first heterologous nucleotide sequence, an internal AAV ITR sequence, a second heterologous nucleotide sequence, and a 3′ AAV ITR sequence" ('054 patent, claims 1-7, 9, 11-13, 15, 17-27, 30-32, 34, 36)**

    a. *Plaintiffs' proposed construction*: "A 5′ AAV inverted terminal repeat (ITR) sequence (as AAV inverted terminal repeat (ITR) sequence is defined), a first heterologous nucleotide sequence (as heterologous nucleotide sequence is defined), an internal AAV ITR sequence (as AAV inverted terminal repeat (ITR) sequence is defined), a second heterologous nucleotide sequence (as heterologous nucleotide sequence is defined), and a 3′ AAV ITR sequence (as AAV inverted terminal repeat (ITR) sequence is defined)"
    b. *Defendants' proposed construction*: "A native 5′ AAV inverted terminal repeat (ITR) sequence . . . and a native 3′ AAV ITR sequence."
    c. *Court's construction*: "A native 5′ AAV inverted terminal repeat (ITR) sequence . . . a native internal AAV ITR sequence . . . and a native 3′ AAV ITR sequence."

2. **"recombinant AAV vector (rAAV vector)" ('888 patent, claims 1-2, 4, 6; '729 patent, claims 1-5, 7-9; '054 patent, claims 1-7, 9, 11-13, 15, 17-27, 30-32, 34, 36)**

    a. *Plaintiffs' proposed construction*: "a polynucleotide vector comprising one or more heterologous sequences (i.e., polynucleotide sequence not of AAV origin) that are flanked by at least one, preferably two, AAV inverted terminal repeat sequences (ITRs)"
    b. *Defendants' proposed construction*: "a polynucleotide vector comprising one or more heterologous sequences (i.e., polynucleotide sequence not of AAV origin) that are flanked by at least one, preferably two, AAV inverted terminal repeat sequences (ITRs), wherein each ITR of the polynucleotide vector is native AAV ITR sequence"
    c. *Court's construction:* "a polynucleotide vector comprising one or more heterologous sequences that are flanked by at least one AAV ITR sequence, wherein each ITR of the polynucleotide vector is a native AAV ITR sequence"[3]

3. **"rAAV vector genome" / "rAAV genome" ('535 patent, claims 1-26, 28-29; '717 patent, claims 1-8, 11-17, 20; '888 patent , claims 1-2, 4, 6; '729 patent, claims 1-5, 7-9)**

    a. *Plaintiffs' proposed construction*: "the genetic material of a recombinant AAV vector or virus"
    b. *Defendants' proposed construction*: "the genetic material of a recombinant AAV vector, i.e., a polynucleotide vector comprising one or more heterologous sequences (i.e., polynucleotide sequence not of AAV origin) that are flanked by at

[3] Both parties propose the language "flanked by at least one, preferably two, AAV inverted terminal repeat sequences." This language apparently comes from the Carter patents' specification. ('535 patent at 9:44). I do not think the phrase "preferably two" changes the meaning of the construction or would be helpful to a jury. I do not include it in my construction.

least one, preferably two, AAV inverted terminal repeat sequences (ITRs), wherein each ITR of the polynucleotide vector is native AAV ITR sequence"

c. *Court's construction*: "the genetic material of a recombinant AAV vector"

The phrases "AAV ITR sequence" and "ITR sequence" are closely associated with all three of these terms. The parties have stipulated to construction for both phrases. (D.I. 101 at 3, 4). The parties' agreed-upon constructions come from the definitions in the specifications of the Carter patents. ('535 patent at 11:10-24). The construction of "inverted terminal repeat"/"ITR sequence" reads, "a term well understood in the art and refers to relatively short sequences found at the termini of viral genomes which are in opposite orientation."[4] (D.I. 101 at 4). The stipulated construction of "AAV inverted terminal repeat (ITR) sequence" is,

> a term well-understood in the art, it is an approximately 145-nucleotide sequence that is present at both termini of the native single-stranded AAV genome. The outermost 125 nucleotides of the ITR can be present in either of two alternative orientations, leading to heterogeneity between different AAV genomes and between the two ends of a single AAV genome. The outermost 125 nucleotides also contain[] several shorter regions of self-complementarity, allowing intrastrand base-pairing to occur within this portion of the ITR.

(*Id.* at 3).

Plaintiffs argue that the stipulated constructions do not exclude the use of non-native ITRs. Further, Plaintiffs argue, the specification makes clear that the claims encompass modified ITR sequences whenever they refer to an "AAV ITR," a "recombinant AAV (rAAV) vector," or an "rAAV genome." (*Id.* at 8).

First, Plaintiffs point to the specification's discussion of "modified ITRs" as evidence that these modified ITRs "can be used as part of" Dr. Carter's invention. (*Id.* at 8, 21). The specification cites prior art such as U.S. patent application No. 09/171,759 ("Feldhaus"), which

[4] The parties should consider whether a definition that includes, "a term well understood in the art and refers to," or the like, is helpful to the jury. Maybe, the agreed construction should just be, "the relatively short sequences found at the termini of viral genomes which are in opposite orientation"? The parties should also clarify if the term should be "inverted terminal repeat" / "ITR," or perhaps "inverted terminal repeat sequence" / "ITR sequence."

the specification describes as disclosing a "modified ITR." ('535 patent at 19:14-18). The specification also discusses the fact that U.S. Patent No. 5,478,745 ("Samulski") describes a non-native ITR. (*Id.* at 20:7-13). Plaintiffs argue that Samulski and its non-native ITR are incorporated by reference. (D.I. 101 at 20-21). Beyond the fact that the patents indicate awareness of the existence of modified ITR sequences, Plaintiffs contend that the modified ITR described in Samulski is part of the preferred embodiment of the claimed invention. (Tr. at 42:21-43:23).

Second, Plaintiffs observe that the claims include no adjectives or descriptors for "AAV ITRs." (D.I. 101 at 10). They argue that this means that the claims do not limit the nature of these ITRs. (*Id.*).

Third, Plaintiffs argue that the specification's use of "approximately 145-nucleotide sequence" indicates that it contemplates non-native sequences. (*Id.* at 19-20). Specifically, Plaintiffs argue that because the native AAV ITR sequence is 145 nucleotides long, the fact that the patent contemplates other lengths means that it must contemplate non-native sequences. (*Id.*).

Defendants argue that the three claim terms encompass only native AAV sequences and, in the case of the second and third terms, vectors and genomes that contain native sequences. Defendants point to part of the stipulated construction for "AAV inverted terminal repeat (ITR) sequence," which reads, "an approximately 145-nucleotide sequence that is present at both termini of the native single-stranded AAV genome." (*Id.* at 15). In defining the sequence as present in the native genome, Defendants argue, the stipulated construction expressly requires that the sequence be native. Further, Defendants note that each example in the specification uses native AAV ITR sequences. (*Id.* at 16).

As for Plaintiffs' first argument about the specification's discussion of non-native sequences, Defendants argue that the prior art refers to modified sequences—in which the 145-nucleotide sequence has been changed and is not present—as "transcriptionally activated ITR[s]," not "modified ITRs." (*Id.* at 17). Defendants observe that the patents do not even cite to the parts of Feldhaus that discuss these transcriptionally activated ITRs. (*Id.*). Defendants notes that, instead, the patent cites to the parts of Feldhaus that discuss native sequences with extra nucleotides added on, which means that the 145-nucleotide native sequence is still present and intact. (*Id.* at 16-17, 22). Thus, native ITRs are present in any embodiments that use those sequences.

Defendants also argue that the Samulski patent's notice of allowance states that the Carter patents, unlike the Samulski patent, feature an ITR that "is not modified," suggesting that even if the Samulski patent discloses a modified ITR, the Carter patents do not use it. (*Id.* at 23). Defendants challenged at oral argument the assertion that Samulski is part of the preferred embodiment. (Tr. at 41:2-8).

In response to Plaintiffs' second argument, Defendants contend that the descriptor "AAV" is itself a limitation on "ITR sequence." (D.I. 101 at 16). Here, Defendants point again to the stipulated construction of "AAV ITR sequence" as compared to "ITR sequence."

In response to Plaintiffs' third argument, Defendants cite to prior art indicating that native sequences vary slightly in length depending on the serotype of AAV. (*Id.* at 22-23). Defendants argue that the word "approximately" was intended to accommodate this natural variation between strains of the virus, of which a POSA would have been aware. (*Id.*).

I agree with Defendants. The mere fact that modified ITR sequences are mentioned in the specification does not mean that they are claimed. Plaintiffs say that "the specification makes it

clear that . . . non-native modified sequences are still 'AAV ITR sequences.'" Yet, each example it points to refers to the non-native sequence as an "ITR," not an "AAV ITR." ('535 patent at 19:14-18, 20:7-13). I do not believe there is any place in the specification where the entire phrase "AAV ITR" is used to describe a non-native sequence. "ITR" and "AAV ITR" are defined separately in the patent, and the parties stipulated to distinct constructions for each phrase. This undercuts Plaintiffs' argument that the patent does not place any requirements on an "AAV ITR sequence." Under the parties' agreed-upon constructions and in light of the specification, I find an AAV ITR sequence is required to be native even though an ITR sequence is not so required.

Plaintiffs' other arguments do not disturb this conclusion. As for Plaintiffs' preferred embodiment argument, I see no indication in the Carter patents' specification that the Samulski sequence is part of the preferred embodiment. (*See generally* '535 patent at 19:64-20:15). Although the specification of the Carter patents discloses preferred embodiments, it does not connect any of them with a particular ITR sequence. In fact, Plaintiffs' counsel admitted at oral argument that the patent "does not say" that the Samulski sequence is part of a preferred embodiment. (Tr. at 44:12-17). Therefore, I am not persuaded by this argument.

I also agree with Defendants' interpretation of "approximately 145-nucleotide." Extrinsic evidence shows that genome length differs by serotype in native AAVs, and Plaintiffs do not challenge this fact. Nowhere does the specification limit itself to a particular serotype. Therefore, I conclude that for each of these claims terms, the "AAV ITR sequence" must be a native sequence.

With regard to the term "a 5′ AAV . . .", Plaintiffs also object that Defendant's proposed construction inserts native to describe the 5′ and 3′ sequences, but not the "internal AAV ITR sequence." However, Defendant responds that the internal AAV ITR sequence must also be

native. (D.I. 101 at 15 n.7). I agree with Defendant that all sequences described as "AAV ITR" sequences must be native. Therefore, in the Court's construction, for consistency, I insert native before "internal AAV ITR sequence."

With regard to the term "rAAV vector genome" / "rAAV genome," I think it is redundant to repeat the construction of "recombinant AAV vector" when construing this term. Therefore, I reduce the construction simply to "the genetic material of a recombinant AAV vector," while noting that my construction of "recombinant AAV vector," requiring native ITR sequences, still applies.

4. **"along most or all of its length" / "along its length" ('535 patent, claims 2-5, 8-11, 13-15, 17-26, 28-29; '717 patent, claims 3-6, 12-15; '888 patent, claims 1-2, 4, 6; '729 patent, claims 1-5, 7-9; '054 patent, claims 1-7, 9, 11-13, 15, 17-27, 30-32, 34, 36)**

    a. *Plaintiffs' proposed construction*: "along most (as most is defined) or all of its length" or "along its length"
    b. *Defendants' proposed construction*: Indefinite
    c. *Court's construction*: plain and ordinary meaning

    I ruled that I would not find this term indefinite at oral argument. (Tr. at 50:3-10).

5. **"conditions that allow" / "conditions which allow" ('535 patent, claims 22-26, 28-29; '717 patent, claims 1-8, 11-17, 20; '729 patent, claims 1-5, 7-9; '054 patent, claims 18-27, 30-32, 34, 36)**

    a. *Plaintiffs' proposed construction*: "conditions that do not prevent events from occurring"
    b. *Defendants' proposed construction*: Indefinite
    c. *Court's construction*: plain and ordinary meaning

    Plaintiffs argue that a POSA would understand that certain events, such as AAV replication and encapsidation, occur under specific conditions. (D.I. 101 at 29). Plaintiffs assert that a POSA would be able to determine the requisite conditions for a given event and would thus be reasonably certain of the scope of the claims. (*Id.*). Plaintiffs offer "conditions that do not prevent" as a construction based on the specification, which states that "conditions that 'allow'

an event to occur . . . are conditions that do not prevent such events from occurring." ('535 patent at 14:1-5).

Defendants assert that the term is indefinite. They bear the burden of proving indefiniteness by clear and convincing evidence. *See BASF*, 875 F.3d at 1365. Defendants argue that, although a POSA might know that certain conditions would not be conducive to AAV replication and encapsidation, a POSA "could not have determined with reasonable certainty the conditions that allow replication and encapsidation" in the broad array of cell types contemplated by the patent. (D.I. 101 at 32). Defendants note that as of 1999, the priority date, a POSA would not have known how to use AAV in yeast, avian, or plant cells, all of which are mentioned in the specification. (*Id.*). Defendants argue that although Plaintiffs provide a definition, the definition "does not define the required claim conditions or even suggest what they may be." (*Id.* at 31 (citing *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1251 (Fed. Cir. 2008))). Defendants argue under *Halliburton* that the scope of the claims is not sufficiently precise. (D.I. 101 at 31). They object that the specification's examples of conditions under which the relevant processes occur do not make clear which of the listed conditions are necessary or sufficient. (*Id.* at 32-33). Defendants also argue that the examples cover only certain types of cells, and conditions that work for one type of cell might not work for another. Defendants argue that this leads the claims to have "sweeping breadth." (*Id.* at 32).

Plaintiffs respond that the term is not indefinite because a POSA in 1999 would have been able to determine whether a given set of conditions would infringe. (*Id.* at 34). Plaintiffs argue that Defendants' reasoning "is the province of enablement . . . rather than definiteness." (*Id.*). Plaintiffs distinguish this term from the one at issue in *Halliburton* because, in *Halliburton*, the specification did not provide guidance on how to determine if a material had the properties

required by the claim construction. (*Id.* at 34-35). Here, Plaintiffs argue, conditions are within the scope of the claim if they do not prevent introduction of the rAAV vector. Plaintiffs say that this is easily ascertained. (*Id.* at 34).

I do not think that "conditions that allow" / "conditions which allow" has been shown to be indefinite. The scope of the claim is broad, but well-defined. As noted in section II, *supra* p. 4, "breadth is not indefiniteness." *BASF*, 875 F.3d at 1367 (quoting *SmithKline*, 403 F.3d at 1341). Defendants' objections boil down to the fact that a POSA in 1999 could not have known a general formula for predicting whether a given set of conditions would allow events to occur for a given cell type. However, even accepting that as true, I do not think the boundaries of the claim are unclear. Instead, it seems to me the Carter patents, unlike the patents in *Halliburton,* have "distinctly identifie[d] the boundaries of their claims." *Halliburton*, 514 F.3d at 1253. If in the performance of a method, the event required by a claim occurs, the method infringes that claim—and Defendants have not provided any evidence that a POSA would be uncertain whether or not an event such as "encapsidation" or "expression" had occurred. I do not think that Defendants have provided clear and convincing evidence of indefiniteness. Therefore, I do not find "conditions which allow" / "conditions that allow" indefinite.

While I am unpersuaded by Defendants' indefiniteness argument, I also decline to adopt Plaintiffs' construction. I do not think it is necessary or illuminating to replace "allow" with "do not prevent," or with any of the other definitions of "allow" provided in the specification. All of the definitions in the specification fall within the plain meaning of allow, and I think "allow" is clear and easily understood. Therefore, I construe "conditions that allow" / "conditions which allow" to have its plain and ordinary meaning.

6. **"enhanced" / "enhance" ('535 patent, claims 1-26, 28-29; '717 patent, claims 1-8, 11-17, 20; '888 patent, claims 1-2, 4, 6; '729 patent, claims 1-5, 7-9)**

    a. *Plaintiffs' proposed construction*: "intensify, increase, or improve the rate, level, or efficiency of expression"
    b. *Defendants' proposed construction*: Indefinite
    c. *Court's construction*: See below

The parties argued this term jointly with the following term during oral argument. (Tr. at 57:9-14). It is contained within the following term and never appears independently in the asserted patents. I find that the longer term is indefinite, for reasons that I discuss below. Therefore, I do not address "enhanced" / "enhance" in isolation.

7. **"Forms intrastrand base pairs such that expression of a coding region of [a] heterologous sequence is enhanced relative to a second rAAV vector that lacks sufficient intrastrand base pairing to enhance said expression" ('535 patent, claims 1-26, 28-29; '717 patent, claims 1-8, 11-17, 20; '888 patent, claims 1-2, 4, 6; '729 patent, claims 1-5, 7-9)**[5]

    a. *Plaintiffs' proposed construction*: "self-anneals to a compl[e]mentary sequence of the same polynucleotide strand, such that expression of a coding region (as coding region is defined) of a heterologous sequence (as heterologous sequence is defined) is enhanced (as enhanced is defined) relative to the expression of a coding region of an rAAV vector (as rAAV vector is defined) that lacks sufficient complementarity in sequence to another region in the same strand to be capable of forming base pairs with the complementary sequence (or self-anneal) to enhance (as enhance is defined) expression"
    b. *Defendants' proposed construction*: Indefinite
    c. *Court's construction*: Indefinite

Plaintiffs' construction substitutes "self-anneals to a compl[e]mentary sequence of the same polynucleotide strand" for "forms intrastrand base pairs" and "sufficient complementarity in sequence to another region in the same strand to be capable of forming base pairs with the complementary sequence (or self-anneal)" for "sufficient intrastrand base pairing." It otherwise relies on agreed-upon constructions and plain and ordinary meaning. Plaintiffs observe that this

[5] I state the disputed term the way the parties state it. (D.I. 101 at 40). There is some variation in the actual language in the claims of the different patents, but no one suggests that it makes any difference.

term explains that snapback molecules work because they can more quickly form double-stranded DNA. (D.I. 101 at 41). Plaintiffs do not argue for any additional construction.

Defendants argue that this claim term is indefinite, an assertion they again bear the burden of proving by clear and convincing evidence. *See BASF*, 875 F.3d at 1365. Specifically, Defendants argue that this claim term is circular because it compares the expression of a coding region that has been enhanced to the expression of a coding region that has not been enhanced. (D.I. 101 at 42). Thus, a POSA could arrive at different results for the same sequence depending on the comparator. (*Id.*). Defendants analogize this to "defining a fast swimmer as someone who [is] fast relative to someone who is insufficiently fast." (*Id.*).

Plaintiffs respond that the term is not indefinite because the metric of comparison is clearly specified. Plaintiffs argue that whether expression is enhanced can be measured by "comparing the rate, level, or efficiency" of expression, and cites several references that make such comparisons. (D.I. 101 at 45). Plaintiffs also argue that the comparator is clearly specified: it should be a "conventional, single-stranded vector[]" (*id.*), or "basically what was done before, the prior art, what preceded this invention." (Tr. at 59:23-25). At oral argument, Plaintiffs pointed to the comparisons in Table 2 and Table 3 of the specification as evidence of how to construct the comparator, arguing that "the description of the full-size vectors that they have are presumptively the comparator." (*Id.* at 64:2-4). Those "full-size vectors" were created by using "stuffer" DNA that would not pair with the target gene. (*Id.* at 60:15-62:3).

As far as I can tell, the parties agree that the ability to form intrastrand base pairs is a property of certain DNA sequences. They also seem to agree that the amount of intrastrand base pairing that a sequence may be capable of can vary over a wide range. Generally, they agree that

an increased ability to form intrastrand base pairs may lead to increased expression of the gene that the sequence is coding.

As I understand it, the patent is attempting to claim sequences that are designed to have an increased ability to form intrastrand base pairs and thus will serve as better gene therapy vectors. To determine whether a sequence infringes, a POSA would need to determine whether it has intrastrand base pairing that leads to expression being "enhanced." According to the claim term, whether that sequence's expression is "enhanced" should be determined relative to another sequence that "does not have enough intrastrand base pairing to have enhanced expression."

I agree with Defendants that this is plainly circular. Such a circular definition fails to provide a POSA with any reasonable certainty about how much additional expression is required, not to mention how much intrastrand base pairing is required. Thus, it seems that for any given sequence, one could always find a comparator with less intrastrand base pairing that would consequently have less enhanced expression, leading to the result that the claim term has no definite meaning because it does not give any guidance on what the comparator should be.

Plaintiffs' contention that the specification makes clear that the proper comparator is a "full-size vector" with "stuffer" does not persuade me. My understanding from oral argument is that, depending on the "stuffer" used in a comparator, the amount of intrastrand base pairing—and the resulting level of expression—could vary, perhaps even widely. (Tr. at 63:13-24). Thus, the only thing the specification provides is two particular examples of how to construct a comparator and to conduct a comparison. Plaintiffs essentially suggest that these two examples from the specification make clear how to construct a comparator in all cases. The claim itself says nothing about constructing a comparator, however. Requiring comparators to be constructed in the same way as they are in the specification examples would be, as far as I can tell,

"importing limitations from the specification." *Phillips*, 415 F.3d at 1323. Thus, I am left with a claim term that has an uncertain scope and a specification that provides no guidance as to the boundaries of that scope—only examples of what may lie inside it. I conclude that it is indefinite.

Ultimately, the plain language of the claims that include this claim term is circular. Defendants have shown by clear and convincing evidence that a POSA reading the disputed claim term in light of the specification could not be reasonably certain of its scope. Therefore, I find the disputed term as it appears in claims 1-26 and 28-29 of the '535 patent; claims 1-8, 11-17, and 20 of the '717 patent; claims 1-2, 4, and 6 of the '888 patent; and claims 1-5 and 7-9 of the '729 patent to be indefinite.

V. THE '542 PATENT

A. Background and Claims

The '542 patent discloses a method of preparing virions, or viral particles, so that they can be stored without clumping. ('542 patent at 3:16-21). This is necessary to ensure that gene therapies can be prepared and then stored until needed. AAV virions are stored in solutions, but their solubility is limited. (*Id.* at 1:41). This can lead to clumping, which can have various negative consequences at the testing and administration stages. (*Id.* at 2:9-14). The '542 patent teaches increasing the ionic strength of—or the amount of salt in—the solution, which prevents clumping. (*Id.* at 3:11-15; D.I. 101 at 53, 54-55).

The parties agree that claim 5, which depends on claim 1, is representative for claim construction purposes. (D.I. 101 at 2).

> 1. A composition for the ***storage*** of ***purified***, recombinant adeno-associated virus (AAV) vector particles, comprising:
> ***purified***, recombinant AAV vector particles at a concentration exceeding 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml;
> a pH buffer, wherein the pH of the composition is between 7.5 and 8.0; and

excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate; wherein the ionic strength of the composition is greater than 200mM, and wherein the purified AAV vector particles are ***stored*** in the composition without ***significant aggregation***.

. . .

5. The composition of claim 1, wherein the ***purified*** recombinant AAV vector particles have an average particle radius (Rh) of less than about 20 nm as measured by ***dynamic light scattering***.

('542 Patent at 14:15-26, 34-37 (disputed terms bolded and italicized)). The only other claim now asserted is claim 6,[6] which I also reproduce, because its content is relevant to the construction of the term "significant aggregation."

6. The composition of claim 1, wherein recovery of the purified, recombinant virus particles is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22 μm filter.

(*Id.* at 14:38-41).

B. Construction of Disputed Terms

1. "dynamic light scattering" ('542 patent, claim 5)

a. *Plaintiffs' proposed construction*: "a specific technique in physics that can be used to determine a size distribution profile of small particles in suspension or polymers in solution that is based generally on analyzing temporal fluctuations using the intensity or photon auto-correlation function"
b. *Defendants' proposed construction*: "a technique in physics that can be used to determine a size distribution profile of small particles in suspension or polymers in solution"
c. *Court's construction*: "a technique in physics that can be used to determine a size distribution profile of small particles in suspension or polymers in solution"

The parties rested on the briefs for this term. (Tr. at 86:25-87:1). They agree that "the only dispute is how specifically the technique should be described." (D.I. 101 at 54). Plaintiffs argue that dynamic light scattering is a specific technique that is performed with specific methods. (*Id.*). Plaintiffs point to an example in the specification, which names a specific device

[6] Claim 1 was asserted at the time of briefing, but the parties indicated at oral argument that it had been dropped. (Tr. at 104:7-13).

used for the dynamic light scattering measurement. (*Id.* (citing '542 patent at 12:38-39)). Plaintiffs' construction draws on the user manual for that device. (D.I. 101 at 54).

Defendants respond that dynamic light scattering as used by a POSA refers to a well-defined class of techniques. Defendants point to contemporaneous art that describes multiple methods of measurement, all of which are referred to as "dynamic light scattering." (*Id.* at 55 (citing D.I. 108 at A0655)).

I am not persuaded that this term requires construction. There has been no indication that the parties' experts disagree on what is or what is not dynamic light scattering. I nevertheless will adopt Defendants' construction, since both parties seem to agree that dynamic light scattering is "a technique in physics that can be used to determine a size distribution profile of small particles in suspension or polymers in solution."

I decline to adopt each of Plaintiffs' two additions to that construction. First, describing what a technique is "based generally on" does not seem necessary or helpful. Indeed, the word "generally" does not even convey that the technique is always based on "analyzing temporal fluctuations using the intensity or photon auto-correlation function." (D.I. 101 at 56). To the extent that Plaintiffs want the language "based generally on" to limit the scope of the term based on language from a user manual for a specific device mentioned in the '542 patent's specification, I think that doing so would be "importing limitations from the specification." *Phillips*, 415 F.3d at 1323.

Second, I do not think the word "specific" adds any meaning to the construction. Plaintiffs acknowledge that the word "specific" is intended to distinguish dynamic light scattering from other techniques "for determining size distribution in solution or suspension," such as "photon correlation spectroscopy and visual inspection." (D.I. 101 at 56). Plaintiffs

provide no argument for why adding the word "specific" helps to distinguish dynamic light scattering from those, or any other, techniques. Plaintiffs also do not suggest that there are any techniques that a POSA would call "dynamic light scattering" that would not fall within the scope of the claims. Absent such arguments, I decline to include a word that, in context, seems meaningless.

2. "purified" ('542 patent, claims 5, 6)

a. *Plaintiffs' proposed construction*: "the state of a product after a completed purification process, not an intermediate that has been subjected only to some refinement"
b. *Defendants' proposed construction*: "having been subjected to a purification procedure, including, for example, ultracentrifugation and/or column chromatography"
c. *Court's construction*: "having been subjected to a purification procedure"

The dispute is essentially how much purification is needed for a product to be considered "purified." Plaintiffs argue, based on the prosecution history of the '542 patent, that the purified particles must be a "final product." (D.I. 101 at 57). Plaintiffs argue that the '542 patent was distinguished from U.S. Patent No. 6,146,874 ("Zolotukhin") because Zolotukhin taught increasing the ionic strength of an "intermediate," and not of a final product. (*Id.*). Plaintiffs argue that the Examiner allowed the claims after the applicants clarified this distinction. (*Id.* at 58). Plaintiffs object to Defendants' construction because "a purification procedure" is not a term that is used in the specification (Tr. at 87:9-12) and potentially overlaps with Zolotukhin. (D.I. 101 at 58).

Defendants argue that the specification only requires the product to have been subjected to a purification procedure. Defendants assert that Plaintiffs' "completed purification process" requirement is ambiguous. (*Id.* at 58). Defendants point out that the specification describes several purification methods: "Method 1 (double CsCl gradient); Method 2 (cation exchange chromatography); Method 2 plus nuclease digestion; or Method 3 (chromatography plus one

CsCl gradient)." ('542 patent at 4:28-32). Method 3 requires first performing Method 2 and then performing another step.[7] (*Id.* at 11:36-39). Defendants argue that this means that performing only chromatography might result in an intermediate product in some cases but a final product in others. (D.I. 101 at 58-59; Tr. at 94:6-21). Defendants also argue that Plaintiffs' "final product" requirement requires an inquiry into the intent of the user. (Tr. at 94:22-25). Defendants finally assert that the prosecution history does not support Plaintiffs' construction, because Plaintiffs misrepresent the Examiner's basis for eventually allowing the claims. (D.I. 101 at 61).

I agree with Defendants that, based on the specification, purification "processes" can involve one or multiple "procedures." I find particularly persuasive Defendants' argument that the specification considers "cation exchange chromatography" and "chromatography plus one CsCL gradient" both to be procedures that result in a purified product. While the prosecution history suggests that the Examiner may have considered the finality of the purification to be relevant, the claims and the specification say nothing about finality or what it would entail. I think that Plaintiffs' proposed construction is ambiguous and would contradict the specification's clear descriptions of purification. Therefore, I adopt the essence of Defendants' construction. I decline to include the non-limiting examples Defendant offers in my construction.

3. "significant aggregation" ('542 patent, claims 5, 6)

a. *Plaintiffs' proposed construction*: "as determined by dynamic light scattering, photon correlation spectroscopy or visual appearance, aggregation sufficient to create a threat of losses during purification, inconsistencies in testing of purified vector preparations, influence on biodistribution following in vivo administration, adverse immune responses, or affected testing protocols"
b. *Defendants' proposed construction*: Indefinite
c. *Court's construction*: plain and ordinary meaning

[7] It seems likely that "Method 2 plus nuclease digestion" also entails performing Method 2 and then an additional step, but neither party mentioned this.

Plaintiffs argue that the patented technology seeks to prevent clumping in gene therapy preparations to avoid specific negative consequences. Therefore, "significant aggregation" should be construed to mean any aggregation that causes those negative consequences. (D.I. 101 at 66). Plaintiffs' construction lists "losses during purification, inconsistencies in testing of purified vector preparations, influence on biodistribution following in vivo administration, adverse immune responses, or affected testing protocols" as the possible negative consequences. (*Id.*).

Defendants assert that the term "significant aggregation" is indefinite. They argue that neither the specification nor the prosecution history provide any guidance as to what the applicants meant by "significant." (*Id.* at 68-69). Defendants also object that Plaintiffs' construction is not supported by the specification. (*Id.* at 70). Specifically, the consequences Plaintiffs list are not discussed in relation to the word "significant" nor to any of the metrics in the claims. Defendants also object that Plaintiffs' construction is no more definite than the original phrase. (*Id.* at 69-70).

Plaintiffs point out that claims 5 and 6 recite additional limitations that themselves are measures of aggregation. (Tr. at 107:8-25, 108:6-7). Claim 5 says "the purified recombinant AAV vector particles have an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering." Claim 6 says "recovery of the purified, recombinant virus particles is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22 μm filter." ('542 patent at 14:38-41)

I agree with Plaintiffs that claims 5 and 6 are not indefinite. I do not think that Defendants have provided clear and convincing evidence of indefiniteness. As previously noted, a claim is indefinite if, "read in light of the specification delineating the patent, and the

prosecution history, [it fails] to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus*, 572 U.S. at 901. The asserted claims clearly set out both metrics and thresholds for significant aggregation. A POSA would consequently be reasonably certain of the scope of the claims. The asserted claims are, therefore, not indefinite. I need not reach the issue of whether "significant aggregation" would be indefinite if not accompanied by additional limitations specifying metrics.

I also note that the details provided in claims 5 and 6 provide enough certainty that no additional construction is needed. Further construction would involve muddying clear claim language with examples from the specification. Therefore, I also decline to adopt Plaintiffs' construction.

4. "storage" / "stored" ('542 patent, claims 5, 6)

a. *Plaintiffs' proposed construction*: "maintenance in a non-frozen state"
b. *Defendants' proposed construction*: "maintenance in a frozen or non-frozen state for a period of time"
c. *Court's construction*: "maintenance in a frozen or non-frozen state"

The dispute concerns whether "storage" includes "frozen storage." Plaintiffs observe that stored composition has a pH, ionic strength, and solubility. (D.I. 101 at 74). Plaintiffs point to extrinsic evidence that these are all properties of liquid solutions. (*Id.* at 75). Plaintiffs argue that the claims therefore "indicate that the purified composition is 'stored for at least part of the time before use in a non-frozen state.'" (*Id.*). Plaintiffs also note that in embodiments where the storage temperature is stated, it is said to be 4° C. Since 4° C is above the freezing temperature of water and aqueous solutions, Plaintiffs argue that this must mean that storage is intended to be non-frozen. (*Id.*). Plaintiffs say that the patent generally talks only about freezing temperatures in relation to freeze-thaw cycling. They point to the phrase "after storage or freeze-thaw cycling" as evidence that freeze-thaw cycling is distinct from storage. (*Id.* at 78-79)

Defendants counter by pointing to language in the specification that says "refrigerated storage or freeze-thaw cycling" and a sentence that refers to "non-frozen storage," both of which suggest that storage may also be frozen. Defendants also note that one of the examples discusses "an AAV2-AADC reference previously prepared in CF stored at −80° C." (*Id.* at 76). Defendants also cite to extrinsic evidence that a solution can be frozen and still be referred to as a solution and have the properties of a solution. (*Id.* at 77, 79).

I agree with Defendants that the claims encompass frozen storage. The fact that some embodiments involve non-frozen storage does not mean that the claims only encompass non-frozen storage. Once again, this would be importing limitations from the specification. *Phillips*, 415 F.3d at 1323.

I acknowledge that the phrasing "storage or freeze-thaw cycling" may suggest that "storage" and "freeze-thaw cycling" are a dichotomy. I find this argument unpersuasive in construing "storage" for two reasons. First, as Defendants noted, the patent's reference to "refrigerated storage . . . or multiple freeze-thaw (F/T) cycles" suggests just as strongly that there is no strict dichotomy, and storage may be non-refrigerated. ('542 patent at 9:23-24). Second, as Defendants observe, the patent refers to a control sample being "stored at −80° C." (*Id.* at 13:18-19). This sample was presumably not freeze-thaw cycled, but stored at a constant freezing temperature. This language is clear evidence that the patentees used the word "storage" in relation to frozen solutions. Finally, I find that Defendants' extrinsic evidence does support their assertion that a solution may be frozen.

I note that Plaintiffs argue that the word "maintenance" implies that something is being done "for a period of time." (D.I. 101 at 74 n.1). Defendant does not seem to disagree. (*Id.* at 76).

I agree that the word "maintenance" itself implies the passage of time. Therefore, I do not include the phrase "for a period of time" in my construction.

VI. CONCLUSION

Within five days the parties shall submit a proposed order consistent with this Memorandum Opinion.