IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

GENZYME CORPORATION and AVENTIS INC., Plaintiffs, v. NOVARTIS GENE THERAPIES, INC., NOVARTIS PHARMACEUTICALS CORPORATION, and NOVARTIS AG, Defendants.	C.A. No. 21-1736-RGA **CONTAINS PLAINTIFFS' HIGHLY CONFIDENTIAL INFORMATION – SUBJECT TO PROTECTIVE ORDER** **FILED UNDER SEAL**

JOINT CLAIM CONSTRUCTION BRIEF[1]

[1] Novartis AG disputes that it is a proper party in this suit and reserves all rights related thereto.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Other Authorities

I(A). Representative Claims for U.S. Patent Nos. 6,596,535; 7,125,717; 7,785,888; 7,846,729; and 8,093,054[2]

A. The '717 Patent

Claim 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.

B. The '729 Patent

Claim 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 nucleotide 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 a coding region of the***

[2] 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"); and 8,093,054 ("the '054 Patent") are collectively referred to as the "Carter Patents" herein.

heterologous sequence is enhanced relative to a rAAV vector that lacks sufficient intrastrand base pairing to enhance said expression.

C. The '054 Patent

Claim 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 a 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***.

I(B). Representative Claims for U.S. Patent No. 9,051,542

Claim 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 200 mM, and wherein the purified AAV vector particles are ***stored*** in the composition without ***significant aggregation***.

Claim 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***.

II(A). Agreed-upon Constructions for U.S. Patent Nos. 6,596,535; 7,125,717; 7,785,888; 7,846,729; and 8,093,054

Claim Term	Joint Proposed Construction
"AAV inverted terminal repeat (ITR) sequence" ('535 Patent, claims 22-26, 28-29; '729 Patent, claims 1-5, 7-9; '054 Patent, claims 1-7, 9, 11- 13, 15, 17-27, 30-32, 34, 36)	"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 contains several shorter regions of self-complementarity, allowing intrastrand base-pairing to occur within this portion of the ITR."
"coding region"/"coding sequence" ('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; '054 Patent, claims 6-7, 9, 11-13, 15, 19-27, 30-32, 34, 36)	"for a polynucleotide, a sequence of contiguous nucleotides which gives rise in a host cell to a transcription and/or translation product"
"flank"/"flanking"/"flanked" ('535 Patent, claims 3, 5, 8-11, 13, 15, 18-26, 28-29; '717 Patent, claims 1-8, 11-17, 20; '888 Patent, claims 1-2, 4, 6; '729 Patent, claims 1-5, 7-9)	"situate(d) to the side of, although not necessarily directly adjacent to"
"helper function"/"helper virus function" ('535 Patent, claims 22-26, 28, 29; '729 Patent, claims 1-5 and 7- 9)	"an activity that is required for replication and/or packaging of a parvovirus, such as AAV, but is not encoded within that parvovirus"
"helper virus" ('717 Patent, claims 1-8, 11-17, 20; '888 Patent, claims 1-2, 4, 6; '729 Patent, claim 9; '054 Patent, claims 2, 18-27, 30-32, 34, 36)	"a virus that allows AAV (which is a defective parvovirus) to be replicated and packaged by a host cell"
"heterologous" ('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; '054 Patent, claims 1-7, 9, 11-13, 15, 17-27, 30-32, 34, 36)	"derived from an entity that is genotypically distinct from an entity to which it is compared or into which it is introduced or incorporated. For purposes of this invention, 'heterologous' means heterologous with respect to a virus which is the basis of a recombinant viral vector. Accordingly, and as an example, an

	rAAV vector of the invention can be used to introduce and/or express a mammalian, and thus 'heterologous' sequence, into a mammalian cell."
"heterologous nucleotide sequence" ('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; '054 Patent, claims 1-7, 9, 11- 13, 15, 17-27, 30-32, 34, 36)	"a nucleotide sequence derived from a genotypically distinct entity from that of the rest of the sequence to which it is compared or into which it is introduced or incorporated"
"heterologous sequence" ('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 heterologous polynucleotide sequence that can comprise a sequence of interest in gene therapy (such as a gene encoding a protein or RNA transcript, such as an antisense transcript or a ribozyme, of therapeutic interest) and/or a selectable or detectable marker"
"host cell" ('535 Patent, claims 6-11, 22- 26, 28-29; '729 Patent, claims 1-5, 7-9)	"a cell which has been or can be a recipient for a vector or vectors of this invention and the progeny thereof"
"inverted terminal repeat"/"ITR sequence" ('535 Patent, claims 3, 5, 8-11, 13, 15, 18-21; '717 Patent, claims 1-8, 11-17, and 20; '888 Patent, claims 1-2, 4, 6)	"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"
"most" ('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; '054 Patent, claims 1-7, 9, 11-13, 15, 17-27, 30-32, 34, 36)	"more than half"
"operably linked" ('054 Patent, claims 11-13, 15, 30-32, 34)	"an arrangement of two or more components, wherein the components are in a relationship permitting them to function in a coordinated manner. By way of illustration, a transcriptional regulatory sequence or a promoter is operably linked to a coding sequence if the transcriptional regulatory sequence or promoter facilitates some aspect of the transcription of the coding sequence."
"polynucleotide"	"a polymeric form of nucleotides of any length"

('717 Patent, claims 1-8, 11-17, 20; '888 Patent, claims 4, 6;'054 Patent, claims 7, 19-27, 30-32, 34, 36)	
"promoter" ('054 Patent, claims 11-13, 30-32)	"a nucleotide sequence that directs the transcription of a gene or coding sequence to which it is operably linked"
"recombinant" ('535 Patent, claims 1-26, 28-29; '717 Patent, claims 2, 12-17, 20; '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 genetic entity distinct from that generally found in nature. As applied to a polynucleotide or gene, this means that the polynucleotide is the product of various combinations of cloning, restriction and/or ligation steps, and other procedures that result in the production of a construct that is distinct from a polynucleotide found in nature."
"recombinant adeno-associated virus (rAAV)" ('535 Patent, claims 12-15, 28; '717 Patent, claims 1-8, 11-17, 20; '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)	"an rAAV vector packaged into an AAV virus"
"region which forms intrastrand base pairs"/ "sequence forms intrastrand base pairs"/ "rAAV genome which forms intrastrand base pairs"/"nucleotide sequence can form intrastrand base pairs" ('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; '054 Patent, claims 1-7, 9, 11-13, 15, 17-27, 30-32, 34, 36)	"a region (such as a coding region) which is complementary in sequence to another region in the same strand, and is thus capable of forming base pairs with the complementary sequence, i.e., is self-annealing"
"sequence complexity"/"complexity" ('535 Patent, claims 2-3, 5, 8-11, 13-15, 17-26, 28-29; '717 Patent, claims 3-4, 12-13)	"the total amount of unique sequence present in a polynucleotide"
"vector" ('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; '054 Patent, claims 1-7, 9, 11-13, 15, 17-27, 30-32, 34, 36)	"a recombinant plasmid or virus that comprises a polynucleotide to be delivered into a host cell, either in vitro or in vivo"

II(B). Agreed-upon Constructions for U.S. Patent No. 9,051,542

Claim Term	Joint Proposed Construction
"filtration . . . through a 0.22 µm filter" ('542 Patent, claim 6)	"passing a liquid through a 0.22 µm filter to remove materials"[3]
"ionic strength" ('542 Patent, claims 1, 2, 5, 6)	"one half of the sum of the molar concentration of each solute species times the square of the charge on each species for all excipients present in the solution (calculated according to the equation: $\mu=\frac{1}{2}\Sigma c_i z_i^2$)"
"multivalent ion" ('542 Patent, claims 1, 2, 5, 6)	"an ionic species having a charge valency greater than one (whether positive or negative)"
"recombinant adeno-associated virus (AAV) vector particles"/"AAV vector particles"/ "recombinant virus particles" ('542 Patent, claims 1, 2, 5, 6)	"recombinant AAV virion or virus particles"

[3] Defendants reserve the right to challenge this term as indefinite (as applied) during the expert discovery phase of the case.

III(A). Disputed Constructions for U.S. Patent Nos. 6,596,535; 7,125,717; 7,785,888; 7,846,729; and 8,093,054[4]

A. "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"/"A 5' AAV inverted terminal repeat (ITR) sequence . . . and a 3' AAV ITR sequence"

Claim Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"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"/"a 5' AAV inverted terminal repeat (ITR) sequence . . . and a 3' AAV ITR sequence" ('054 Patent, claims 1-7, 9, 11- 13, 15, 17-27, 30-32, 34, 36)	"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 inverted terminal repeat (ITR) sequence (as AAV inverted terminal repeat (ITR) sequence is defined)"	"a native 5' AAV inverted terminal repeat (ITR) sequence . . . and a native 3' AAV ITR sequence"

I. Plaintiffs' Opening Position

The Carter Patents

The '535, '717, '888, '729, and '054 Patents (the "Carter Patents") solved a problem that bedeviled gene therapy: how to overcome the rate-limiting step of converting the single-stranded DNA in a recombinant adeno-associated virus ("AAV") vector to the double-stranded replicative form that expresses the desired gene. Dr. Barrie Carter discovered that a rAAV vector could be manipulated to form a "snapback" molecule where one portion of the desired nucleotide

[4] In addition to the arguments herein, Defendants reserve the right to challenge disputed terms B, C, D, and E as indefinite (as applied) during the expert discovery phase of the case.

sequence in the genome forms intrastrand base pairs with another self-complementary version of the same desired sequence. His invention enhanced the rate, level, and efficiency of replication of the desired heterologous sequence, making it a viable option for improving gene therapy.

Spinal Muscular Atrophy and Zolgensma®

Spinal muscular atrophy ("SMA") is a debilitating neurodegenerative disease caused by the lack of functional survival motor neuron (SMN) protein, coded for by the survival motor neuron 1 (SMN1) gene. Absent functional copies of this gene, motor neurons die, which can cause paralysis and eventual death in young children.

Novartis's Zolgensma®, one of only two FDA-approved gene therapy products, is the standard of care for treating children less than two years of age with SMA. Zolgensma®, a single-dose cure for SMA, is an AAV-based gene therapy product that delivers a copy of the human SMN1 gene into target motor neuron cells of the child, which results in expression of the SMN protein in the motor neuron cells. Zolgensma® is based on a snapback molecule according to Dr. Carter's patented invention.

Construction of the Claim Term

Novartis seeks to limit some – but not all – of the references to an "inverted terminal repeat" or "ITR" in the Carter Patents' claims to "native" ITRs. However, Dr. Carter's specification makes it clear that modified ITRs (i.e., non-native ITRs) can be used as part of his snapback molecules.

> As described above, the recombinant viral vectors of this invention comprise a heterologous polynucleotide. … Various types of promoters and enhancers are suitable for use in this context. For example, Feldhaus (U.S. patent application in Ser. No. 09/171,759, filed Oct. 20, 1998) describes a ***modified ITR*** comprising a promoter to regulate expression from an rAAV.

'535 Patent, col. 19, lines 7-18 (emphasis added).[5] The Feldhaus patent application, which is incorporated by reference into the Carter specification ('535 Patent, col. 4, lines 41-42), describes these modified ITRs as follows:

> A transcriptionally-activated ITR … can be derived from [a wild-type] ITR sequence but will also carry a mutation (e.g., a deletion, inversion, substitution, addition or other change), or multiple such mutations, that renders the ITR transcriptionally-activating in that it can enhance the level of transcription of a transgene to which it is juxtaposed in an rAAV vector.

Ex. B3, p. 12, lines 22-25; *see also* '535 Patent, col. 20, lines 7-13 (discussing modified single ITR that can carry out functions normally associated with two ITR configurations; citing U.S. Patent No. 5,478,745 (Ex. B4)).

The claim phrase "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" appears only once in the Carter Patents, in claim 1 of the '054 Patent as a description of the rAAV genome in the claimed composition. But it is nothing more than a list (from the 5′ end to the 3′ end) of otherwise defined elements. That is, the parties have agreed on how to construe an "AAV inverted terminal repeat (ITR) sequence" and a "heterologous nucleotide sequence." There is no magic in putting these claim terms together. Moreover, there is no basis for importing the additional limitation that the two outer AAV ITR sequences must be "native" AAV ITR sequences. Thus, this claim phrase should be construed as it is, a list of terms with agreed definitions.

[5] The Carter patents share the same specification. For ease of reference, all citations to the specification are to the '535 patent regardless of which Carter patent a claim term appears.

While the exact language of the disputed phrase does not appear in the specification of the Carter Patents, a description of the same structure does. That description does not limit the nature of the AAV ITR sequences:

> In another aspect, the invention provides an rAAV vector comprising a single-stranded polynucleotide, with a 5′ terminus and a 3′ terminus, which contains a heterologous sequence flanked at one or both ends by an AAV inverted terminal repeat (ITR), said heterologous sequence containing one or more regions capable of intrastrand base-pairing (i.e., which form intrastrand base pairs). In preferred embodiments, sequences in the coding region form intrastrand base pairs. In preferred embodiments, the rAAV vectors of the invention are capable of being packaged in an AAV virus particle.
>
> In some embodiments, the heterologous sequence forms base pairs essentially along its entire length, thus analogous to an AAV replicative form (RF). In such embodiments, the sequence complexity of the heterologous sequence is about one half of the length of the heterologous sequence. In some embodiments, the polynucleotide of the rAAV contains an additional, internal ITR (i.e., a non-terminal ITR), preferably approximately in the center of the single strand.

'535 Patent, col. 4, line 66-col. 5, line 17.

Another portion of the specification describes the same structure from the center of the rAAV genome outward, without limiting the nature of the ITR sequences, as

> [A]n rAAV vector, further compris[ing] an internal ITR (i.e., an ITR that is flanked on both sides by heterologous sequences), which is other than the ITR(s) flanking the heterologous sequence. This internal ITR preferably divides the heterologous sequence, such that intrastrand base pairing occurs between region(s) on either side of the internal ITR. Most preferably, essentially all of the heterologous sequence on either side of the ITR are engaged in intrastrand base pairing.

'535 Patent, col. 15, lines 34-43. Thus, the specification describes a structure that can include an AAV ITR sequence; a heterologous nucleotide sequence capable of intrastrand base pairing; an additional, internal ITR sequence approximately in the center of the single strand; another heterologous nucleotide sequence capable of intrastrand base pairing with the first heterologous nucleotide sequence; and a final AAV ITR sequence without limiting the structure of the ITRs.

That is the structure of a snapback molecule as described in claim 1 of the '054 patent and as set forth in Plaintiffs' proposed construction.

From these descriptions, there is no reason to believe that the Carter Patents intended to attach any idiosyncratic meaning to the AAV ITR sequences at the 5′ end and the 3′ end of the rAAV genome as identified, let alone reason to believe that those sequences were required to be "native" AAV ITR sequences. To the contrary, the Carter Patents' specification explicitly describes the use of "modified ITRs" as well as native ITRs.

In contrast, Defendants' proposed construction is internally inconsistent. Defendants want to limit the first and third "AAV ITRs" to native ITRs, while not limiting the second identical reference to "AAV ITR" (the "internal ITR") to native ITRs. If the internal AAV ITR can include native and non-native ITRs, so can the other two. Presumptively, "the same terms appearing in different portions of the claims should be given the same meaning unless it is clear from the specification and prosecution history that the terms have different meanings at different portions of the claims." *PODS, Inc. v. Porta Stor, Inc.*, 484 F.3d 1359, 1366 (Fed. Cir. 2007). Nothing overcomes that presumption here.

II. Defendants' Answering Position

Technology Overview

The technology of the Carter Patents relates generally to the use of naturally occurring viruses, specifically adeno-associated virus (AAV), for gene therapy. In broad strokes, AAV can be utilized as a recombinant vector to deliver and express a desired gene to replace a defective or missing gene in a human patient. Kay Declaration ¶¶ 23-31. For example, Novartis's Zolgensma® product was approved by the FDA in 2019 as only the second recombinant AAV ("rAAV") gene therapy. *Id.* ¶ 30. Zolgensma® is used to treat the pediatric condition of spinal muscular atrophy (SMA) by delivering the Survival Motor Neuron 1 (SMN1) gene. *Id.* Without

treatment, children with a defective SMN1 gene experience severe motor neuron degeneration, which impairs normal motor growth and, tragically, is often fatal in the first few years of life. *Id.*

The technology of rAAV gene therapy is complex. At a very high level, the naturally occurring, or "native," AAV genome is a single-stranded DNA sequence that is bounded at each end by a particular sequence known as an "AAV inverted terminal repeat (ITR)" sequence. *Id.* ¶¶ 23-25. Between these two terminal AAV ITRs are the AAV "rep" and "cap" sequences. *Id.* ¶ 24. To use AAV for gene therapy, the rep and cap sequences are removed and replaced with the desired gene. '535 Patent, col. 3, lines 25-28; *see* Figure 1 *infra*; Kay Declaration ¶ 26. The retained AAV ITRs are responsible for initiating replication to form a double-stranded DNA structure of that gene, which ultimately is made into the therapeutic protein needed by the patient. Kay Declaration ¶¶ 25-28. In practice, the development of a safe and effective gene therapy is exceedingly difficult. To date, only two rAAV gene therapies have received FDA approval, both within the last five years. *Id.* ¶ 30.

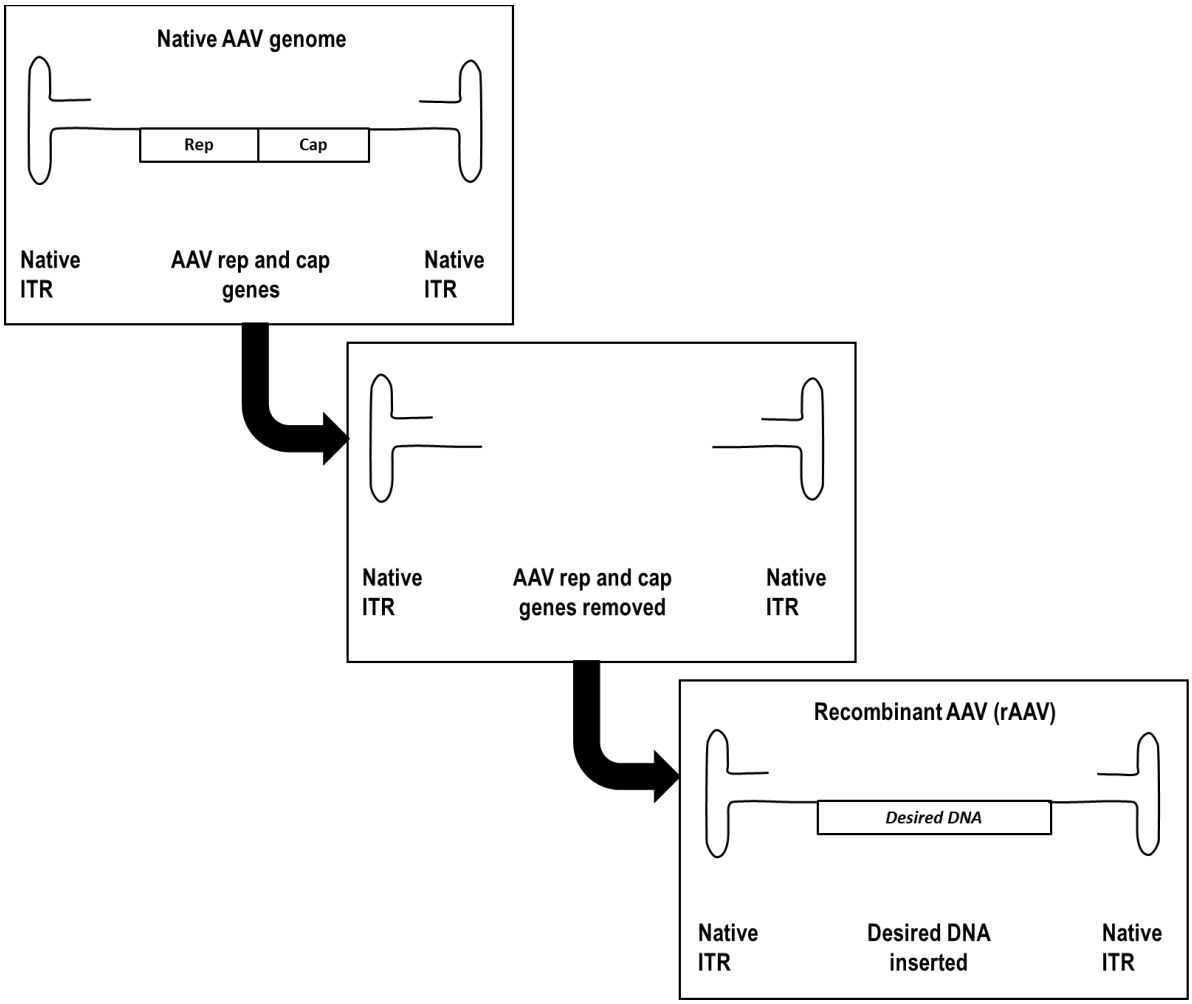

Figure 1

In 1999—the priority date of the Carter Patents—rAAV gene therapy was a nascent technology. *Id.* ¶ 32. No rAAV gene therapies had been approved by the FDA to treat any disease, and none would be for nearly two decades. *Id.* The Carter Patents nonetheless purported to solve an efficiency problem of rAAV vectors. '535 Patent, col. 4 lines 36-39; col., 8, lines 58-64. Namely, the Carter Patents describe a so-called "snapback" molecule, in which DNA in the vector folds back onto itself to form a double-stranded structure, exemplified by a single purportedly working embodiment. *E.g.*, '535 Patent, col. 15, lines 25-33; col. 29, lines 10-26; Kay Declaration ¶¶ 34-38. All of the disclosures and experiments reported in the Carter Patents

relate to this purported "snapback" molecule. Kay Declaration ¶ 39. None of the disclosures or experiments in the Carter Patents relate to mutating the native AAV ITRs. *Id.*

Zolgensma® was developed nearly a decade later with technology based on an entirely different breakthrough by Drs. Samulski and McCarty at the University of North Carolina. *Id.* ¶ 40. These scientists developed an rAAV vector containing a *mutated* ITR that provided a critical change in the vector's ability to replicate and maintain a double-stranded structure. *Id.* In particular, by mutating a specific terminal resolution site of the native AAV ITR, Drs. Samulski and McCarty were able to bypass a rate-limiting step in the rAAV vector's production of the desired gene. *Id.* The Carter Patents do not disclose or contemplate this mutant ITR developed years later. *Id.*

Despite Plaintiffs' assertion that their snapback molecule purportedly made rAAV gene therapy "viable" (*supra*, p. 8), Plaintiffs have not obtained FDA approval for any rAAV gene therapies using their purported snapback molecule. Kay Declaration ¶ 30. Indeed, Plaintiffs have never obtained FDA approval for a single rAAV gene therapy. *Id.* Nor have Plaintiffs obtained FDA approval for any molecule to treat SMA. *Id.* Instead, Plaintiffs have asserted 84 claims from the five Carter Patents, all of which are expired, and none of which reports or suggests the mutant ITR invented years later by Drs. Samulski and McCarty.

Defendants' proposed constructions are grounded in the intrinsic evidence as viewed by a person of ordinary skill in the art.[6] The disputes herein have arisen from Plaintiffs' attempts to

[6] A person of ordinary skill in the art with respect to the Carter Patents would have had, by August 9, 1999, an advanced degree in microbiology, molecular biology, immunology, biochemistry, genetics, medicine, or a related discipline, with several years of experience in the research, design, of development or viral vectors for gene therapy. Kay Declaration ¶ 19. Plaintiffs have posited a slightly different definition. While Defendants disagree with Plaintiffs'

seek overbroad constructions entirely unsupported by the specification of the Carter Patents and the understandings of a skilled artisan in 1999.

Construction of the Claim Term

All asserted claims of the '054 Patent require "a 5' AAV inverted terminal repeat (ITR) sequence . . . and a 3' AAV ITR sequence."[7] The intrinsic evidence demonstrates that each of these AAV ITR sequences is *native* AAV ITR sequence. The specification is unambiguous in this regard, expressly defining "AAV ITR sequences" to be native: "An 'AAV inverted terminal repeat (ITR)' sequence, a term well-understood in the art, is an approximately 145-nucleotide sequence that is present at both termini of the *native* single-stranded AAV genome." '535 Patent, col. 11, lines 14-17.[8] Critically, Plaintiffs *agree* both that the specification defines "AAV ITR sequence" in this manner and that this definition is incorporated into the disputed claim term. *Supra* § II(A). That should be the end of the dispute.

But Plaintiffs nonetheless argue that the specific "5' AAV ITR" and "3' AAV ITR" that are recited in the claims of the '054 Patent should *not* be limited to native AAV ITR sequences, and instead should be construed broadly to encompass non-native, mutated AAV ITR sequences. *E.g.*, *supra*, p. 8. Plaintiffs' construction is contrary not only to the express definition of "AAV

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definition, Defendants' proposed constructions are correct regardless of which definition is adopted.

[7] During the parties' claim construction exchanges, Defendants identified this shorter term for construction; Plaintiffs responded by identifying the longer, unelided phrase for construction, which additionally recites "an internal AAV ITR sequence." This is a distinction without a difference. The specification requires that each AAV ITR is native, including the internal AAV ITR (which is simply one that may be created during AAV replication when the terminal native AAV ITR is copied). Kay Declaration ¶ 36. There is no inconsistency in Defendants' proposed construction, and Plaintiffs' suggestion to the contrary (*supra*, p. 11) is a red herring.

[8] Unless otherwise indicated, all emphasis has been added.

ITR" provided in the patent (to which they have agreed), but also to the specification's Examples. Each of the relevant experiments reported in the specification follows the then-conventional method of generating rAAV vectors: removing the rep and cap genes from the native AAV genome, retaining the native AAV ITR sequences at both termini of the genome, and inserting a gene between the retained native AAV ITR sequences. '535 Patent, col. 3, lines 17-28 ("Recombinant AAV (RAAV) vectors [are] based on the native AAV genome"); col. 29, lines 10-56 (Examples 1 and 2); Kay Declaration ¶ 38. There is no data in the specification demonstrating use of a mutated ITR. Kay Declaration ¶ 38.

Plaintiffs cite several passages from the specification that they argue "do[] not limit the nature of the AAV ITR sequences." *Supra*, p. 10. But each of those passages employ the term "AAV ITR," which is expressly defined in the specification to be "of the native single-stranded AAV genome." '535 Patent, col. 11, lines 14-17. By using a term expressly defined in the specification, those passages confirm that each AAV ITR is a native AAV ITR. Kay Declaration ¶¶ 43-49.

Plaintiffs' only other alleged support for expanding the claims to cover mutated ITRs is a citation in column 19 of the specification to a Feldhaus patent application utilizing a "modified ITR comprising a promoter." *Supra*, pp. 8-9, citing '535 Patent, col. 19, lines 7-18. But this passage confirms the correctness of Defendants' proposed construction, not Plaintiffs'. The discussion in column 19 of the Carter specification relates to using "promoters and enhancers" to regulate transcription by having them "operably linked" to the relevant sequence ('535 Patent, col. 19, lines 7-18), which is defined as a locational relationship with the promoter "generally joined in cis [i.e., on the same DNA molecule] . . . but [] not necessarily adjacent to" the relevant sequence (*id.* col. 11, lines 46-61). The Carter specification's citation to Feldhaus's "modified

ITR comprising a promoter" is exemplary of such constructs: Feldhaus discloses the making and testing of nine ITR constructs, wherein the native AAV ITRs are preceded by different promoter sequences. Ex. B3, p. 31, line 3-p. 38, line 14; Kay Declaration ¶¶ 50-53. All nine of Feldhaus's examples tack a promoter onto the end of the 145-nucleotide native AAV ITR sequence. Kay Declaration ¶ 50. None describes mutating the native AAV ITR sequence. *Id.* The Carter specification's citation to Feldhaus's "modified ITRs comprising a promoter" is therefore entirely consistent with the specification's definition of "AAV ITR" as requiring *native* AAV ITR sequence.

Plaintiffs point to a single sentence at page 12 of Feldhaus that posits the theoretical use of mutated ITRs. *Supra*, p. 9, citing Ex. B3, p. 12, lines 22-25. But Feldhaus uses a *different* term to encompass those theoretical mutated ITRs: "transcriptionally activated ITR." Ex. B3, p. 12, lines 17-25. That term (and that passage of Feldhaus) is not referenced anywhere in the Carter specification. Instead, the inventor of the Carter Patents, in the claims and in the specification, used the term "AAV ITR" and gave it an express definition. '535 Patent, col. 11, lines 14-17. Feldhaus's discussion of a different term does not override the express definition for the claim term provided by the inventor. *E.g.*, *Modine Mfg. Co. v. U.S. Intern. Trade Cm'n*, 75 F.3d 1545, 1553 (Fed. Cir. 1996), *abrogated on other grounds by Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558 (Fed. Cir. 2000) (en banc) (rejecting argument to construe claim in accordance with incorporated patent when doing so would "overrid[e]" contrary language in the specification at issue); *X2Y Attenuators, LLC v. Intern. Trad Com'n*, 757 F.3d 1358, 1363 (Fed. Cir. 2014) (definitional statements in incorporated patents may not apply "when placed in the context of the disclosure of the host patent"). A skilled artisan would not have understood the Carter Patents to encompass Feldhaus's differently labeled, theoretical mutated ITRs—especially

when doing so runs headlong into the inventor's express definition of "AAV ITR" in his own patent. Kay Declaration ¶ 42; *e.g.*, *Finjan LLC v. Eset LLC*, No. 2021-2093, 2022 WL 16557653, at *3 (Fed. Cir. Nov. 1, 2022) ("The disclosure of the host patent [i.e., the Carter specification] provides context to determine what impact, if any, a patent incorporated by reference will have on construction of the host patent claims.").

In short, the Carter Patents do not disclose or contemplate the use of anything but the native AAV ITR sequence. The later-invented mutated ITR that actually works for its intended purpose and that Genzyme now tries to encompass is the subject of separate scientific publications and has received its own patent protection. *See, e.g.*, Exs. 5-9. It is improper for Plaintiffs to attempt to cover a genus of structures, via overbroad claim constructions, that was never disclosed or suggested by the Carter Patents.

III. Plaintiffs' Reply Position

Relying on its declarant's reading of extrinsic evidence relating to self-complementary AAV vectors as evidence of the development of Zolgensma®, Novartis argues that a different patent portfolio also covers the accused product. Not only did Novartis's declarant, Dr. Kay, recant any knowledge of the development of Zolgensma® (Ex. 14, p. 203-07),[9] the record shows that Carter's prior invention is the dominating technology without which Zolgensma® could not have worked. Kurtzman Declaration, ¶ 22.

Of course, the fact that Zolgensma® may also fall within another, later-filed patent does not mean that it does not also infringe the patents-in-suit. *National Presto Indus., Inc. v. West Bend Co.*, 76 F.3d 1185, 1191-92 (Fed. Cir. 1996) ("[t]he grant of a separate patent on the

[9] Dr. Kay testified, "I mean, I would have no way of knowing what went into the development of Zolgensma." Ex. 14, p. 207.

accused device does not automatically avoid infringement, either literal or by equivalency"). That is especially true, as here, when one patent is a "dominating" patent that covers the breakthrough technology and another patent covers an improvement on the invention disclosed in that patent. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1580-81 (Fed. Cir. 1984). The Carter Patents cover the basic invention that allows recombinant AAV vectors to form double-stranded DNA; the later Samulski & McCarty patents cited by Novartis originally tried to claim Dr. Carter's invention but eventually had to settle for narrower claims in light of the earlier-filed Carter Patents.

Samulski & McCarty originally sought claims nearly identical to the ones here, but the examiner repeatedly found the Carter '535 patent anticipated those claims. Ex. 15 (May 12, 2006 Office Action), p. 8-9; Ex. 16 (January 12, 2007 Office Action), p. 4-5; Ex. 17 (August 23, 2007 Office Action), p. 7-9. Samulski & McCarty then narrowed the claims to obtain allowance over Carter. Ex. 18 (July 29, 2008 Interview Summary). If there were any question, the Notice of Allowance establishes that Carter's invention creates double-stranded (or duplexed) vectors along with monomers, and Samulski & McCarty's improvement is only that it "does not comprise a mixed population of vectors." Ex. 19 (August 21, 2008 Notice of Allowance), p. 5-6.

Both the Carter Patents and the Samulski & McCarty patents allow the use of modified AAV ITR sequences as part of their inventions. It is a fact that native ITRs in AAVs have a "sequence of 145 nucleotides." *See* '535 Patent, col. 1, lines 52-55; *see also* Ex. B4, col. 1, lines 58-62. But the Carter Patents never state that ITRs useful in the claimed inventions must have (and only have) this native 145 nucleotide sequence. To the contrary, the Carter Patents make it

clear that ITRs useful in the claimed inventions can have nucleotide sequences that are other than the native 145 nucleotide sequence.[10]

The agreed definition of "ITR" sequence in the Carter Patents notes that ITR is a term well understood in the art "and refers to relatively short sequences found at the termini of viral genomes …." '535 Patent, col. 9, lines 9-12; Kurtzman Declaration, ¶¶ 32, 33, 42. This definition never refers to "native" or a specific length of these sequences, only that they are "relatively short." *Id.*

The agreed definition of "AAV ITR" sequence in the Carter patents notes that this, too, is a term well-understood in the art and "is an *approximately* 145-nucleotide sequence that is present at both termini of the native single-stranded AAV genome." '535 Patent, col. 9, lines 13-24 (emphasis added); Kurtzman Declaration, ¶¶ 32, 33, 42. The reference to "approximately" is a clear signal that this term is not limited to the 145-nucleotide sequence found in native AAVs.

The Carter patents also describe and exemplify ITRs and AAV ITR sequences that are non-native as being part of the invention. The Carter patents describe and claim the inclusion of "an rAAV vector, further compris[ing] an internal ITR (i.e., an ITR that is flanked on both sides by heterologous sequences), which is other than the ITR(s) flanking the heterologous sequences." '535 Patent, col. 15, lines 34-38; Kurtzman Declaration, ¶¶ 26-28. Internal ITRs were known in the prior art, see e.g., as shown in US Patent No. 5,478,745. *See* '535 Patent, col. 20, lines 7-13; Kurtzman Declaration, ¶ 49. This prior art patent (cited by and incorporated by reference into the Carter Patents) describes a "modified AAV ITR nucleotide sequence, herein

[10] Novartis relies on Dr. Kay's erroneous assertion that "'AAV ITR sequence' means native AAV ITR sequence" as the basis for its construction of this term. Kay Declaration, ¶ 46. Dr. Kay's error may have arisen because he did not review the all of the Carter Patents' asserted claims or the full specification, let alone the full prosecution history. Ex. 14, p. 25.

referred to as the double-D sequence." Ex. B4, col. 3, lines 39-41; Kurtzman Declaration, ¶ 50. This "modified terminal repeat structure was constructed containing a single 145 bp ITR sequence with an additional 20 bp D' sequence. The resulting 165 bp sequence has not been identified in any naturally occurring virus." Ex. B4, col. 4, lines 32-37; Kurtzman Declaration, ¶ 50. And yet the Carter patents clearly refer to and claim this non-native internal AAV ITR as an "ITR."[11] '535 Patent, col. 20, lines 7-13; Kurtzman Declaration, ¶ 49.

Like the double-D internal AAV ITR sequence, the modified AAV ITR sequences disclosed in the Feldhaus application (and incorporated by reference into the Carter specification) show that AAV ITR sequences need not be native. The specification refers to Feldhaus's "modified ITR comprising a promoter to regulate expression from an rAAV." '535 Patent, col. 19, lines 15-18 (citing Application Serial No. 09/171,759); Kurtzman Declaration, ¶ 44. There is no question that Carter is referencing Feldhaus's modified construction as an AAV ITR sequence. *Id.* While Novartis argues that Feldhaus – not Carter – calls it a "transcriptionally-activated ITR," that is not only the way that Feldhaus identifies its function and distinguishes it from a native ITR. Kurtzman Declaration, ¶ 48. In fact, Feldhaus also references constructs of this type as a "modified ITR," the same term used in the Carter specification. Ex. B3, p. 15, lines 22-25; Kurtzman Declaration, ¶ 48.

The specification also describes a third non-native construction for AAV ITRs in relation to the replication origin. '535 Patent, col. 12, lines 5-10 ("The AAV replication origin is located within the AAV inverted terminal repeat (ITR) sequence and facilitates replication of sequences

[11] The Carter Patents' specification identifies that a single modified AAV ITR (i.e., an internal, double-D ITR) "can be sufficient to carry out the functions normally associated with configurations comprising two ITRs." '535 Patent, col. 20, lines 7-10 (citing U.S. Patent No. 5,478,745).

to which it is operably linked. In the practice of the invention, an AAV origin can be substituted with an ori-like sequence, as disclosed in co-owned PCT WO 99/20779."). In all of these cases, the specification makes it clear that these non-native, modified sequences are still "AAV ITR sequences." Thus, "A 5′ AAV inverted terminal repeat (ITR) sequence, . . .an internal AAV ITR sequence, . . . and a 3′ AAV ITR sequence" is not limited to only native AAV ITR sequences.

IV. Defendants' Sur-Reply Position

The parties agree the specification defines "AAV ITR sequence" as a sequence present in the "native single-stranded AAV genome." '535 Patent, col. 11, lines 14-17. Plaintiffs' contrary construction, which seeks to capture mutant AAV ITR sequences, should be rejected.

Plaintiffs do not (and cannot) dispute that neither the Carter Patents nor Plaintiffs' cited references report mutations in the native AAV ITR sequence. The Carter Patents report the generation of rAAV vectors having *only* native AAV ITR sequences. '535 Patent, col. 29, line 6-col. 39, line 33. Plaintiffs do not dispute that all nine constructs reported in Feldhaus comprise the 145-nucleotide native AAV ITR sequence with a promoter tacked on. *Supra*, p. 21. Similarly, Plaintiffs concede that the "double-D internal ITR sequence" utilizes the construct reported in U.S. Patent 5,478,745 that comprises the 145-nucleotide native AAV ITR sequence with a naturally occurring D-sequence added on. *Id.* pp. 20-21. And the Carter Patents' citation to WO99/20799 to define a *separate* term, "replication origin," is immaterial (*id.* pp. 21-22), as the Carter Patents never describe the hypothetical construct having replication origin(s) as modified AAV ITRs ('535 Patent, col. 12, lines 1-10).

The specification's reference to an "approximately" 145-nucleotide AAV ITR sequence is not a "clear signal" that the claims should encompass a universe of non-contemplated and after-arising mutated AAV ITRs. *Contra supra*, p. 20. As Plaintiffs' declarant admitted, the term

"approximately" simply captures native AAV ITR sequences that were known to "differ slightly" in length between native AAV genomes. Ex. 21, p. 3998; Ex. 22, p. 161, line 20-p. 168, line 24. Namely, it was known by 1999 that the native AAV ITRs of the AAV-1 genome "are 143 nucleotides long, while those of AAV-2, AAV-3, and AAV-4 are 145 or 146 nucleotides long." Ex. 21, p. 3998.

The extrinsic evidence discussed by Plaintiffs—subsequent prosecution of the unrelated, later Samulski/McCarty patent—refutes Plaintiffs' own proposed construction. There, the examiner expressly concluded the asserted Carter Patents disclose only native ITRs whereas the later Samulski/McCarty patent discloses mutant ITRs. Namely, Samulski/McCarty explained during prosecution that their invention "modif[ies] a terminal repeat sequence . . . , whereas Carter [the '535 Patent] only describes the use of a half-size genome comprising *unmodified* terminal repeats." Ex. 23, p. 19. The examiner agreed, stating in the notice of allowance: "The difference between the two is that the internal ITR of US Patent 6,596,535 *is not modified*." Ex. 19, p. 5.

Plaintiffs' reference to allegedly dominating patents is also misplaced: after-arising technologies, like the Samulski/McCarty patents and Zolgensma®[12], showcase Plaintiffs' transparent attempt to capture what they did not invent by fashioning overbroad constructions contradicted by the intrinsic and extrinsic evidence.

[12] Defendants' declarant testified that he didn't invent Zolgensma® (Ex. 24, p. 28, line 17-p. 29, line 5; p. 207, lines 7-19), not—as Plaintiffs contend (*supra*, p. 18 n.9)—that he lacks knowledge about the mutated ITR contained therein, which is publicly available information and readily known in the field. And despite Plaintiffs' complaint that Defendants' declarant did not review "the entirety" of all five patent prosecution histories and all 84 asserted claims (*id.*, p. 20 n.10, citing Ex. 14, p. 25), Plaintiffs' own declarant did not review *any* of the prosecution histories whatsoever (Ex. 22, p. 22, lines 1-5).

B. "Along most or all of its length" or "Along its length"

Claim Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"along most or all of its length" or "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)	"along most (as most is defined) or all of its length" or "along its length"	Indefinite

I. Plaintiffs' Opening Position

The Carter Patents use the terms "along most or all of its length" or "along its length" to describe where intrastrand base pairing can occur in a heterologous nucleotide sequence. For example, Claim 1 of the '054 patent describes the vector genome as comprising:

> 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, wherein the first heterologous nucleotide sequence can form intrastrand base pairs with the second nucleotide sequence ***along most or all of its length***.

(emphasis added); *see also* '535 Patent, claim 2 ("The rAAV vector of claim 1, wherein the sequence complexity of the heterologous sequence is about one-half of the length of the heterologous sequence, wherein the heterologous sequence forms a double-stranded structure along most or all of its length"). This is part of the description of how the otherwise single-stranded rAAV vector genome doubles back (or snaps back) on itself to form a double-stranded structure with a complementary second nucleotide sequence "along most or all of [the] length" of the first heterologous sequence.

The parties have agreed that "most" means "more than half" in the context of the claims. *See supra*, p. 4. And there should be no question what "all" means in this context. So this claim language means just what it says: the formation of intrastrand base pairing occurs along more than 50% up to 100% of the length of the heterologous sequence of interest.

II. Defendants' Answering Position

The disputed terms "along its length" in all asserted claims of the '729 Patent and "along most or all of its length" in nearly all asserted claims of the '535, '717,'888, and '054 Patents are part of a larger claim term requiring a resultant function, i.e., the intrastrand base pairing "along" the length of the sequence must be "*such that* expression of [a] coding region . . . is enhanced relative to [a] rAAV vector that lacks sufficient intrastrand base pairing to enhance [] expression." As explained *infra* § III(A).E and incorporated herein, this larger functional phrase is hopelessly indefinite, at least because the Carter Patents do not identify what intrastrand base pairing along the length of the sequence is "sufficient" to achieve the claimed enhanced expression. But there are many other reasons both "along" terms are indefinite as well.

As to the term, "along *most or all* of its length," Plaintiffs' contention of definiteness is that the parties have agreed "most" means "more than half" and there is no question what "all" means. *Supra*, p. 25. But simply identifying that over 50% to 100% of the heterologous sequence must be intrastrand base paired does not resolve the ambiguities. The specification states that a region of intrastrand base pairing may be anywhere over a region from 5 to over 500 nucleotides ('535 Patent, col. 10, lines 14-18) and provides no guidance in terms of which nucleotides are paired, how many nucleotides are paired, where they are located (including outside of the coding region, e.g., in a promoter, enhancer, or polyadenylation sequence), whether they are contiguous, or what constitutes sufficient intrastrand base pairing to exhibit enhanced expression. *Id.* col. 14, line 63-col. 15, line 8; Kay Declaration ¶¶ 60-63. According to the specification, an rAAV vector

may contain a 10-nucleotide region having 60% intrastrand base pairing, i.e., 6 nucleotides that are intrastrand base paired, with no clarity as to which 6 nucleotides they are, where the 6 nucleotides are located, or whether 6 nucleotides constitute sufficient intrastrand base pairing to exhibit enhanced expression. Kay Declaration ¶ 63. The specification also contemplates an rAAV vector containing a 200-nucleotide region having 95% intrastrand base pairing, i.e., 190 nucleotides that are intrastrand base paired, again with no clarity as to which 190 nucleotides they are, where the 190 nucleotides are located, or whether the 190 nucleotides constitute sufficient intrastrand base pairing to exhibit enhanced expression. *Id.* Alternatively, perhaps one or both of these constructs are comparators that lack sufficient intrastrand base pairing to enhance expression. *Id.* Skilled artisans using rAAV vectors, e.g., having 6 or 190 or any other number of intrastrand base paired nucleotides encompassed by the claims, could not determine whether or not they infringe the claims. *Id.* As a point of reference, the specification's sole purportedly working embodiment of an intrastrand base paired vector presumes that "the entire genome [100%] of [the 2265-nucleotide vector] is base-paired." '535 Patent, col. 34, lines 36-38; Kay Declaration ¶ 64. Outside of this sole embodiment, the specification fails to define what constitutes intrastrand base pairing along most (but not all) of its length or that such a construct is even feasible. Kay Declaration ¶ 64. In short, a skilled artisan is left with very little guidance, much less reasonable certainty, as to the qualitative features that the regions of intrastrand base pairing must possess. *Id.* ¶¶ 60-64.

As to the term "along its length," Plaintiffs' opening brief ignores it altogether, not even attempting to show that it is definite. The problems for this term are the same as above, exacerbated by the failure to provide *any* contours on the requisite quantity of intrastrand base pairing. *Id.* ¶ 65.

The disputed claim term is also uniquely problematic in the context of the '054 Patent. Those claims merely state that the relevant sequence "*can form* intrastrand base pairs … along most or all of its length." *E.g.*, '054 Patent, col. 41, lines 37-39. The claims and specification provide no guidance whatsoever for how a skilled artisan should determine whether a vector "can form," but does not *actually* form, the intrastrand base pairing along most or all of its length. Kay Declaration ¶ 66.

III. Plaintiffs' Reply Position

Based on the agreed constructions, the term "along most or all of its length" means along more than half or all of the length (of a nucleotide sequence). Novartis does not argue that whether a person of ordinary skill would not understand the meaning of the term. Instead, the meaning of this term is clear and definite. Kurtzman Declaration, ¶ 72. In fact, even Novartis's declarant testified a person of ordinary skill in the art would have understood the phrase. Ex. 14, p. 233-34, 237-38. Plaintiffs' proposed construction is correct.

As to the term "along its length," its meaning is self-evident: along the length of the cited nucleotide sequence. Kurtzman Declaration, ¶¶ 72-73. The specification provides extensive disclosure of what that means, as even Novartis's argument against the former term's construction shows. Col. 14, line 49-col. 15, line 43; Kurtzman Declaration, ¶ 73. A person of ordinary skill would understand those functional and structural descriptions of the meaning of "along its length" and easily be able to determine based on that disclosure whether there was intrastrand base pairing along the length of the nucleotide sequence. Kurtzman Declaration, ¶ 73. Novartis's declarant did not disagree in his testimony. Ex. 14, p. 240-41. Again, the meaning of this term is clear and definite and Plaintiffs' proposed construction is correct.

IV. Defendants' Sur-Reply Position

That intrastrand base pairing along "most or all of its length" means along "more than half" of its length does not conclude the indefiniteness inquiry. While Plaintiffs focus on the fact that Defendants' declarant agreed (as the parties do) that the outermost *quantitative* bounds are identified (*supra*, p. 27), they ignore his testimony regarding the remaining ambiguities. For example, the specification fails to identify "which nucleotides, where they are located," (Kay Declaration ¶ 62), whether they are "contiguous" (*id.* ¶ 63), and what constitutes "sufficient" base pairing (*id.* ¶ 64). *See also* Ex. 24, p. 233, lines 13-21 (skilled artisan "wouldn't know specifically [] which half or which part of the sequence [the patents] were talking about" and would only understand the meaning of "most" "if you're just talking in quantitative numbers"). Indeed, Plaintiffs do not dispute that the Carter Patents encompass sequences spanning 5 to 500+ nucleotides and fail to specify *which* subset of these nucleotides are intrastrand base paired and *where* they are located along the length of the sequence. Plaintiffs also do not dispute that the pairing must produce a functional result and the Carter Patents provide no information about the nucleotides that must be paired to achieve this result.

The separate term, "along its length," is even further problematic, as it omits quantitative information altogether. Kay Declaration ¶ 65. Plaintiffs' declarant concedes the Carter Patents fail to specify *how many* nucleotides are intrastrand base paired, *which* nucleotides are intrastrand base paired, and *where* these nucleotides are located along the length of a sequence, let alone how to achieve the required functional result. Ex. 22, p. 124, line 18-p. 131, line 9.

C. "Conditions that allow"/"Conditions which allow"

Claim Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"conditions that allow"/ "conditions which allow"	"conditions that do not prevent events from occurring"	Indefinite

('535 Patent, claims 22-26, 28, 29; '717 Patent, claims 1-8, 11-17, 20; '729 Patent, claims 1-5, 7-9; '054 Patent, claim 18-27, 30-32, 34, 36)		

I. Plaintiffs' Opening Position

"Conditions that allow" and "conditions which allow" are used in different claims of the Carter Patents to mean that the conditions should not prevent the identified actions from occurring. As the specification points out, person of ordinary skill in the art would know that different conditions would apply to different events. For example, in claim 1 of the '717 Patent, the conditions are those applied to a cell that allow uptake of an rAAV vector into that cell:

> A method for introducing a polynucleotide into a cell, comprising
>
> contacting the cell essentially in the absence of an AAV helper virus with a recombinant adeno-associated virus (rAAV) particle comprising an rAAV vector ***under conditions that allow uptake of the rAAV vector***,
>
> whereby the rAAV vector is introduced into the cell . . . .

'717 Patent, claim 1 (emphasis added). In contrast, in claim 1 of the '729 Patent, the conditions are the incubation conditions that allow the adeno-associated virus (AAV) to replicate and form the viral capsule:

> 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*** . . . 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 a coding region of the heterologous sequence is enhanced relative to a rAAV vector that lacks sufficient intrastrand base pairing to enhance said expression.

'729 Patent, claim 1 (emphasis added). Thus, the "conditions that allow" terms require an understanding of the context of the claim, as claim construction principles require. *See, e.g.*, *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1374 (Fed. Cir. 2019).

The specification of the Carter Patents recognizes the importance of context and expressly defines what "conditions that allow" means. It states:

> ***Conditions that "allow" an event to occur***, such as uptake of an exogenous polynucleotide, such as a recombinant viral vector, into a cell, such as a mammalian cell, or infection by a virus, ***are conditions that do not prevent such events from occurring***. Thus, these conditions permit, enhance, facilitate, and/or are conducive to the event, such as entry of the exogenous polynucleotide into the cell. Such conditions, known in the art and described herein, depend upon the nature of the cell as well as the exogenous polynucleotide (i.e., whether introduced as a naked, complexed, or packaged vector). These conditions also depend on what event is desired, such as expression or infection.

'535 Patent, col. 14, lines 1-12 (emphasis added). That is, the "conditions that allow" depend on what events are being allowed to occur, but in all cases are "conditions that do not prevent [those] events from occurring."

The specification provides many of the potential conditions for different events to occur, both in extensive discussion of known techniques for introducing rAAV vectors into cells (*see*, *e.g.*, '535 Patent, col. 22, lines 15-64 (citing examples of different approaches to introducing rAAV vectors into cells)) and in specific examples (including Examples 3, 4, 6, and 7) of how rAAV particles were made in cells or introduced into cells. '535 Patent, col. 29, line 62-col. 31, line 27; *Id.*, col. 32, line 29-col. 33, line 17.[13] In adopting the express definition from the

[13] The specification also incorporates by reference general techniques "in virology, biochemistry, molecular biology, microbiology, genetics, recombinant DNA, and related fields as are within the skill of the art," such as those from Maniatis *et al.*, Molecular Cloning: A Laboratory Manual; Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Second Edition; and Ausubel *et al.*, Current Protocols in Molecular Biology. '535 Patent, col. 8, line 66-col. 9, line 11.

specification, Plaintiffs' proposed construction reflects the knowledge of a person of ordinary skill in the art that different events require different conditions.

II. Defendants' Answering Position

Several asserted claims, in four of the five Carter Patents, require use of "conditions that/which allow" certain events to occur, namely: "conditions that allow AAV replication and encapsidation," "conditions that allow uptake of the rAAV vector," or "conditions which allow expression of the coding region." These "conditions that/which allow" terms are indefinite, as the Carter specification provides no reasonable certainty as to what those conditions may be.

Plaintiffs' proposed construction parrots the specification's meaningless definition for this claim language: "[c]onditions that 'allow' an event to occur . . . are conditions that do not prevent such events from occurring." '535 Patent, col. 14, lines 1-5. This circular definition provides no guidance as to what the disputed term actually means. It is an unhelpful restatement of the claim language using different words, still leaving a skilled artisan with no guidance as to what the required conditions may be. The subsequent statement of the specification is equally unhelpful, stating merely that the conditions may "permit, enhance, facilitate, and/or [be] conducive to the event." *Id.* col. 14, lines 5-7. Again, this language does not define the required claim conditions or even suggest what they may be. *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1251 (Fed. Cir. 2008) ("Even if a claim term's definition can be reduced to words, the claim is still indefinite if a person of ordinary skill in the art cannot translate the definition into meaningfully precise claim scope.").

Although the specification states that "[s]uch conditions [are] known in the art and described herein," it admits that the requisite conditions will "depend upon the nature of the cell, . . . the exogenous polynucleotide (i.e., whether introduced as a naked, complexed, or packaged vector[, and] . . . what event is desired." *Id.* col. 14, lines 7-12. The Carter specification's

overbroad claims provide no limitation as to the cell, polynucleotide, or how to achieve a desired event, and the specification admits that universe is nearly limitless. Kay Declaration ¶¶ 54-57. A skilled artisan could not have determined with reasonable certainty the conditions that allow replication and encapsidation in the cells as broad as "yeast, insect, avian, plant and mammalian cells," "cell lines and primary cells," and "HeLa, 293, and primary fetal foreskin fibroblast cells" ('535 Patent, col. 17, lines 41-47; Kay Declaration ¶ 55) or the conditions that allow uptake or expression in the cells as broad as "eucaryotic cells, procaryotic cells and Archaea," "animal cells, plant cells, [and] yeast cells" ('535 Patent, col. 26, lines 51-58; Kay Declaration ¶ 57). A skilled artisan in 1999 would have understood that AAV has evolved to target certain vertebrate cells using their cellular machinery, and the skilled artisan would not know how to replicate, encapsidate, uptake, or express in cells that lack this machinery and/or are difficult to cultivate, e.g., yeast, avian, or plant cells. Kay Declaration ¶¶ 54-57. Even today, a skilled artisan does not know the conditions under which, for example, an rAAV vector can encapsidate in a plant cell or express in a procaryotic cell. '535 Patent, col. 26, lines 51-58; *see also id.* col. 17, lines 38-47; Kay Declaration ¶¶ 54-57. Given the sweeping breadth of the claims, the public is not put on notice of what the claimed invention is—i.e., what the parameters of the requisite "conditions" are—thus making it impossible to know whether one is potentially infringing.

Plaintiffs argue that the specification contains "extensive discussion of known techniques" and "specific examples" that give meaning to the claim language. *Supra*, p. 30, citing '535 Patent, col. 22, lines 15-64 and Examples 3-7. But column 22 merely references approaches that have been used. It does not identify within those approaches what the conditions were that "allowed" the claimed event to occur. All of the conditions utilized in each cited reference? Some subset of those conditions? A specific combination of those conditions? Nor do

any of the approaches describe conditions for the universe of cells, polynucleotides, and events encompassed by the claims. Kay Declaration ¶¶ 54-57. A skilled artisan is left with no guidance as to what conditions within the cited references would allow him to practice the invention (or determine if he has infringed). The Examples are equally unhelpful. The Carter specification describes a set of experiments, involving a single working embodiment of a half-size vector ('535 Patent, col. 29, lines 10-26 (Example 1)), in which encapsidation is purportedly achieved in a HeLa cell line (*id.* col. 30, lines 48-59 (Example 4)) and expression is purportedly measured in HeLa and 293 cell lines (*id.* col. 32, line 25-col. 33, line 34 (Examples 6 and 7); col. 36, line 36-col. 37, line 27 (Example 11)). Kay Declaration ¶¶ 55, 57. While it describes some of the conditions and parameters used, it does not identify which were necessary or sufficient, or which a skilled artisan is required to follow to practice the claimed invention(s). Moreover, the specification provides no guidance whatsoever regarding the claimed "conditions" for use in the long list of non-exemplified cells, e.g., yeast, insect, avian, plant, prokaryotic, Archaea, or primary cells. Kay Declaration ¶¶ 54-57. Not only were most of these conditions unknown in 1999, they remain unknown even today. *Id.*

Finally, Plaintiffs point to the specification's nod to techniques "fully explained in the literature," followed by mention of three laboratory manuals and "related references." *Supra*, p. 30 n.13, citing '535 Patent, col. 8, line 66-col. 9, line 11. Notably, Plaintiffs have not cited anything in these (or other) prior-art literature references that identify the claimed "conditions that/which allow . . . . " The law requires the claims of a patent "particularly point[] out and distinctly claim[]" the invention. 35 U.S.C. § 112. Neither the claims nor the specification does so.

III. Plaintiffs' Reply Position

The claim terms "conditions that allow" and "conditions which allow" are used in a number of contexts in the claims to identify that a person of ordinary skill in the art should use appropriate conditions (already known in the art) for that step. Kurtzman Declaration, ¶¶ 54-56. Unquestionably, a person of ordinary skill would understand as much from the context of the claims and the express definition of "conditions that allow" in the specification. *Id*. Novartis does not dispute that and its declarant admitted as much in his testimony. Ex. 14, p. 166-69. Instead, Novartis argues that a person of ordinary skill might not be able to make or use the full scope of the claimed invention because there may not be conditions that allow certain events to occur. But that is the province of enablement – not at issue at this stage – rather than definiteness. Kurtzman Declaration, ¶¶ 57-61.

Here, unlike in the *Halliburton* case cited by Novartis, the claims provide a context from which a person of ordinary skill in the art can easily determine the bounds of the claims. For example, claim 1 of the '717 patent covers "A method for introducing a polynucleotide into a cell, comprising contacting the cell . . . with a recombinant adeno-associated virus (rAAV) particle comprising an rAAV vector under conditions that allow uptake of the rAAV vector, whereby the rAAV vector is introduced into the cell." '717 Patent, col. 41, lines 53-67. A person of ordinary skill would know if the conditions were within the scope of the claim or not based on whether the rAAV vector was introduced into the cell or if the conditions prevented introduction.

This clear demarcation between whether or not the conditions allow events to occur is fundamentally different from *Halliburton*. There, the composition of matter term "fragile gel" was described in the specification but without any indication of how to determine whether a

composition had the ambiguously-described properties of a "fragile gel." 514 F.3d 1244, 1251 (Fed. Cir. 2008). Further, the patent provided no basis for distinguishing the novel "fragile gels" from the prior art compositions or any limit on the scope of what was invented beyond the prior art. *Id.* at 1253-54. In contrast, the "conditions that allow" events here are based on the prior art, and expressly do not serve as a distinction over that art. And the claims themselves provide the guidance needed by a person of ordinary skill to determine whether the conditions fall within the claims.

Novartis also argues (based on Dr. Kay's declaration) that the claims are indefinite because a person of ordinary skill would not be able to make and use certain embodiments of the claims because there are no "conditions that allow" events for those embodiments.[14] Whether an embodiment can be made or used is a different question under section 112: whether the claims are enabling under paragraph 1. *Compare* 35 U.S.C. § 112, ¶ 1 *to* 35 U.S.C. § 112, ¶ 2. And the fact that both Novartis and Dr. Kay could understand the meaning of "conditions that allow" clearly enough to determine whether such conditions exist for specific embodiments shows that the claims are sufficiently definite. Kurtzman Declaration, ¶ 57. Thus, Novartis's argument by itself shows that its conclusion of indefiniteness is wrong.

IV. Defendants' Sur-Reply Position

Plaintiffs' declarant concedes the asserted claims encompass cells as broad as yeast, insect, avian, and plant cells, and recite unspecified "conditions that allow" rAAV replication, encapsidation, uptake, and expression in these cells. *See, e.g.,* Ex. 22, p. 68, line 23-p. 69, line 6;

[14] Notably, Dr. Kay and Novartis do not argue that there are no "conditions that allow" the claimed events to occur for most of the embodiments (such as in mammalian cells). Thus, their argument is directed only an allegedly non-functional embodiments, an issue arguably relevant to enablement, but not definiteness.

p. 79, line 9-p. 83, line 25. Plaintiffs' declarant also concedes that the full scope of conditions was not exemplified in the Carter Patents or known in 1999 (*id.* p. 108, lines 13-25; p. 116, line 17-p. 119, line 12), and Plaintiffs do not dispute that these conditions remain unknown even today. Moreover, contrary to Plaintiffs' suggestion that Defendants' declarant "admitted" the definiteness of this claim term (*supra*, p. 34), the very testimony Plaintiffs cite demonstrates the opposite: that a skilled artisan would have had "no clue as to what kind of conditions that they might need to use to do any of the things listed here." Ex. 14, p. 167, line 24-p. 168, line 3; *see also id.* p. 166, lines 9-16.

Despite the lack of guidance in the specification, Plaintiffs assert that a skilled artisan would "unquestionably understand" the requisite conditions and that the claims provide "context from which a person of ordinary skill in the art can easily determine" them. *Supra*, p. 34. But glaringly absent from Plaintiffs' argument and declarant testimony is any identification of what the requisite claim conditions *actually are*. Ex. 22, p. 114, line 1-p. 117, line 13. The closest Plaintiffs come is a single sentence in their supporting expert declaration that refers to "some" exemplified methods of the Carter patents and, possibly, the use of "ionizing radiation." Kurtzman Declaration ¶ 58; Ex. 22, p. 115, line 6-p. 116, line 16. But Plaintiffs' declarant admitted that the metes and bounds of the claimed "conditions" were unknown in numerous ways: that ionizing radiation might *not* work for all claimed cell types (Ex. 22, p. 118, line 11-p. 119, line 1); that he could only "speculate" as to the conditions that would be required (*id*. p. 119, lines 4-12); that he could not provide "specific" examples (*id.* p. 120, line 21-p. 122, line 13); and that a skilled artisan would need to "design an experiment to either demonstrate it or

not" (*id.* p. 123, lines 5-25).[15] Plaintiffs' circular argument—that a skilled artisan "would know if the conditions were within the scope of the claim or not based on whether the [method works, e.g., the rAAV vector is successfully introduced into the cell]" (*supra*, p. 34) is not an identification of the claimed conditions with reasonable certainty.

D. "enhanced"/"enhance"

Claim Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"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)	"intensify, increase, or improve the rate, level, or efficiency of expression in comparison to a comparator"	Indefinite

I. Plaintiffs' Opening Position

The Carter Patents use the term "enhance" to describe the improvement of expression that arises due to intrastrand base pairing, relative to a sequence that does not form intrastrand base pairs. For example, claim 1 of the '535 patent covers:

> A recombinant adeno-associated virus (rAAV) vector comprising a single-stranded heterologous nucleotide sequence comprising a region which forms intrastrand base pairs such that expression of a 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 region which forms intrastrand base pairs is in a coding region.

'535 Patent, col. 39, lines 44-51 (emphasis added).

The specification indicates what that enhancement is by describing increased or improved rates, levels, or efficiency of expression:

> Without wishing to be bound by theory, the ***enhanced level and/or rate*** of expression by the rAAV vectors of the invention may be due to their facility for forming a double-stranded structure. . . . If an incoming vector genome is either in

[15] The claims are therefore not only indefinite, but also suffer from enablement problems, as Plaintiffs rightly acknowledge.

> double-stranded form or is in a form from which it can rapidly adopt a double-stranded conformation, providing transcriptional templates ***more efficiently and/or earlier*** during the infective cycle, expression of an inserted sequence is enhanced, as compared to other rAAV vectors.

'535 Patent, col. 8, lines 15-32 (emphasis added). The specification also contrasts the slow expression of the single-stranded form and the "more rapid and efficient expression" of the double-stranded form:

> A significant period of time, often on the order of weeks, can be required to obtain useful levels of a gene product of interest. In contrast, the metabolically activated vectors of the invention can efficiently and rapidly form duplex templates for transcription, thereby providing enhanced expression of transgenes and reducing the time required for accumulation of a gene product of interest to days, rather than weeks. Since the metabolically activated vectors of the invention provide ***more rapid and efficient expression*** of a transgene, they will also facilitate procedures known in the art in which rapid expression of a gene product of interest is desirable.

'535 Patent, col. 25, line 63-col. 26, line 7 (emphasis added). Then, in Examples 6 and 7, the specification gives actual examples of enhancement in which "half-complexity" vectors – which form intrastrand base pairs – "had a ***significantly higher ability to express*** detectable levels of GFP as indicated by percentage of fluorescent [293 and HeLa] cells, compared to the full-size vector," which does not form intrastrand base pairs. *Id.*, col. 32, lines 29-44; *id.*, col. 33, lines 1-17 (emphasis added).

Clearly, the specification identifies rate, level, and efficiency as the three parameters that can be intensified, increased, or improved by enhancement of expression, in all cases relative to a sequence that does not form intrastrand base pairs. Thus, the specification of the Carter patents provides the proper construction of the term "enhance"/"enhanced" to mean "intensify, increase, or improve the rate, level, or efficiency of expression in comparison to a comparator."

II. Defendants' Answering Position

This term, recited in all asserted claims of four of the five Carter Patents, is wholly subsumed by the following disputed term. Defendants address the indefiniteness of this term, including Plaintiffs' arguments thereto, along with the larger term within which it appears, in the next section.

III. Plaintiffs' Reply Position

Despite asserting that the claim terms "enhanced" or "enhance" are independently indefinite, Novartis makes no argument in support of its assertion. Rather, Novartis just argues that the term is "wholly subsumed" in the following term. But Novartis actually asserted in the Amended Joint Claim Construction Chart that "enhance" was indefinite on its own. D.I. 78. In failing to respond substantively to Plaintiffs' claim construction arguments, Novartis has waived the argument and any objection to Plaintiffs' construction. *Nassau Precision Casting Co. v. Acushnet Co.*, 566 F. App'x 933, 937 (Fed. Cir. 2014) (claim construction argument waived by failing to respond to opposing party's claim construction); *see also Pers. Audio, LLC v. Google LLC*, No. CV 17-1751-CFC-CJB, 2019 WL 2403086, at *2 (D. Del. June 7, 2019), *report and recommendation adopted*, No. CV 17-1751-CFC-CJB, 2020 WL 58631 (D. Del. Jan. 6, 2020) (claim construction arguments waived and opposing party's construction adopted where party did not respond to arguments on claim construction issues). Thus, Plaintiffs' construction of the term – intensify, increase, or improve the rate, level, or efficiency of expression in comparison to a comparator – should be adopted. Kurtzman Declaration, ¶ 67.

IV. Defendants' Sur-Reply Position

Plaintiffs' waiver arguments are baseless. Defendants "address the indefiniteness of this term, including Plaintiffs' arguments thereto, along with the larger term within which it appears, in the next section." *Supra*, p. 39. And Plaintiffs acknowledge Defendants' response to precisely

the arguments that Plaintiffs have made regarding this specific claim language—i.e., whether a skilled artisan "would [] know what rate, level, or efficiency was enhanced." *Infra*, p. 46, pp. 44-45, and § III(A).E.

E. "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"

Claim Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"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"/"forms intrastrand base pairs along most or all of its length such that expression of the coding region is enhanced relative to an rAAV vector that lacks sufficient intrastrand base pairing to enhance expression"/"forms intrastrand base pairs along its length, such that expression of a coding region of the heterologous sequence is enhanced relative to a 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)	"self-anneals to a complimentary 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"	Indefinite

I. Plaintiffs' Opening Position

These claim terms define how Dr. Carter's snapback molecules work. The self-complementary, heterologous (nonviral) sequences snap back to form intrastrand base pairs with each other, which necessarily enhances the expression of the heterologous sequence of interest. Once the complementary sequences snap back together, the sequences are in double-stranded form and ready for immediate expression.

The specification of the Carter Patents states

> A "region (or sequence) which forms intrastrand base pairs" (including a coding region which forms intrastrand base pairs) is a region (such as a coding region) which is complementary in sequence to another region in the same strand, and is thus capable of forming base pairs with the complementary sequence, i.e., is self-annealing.

'535 Patent, col. 10, lines 38-43. This supports Plaintiffs' proposed construction because the region of a heterologous sequence that self-anneals to a complementary sequence of the same polynucleotide strand causes expression of a coding region to be enhanced relative to the expression of a coding region of an rAAV vector 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 expression.

II. Defendants' Answering Position

All asserted claims of the '535, '717, '888, and '729 Patents require the claimed rAAV vector "forms intrastrand base pairs . . . such that expression of [a] coding region . . . is enhanced relative to [a] rAAV vector that lacks sufficient intrastrand base pairing to enhance [] expression." This term is entirely circular and lacks any sort of "objective boundaries" to determine where the claim ends and where it begins. *Interval Licensing LLC v. AOL, Inc*., 766 F.3d 1364, 1371 (Fed. Cir. 2014)

While the claim term is lengthy, it essentially boils down to one thing: the claimed vector must form intrastrand base pairs to enhance expression "relative to" one that does not do so. But how does one determine whether one has the former or the latter when they are defined only relative to one another? This is akin to defining a fast swimmer as someone who fast relative to someone who is insufficiently fast. A good swimmer when compared to a bad swimmer would infringe. But when compared to a great swimmer, neither the good swimmer nor the bad swimmer would infringe. The purported comparator is defined only with reference to the thing that is being compared. In short, the problem with the claim term is that no objective baseline is provided. It provides a moving target against which it is impossible to determine whether any given vector is infringing. *See, e.g.*, *Halliburton*, 514 F.3d at 1255 (affirming indefiniteness determination for claim term that "requires that an artisan make a separate infringement determination for every set of circumstances in which the composition may be used, and when such determinations are likely to result in differing outcomes (sometimes infringing and sometimes not)").

The specification provides no help. It instead recites the same circular logic:

> The region(s) of intrastrand complementarity . . . are positionally and/or quantitatively sufficient to enhance expression of a nucleotide sequence of interest contained within the vector as compared to a vector that is structurally analogous except for the position and/or quantity of base pairing, such that the analogous vector lacks sufficient intrastrand complementarity to enhance expression of the nucleotide sequence of interest.

'535 Patent, col. 14, lines 49-57. While this paragraph adds that the intrastrand base pairing must be "positionally and/or quantitatively sufficient to enhance expression," the intrastrand base pairing and enhanced expression is still defined by relative terms; no metes and bounds are provided. And elsewhere the specification is far-ranging indeed. It proclaims that "[t]he regions of intrastrand complementarity may be anywhere along the heterologous sequence and may be

any of a number of sizes, in terms of contiguous nucleotides." *Id.* col. 14, lines 63-65; Kay Declaration ¶¶ 61-63. The intrastrand base pairing may be within a coding region (or not); adjacent to a terminus (or not); or near to the center of the molecule (or not). '535 Patent, col. 14, line 66-col. 15, line 4; Kay Declaration ¶¶ 61-63. The number of intrastrand base paired nucleotides can range from 5 to 500 to 1,000 or more ('535 Patent, col. 15, lines 4-13) and comprise anywhere from 25%-100% of the sequence (*id.* col. 10, line 65-col. 11, line 1)—an essentially limitless universe of intrastrand base paired options. Kay Declaration ¶¶ 63-65. In short, a skilled artisan is left utterly out at sea, both in understanding what the patent covers, and in determining whether any given vector infringes.

Plaintiffs' position is that this claim term is not indefinite because it "define[s] how Dr. Carter's snapback molecules work." *Supra*, p. 40. Whether or not that is so, a patent claim must "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention." 35 U.S.C. § 112; *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 911 (2014) (the statutory requirement is not satisfied merely by "ascrib[ing] *some* meaning to a patent's claims").

Plaintiffs otherwise contend, specifically with respect to the "enhanced/enhance" language, that the specification "identifies rate, level, and efficiency as the three parameters that can be intensified, increased, or improved by enhancement of expression." *Supra*, p. 38. While rate, level, and efficiency may be some ways of assessing gene expression, the Carter Patents provide no definition of *what* rate, *what* level, or *what* efficiency constitutes the claimed "enhanced efficiency." Kay Declaration ¶ 67. Indeed, the only potentially relevant data in the patent reports expression differences ranging from 3.6-fold to about 20-fold, which is summarily labeled in the accompanying text: "a significantly higher ability to express detectable levels of

GFP." '535 Patent, Tables 2 and 3; col. 32, lines 40-44; col. 33, lines 8-12; *see also id.* col. 36, line 36-col. 37, line 27; Kay Declaration ¶ 67. The specification does not identify which of these data, if any, demonstrate sufficient "enhanced expression" or by what metric that determination should be made. Kay Declaration ¶ 67. Nor does the specification define the intrastrand base pairing required to achieve these undefined parameters. *Id.* Indeed, the specification provides no measure of intrastrand base pairing at all, instead merely "presuming" that it occurred. '535 Patent, col. 34, lines 16-36; col. 35, line 18; Kay Declaration ¶ 67.

The disputed claim term is indefinite for another reason as well: the claims are entirely ambiguous as to when, where, or how the intrastrand base pairing and/or enhanced expression must occur or be measured. Kay Declaration ¶¶ 37, 68-70. The claim language and specification fail to define any temporal or environmental aspect to the claimed intrastrand base pairing and/or enhanced expression, and a skilled artisan would understand that results can vary when assessing the same rAAV vector at different time points or under different environments. *Id.*; *see, e.g.*, *Dow Chem. Co. v. Nova Chems. Corp. (Can.)*, 803 F.3d 620, 634 (Fed. Cir. 2015).

III. Plaintiffs' Reply Position

Novartis claims that a person of ordinary skill in the art would not be able to construe the claim phrase because it is a relative determination, rather than absolute one. Through misplaced analogy and bare assertion from Dr. Kay, it argues that the Carter patents do not provide enough guidance to allow one to know whether expression of the coding region is enhanced when there is double-stranded DNA rather than single-stranded DNA. Kurtzman Declaration, ¶ 68. But the evidence that Novartis (and its declarant, Dr. Kay) cites elsewhere in its brief stands for the exact opposite proposition: they use the same metric (expression of the intrastrand-paired form relative to single-stranded form) to show enhancement of expression. Kurtzman Declaration, ¶¶ 68-69.

That is, even the evidence that Novartis itself cites to describe the development of Zolgensma® supports Plaintiffs' construction of the claim phrase.

Novartis and Dr. Kay cite two articles and a family of patents relating to the intrastrand-paired rAAV vectors (which Novartis argues underlie Zolgensma®); the three sources describe comparing the rate, level, or efficiency of intrastrand-paired (or self-complementary) vectors relative to conventional, single-stranded vectors as the proper test for determining whether expression is enhanced. First, McCarty *et al.* described how to test whether intrastrand base pair formation would "overcome the greatest barrier to rAAV transduction . . . the conversion of single-stranded virion DNA to duplex":

> This prediction was supported in a mouse liver transduction experiment comparing an scAAV vector with a conventional rAAV vector. ***The scAAV vector yielded a faster onset and higher level gene expression than the cognate ssAAV vector.***

Ex. 5, p. 2112; *see* Kurtzman Declaration, ¶ 68. Similarly, in reviewing work that had been done in the field based on Carter's invention, McCarty relied on results relative to single-stranded AAV vectors to show that intrastrand-paired vectors had enhanced expression through more efficient transduction:

> An scAAV vector, sometimes called dsAAV, can be made simply by reducing the vector construct size to ~2,500 base pair (bp) (2,200 bp unique transgene sequence plus two copies of the 145-bp ITR), such that the dimeric inverted repeat will be no larger than the normal AAV packaging capacity (~4,700 nucleotides). . . . ***[I]n a recent study in which scAAV vector was made by this method, and contained only 3% dimeric genomes, a 600-fold increase in therapeutic efficacy over ssAAV vector was reported***. This suggests the possibility that SA [strand annealing] from two genomes contained within a single virion might have contributed to efficient transduction."

Ex. 6, p. 1649; *see* Kurtzman Declaration, ¶ 69. Finally, the Samulski & McCarty patent family itself relies on the same relative measurement to show greater efficiency of expression:

> Rather than rely on potentially variable cellular mechanisms to provide a complementary-strand for rAAV vectors, it has now been found that this problem may be circumvented by packaging both strands as a single DNA molecule***. In the studies described herein, an increased efficiency of transduction from duplexed vectors over conventional rAAV was observed in HeLa cells (5-140 fold).***

Ex. 7, col. 2, lines 20-26. These unbiased, prelitigation sources make it clear that a person of ordinary skill would understand the claim phrase – and construe it the way that Plaintiffs propose – rather than rely on the naked assertion to the contrary in a litigation-induced declaration.

Novartis ignores that evidence and, instead, relies on a tortured analogy to swimming. According to Novartis's argument, a relative improvement (a swimmer getting much faster) would not constitute a patentable improvement, only the absolute best, fastest method. That is not the law on patentability, let alone definiteness. But the evidence here shows that Dr. Carter's invention results in a substantial and measurable improvement. Kurtzman Declaration, ¶ 70. Such qualitative and quantitative improvement is both definite and patentable.

Novartis's penultimate argument, that a person of ordinary skill would not know what rate, level, or efficiency was enhanced by the claimed invention, falls apart in the context of the claim phrase to be construed. The phrase requires the enhancement of expression of a coding region (which is itself a term with an agreed construction). Kurtzman Declaration, ¶ 70. Novartis admits that there is an example of enhanced expression in the Carter patent specification, but argues that while it shows improvement, it does not define how much improvement is "sufficient." But sufficiency is built into the proper construction of the claim phrase – if there is not sufficient intrastrand base pairing, there will be no measurable enhancement of expression (which can be determined and measured). Kurtzman Declaration, ¶ 70. Thus, Novartis's argument is incorrect.

Finally, Novartis argues that phrase is indefinite because it does not identify the timing or environment of intrastrand base pairing or increased expression. Kurtzman Declaration, ¶ 71. Novartis does not explain the basis for its argument and fails to provide any factual basis that different timing or environments would lead to different results (other than a citation to a naked, argumentative assertion in the declaration of Dr. Kay). Even the patents and other references Novartis relies on do not disclose that type of information, establishing that its argument is wrong. *See supra*, p. 45-46. Finally, its citation to *Dow Chem. Co. v. Nova Chems. Corp. (Can.)*, 803 F.3d 620, 634 (Fed. Cir. 2015) shows how improper that approach is – indefiniteness there was found only when the infringer showed that there were four different measurements (none of which was identified in the specification) that would give four different results. *Id.* Given the lack of such a record, Novartis's argument here is baseless.

IV. Defendants' Sur-Reply Position

This term (and the prior one) requires an empirical comparison but fails to define an objective comparator. Instead, the purported comparator is a moving target against which it is impossible to determine whether any given vector is infringing. Plaintiffs contend that a comparison can be made using three metrics—rate, efficiency, and level—but Plaintiffs' declarant concedes that *what* rate, *what* efficiency, and *what* level are unspecified. Ex. 22, p. 135, line 6-p. 136, line 15.

To combat indefiniteness, Plaintiffs rely on publications and patents from years after the alleged priority date of the Carter Patents (Exs. 5-9). This fails for multiple reasons. First, information unknown in 1999 cannot support definiteness of asserted claims. *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1299 (Fed. Cir. 2003). Regardless, the later McCarty publications reference evaluating a specific double-stranded rAAV vector and a

specific single-stranded rAAV vector[16]—much more than the nebulous comparison required by the Carter claims, i.e., reciting unspecified vectors that have undefined "sufficient" intrastrand base pairing "relative to" those that do not. The Carter Patents do not even quantify the purported intrastrand base-pairing, simply "presuming" the sole purportedly working embodiment is 100% base-paired (Ex. 22, p. 103, line 11-p. 104, line 23), yet attempting to claim vectors comprising far less. In short, nothing defines the claimed "enhanced" expression with reasonable certainty.

This claim term (and the preceding one) additionally suffers from the textbook indefiniteness problem that different measurements provide different results. *Dow*, 803 F.3d at 634. While Plaintiffs contend Defendants' argument on this ground is "baseless" (*supra*, p. 47), their own declarant admitted that expression from rAAV must be empirically determined (Ex. 22, p. 131, lines 1-9) and that outcomes vary depending on measurement conditions, such as timepoint (*id.* p. 142, lines 10-15).

F. "rAAV vector genome" / "rAAV genome"

Claim Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"rAAV vector genome"/"rAAV genome" ('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)	"the genetic material of a recombinant AAV vector or virus"	"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 least one, preferably two, AAV inverted terminal repeat sequences (ITRs), wherein each ITR of the polynucleotide vector is native AAV ITR sequence"

[16] Plaintiffs' citation does not support a generalized proposition that any other double-stranded rAAV results in any change in any efficacy, let alone a 600-fold increase. To the contrary, the reference cited in McCarty reports prolonged survival in a mouse model of liver disease using a specific capsid at a 600-fold lower dose, which is not observed using a different capsid. Ex. 6, p. 1649; Ex. 25, p. 665.

I. Plaintiffs' Opening Position

The parties agree that the claims of the Carter Patents use the term "rAAV vector genome"/"rAAV genome" to describe the genetic material of a recombinant AAV vector or virus. Novartis again seeks to limit this term to "native" ITR sequences. As discussed in more detail in Section A above, the Carter specification describes the use of modified ITRs (such as in the incorporated Feldhaus patent application), including mutations of wild-type (i.e., non-native) ITRs. Thus, a "native" limitation should not be imported into the claims.

II. Defendants' Answering Position

Plaintiffs agree that the dispute on these terms, found in all asserted claims of the '888, '729, and '054 Patents, boils down to the same dispute as for the first disputed claim term (*supra* § III(A).A), namely—whether the AAV ITRs in the claimed "rAAV vector genomes" and "rAAV genomes" must be *native* AAV ITR. For the reasons explained *supra* § III(A).A and *infra* § III(A).G, Plaintiffs' proposed construction, which purposefully omits the requirement that each AAV ITR must be native AAV ITR, should be rejected. The terms "rAAV vector genome" and "rAAV genome" should be construed to mean the genetic material of a rAAV vector in which each AAV ITR is native AAV ITR sequence.

III. Plaintiffs' Reply Position

Novartis cites nothing in the intrinsic or extrinsic evidence relating to the claim term "rAAV vector genome" itself to support its attempt to limit this term to "native AAV ITR sequences." Rather, it relies on its improper attempt to limit the definition of "AAV ITR sequence" to the native, 145 nucleotide sequence. For the reasons already discussed above, the specification makes it clear that "AAV ITR sequence" is not limited to native ITRs. Therefore,

this Court should adopt Plaintiffs' construction, which accurately reflects the intrinsic definition of the term.

IV. Defendants' Sur-Reply Position

The parties agree that this term means the genetic material of a rAAV vector, which is defined in the specification as requiring "AAV inverted terminal repeat sequences (ITRs)," a term that the parties have proposed for construction and which requires native AAV ITR sequence.

G. "Recombinant AAV vector (rAAV vector)"

Claim Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"recombinant AAV vector (rAAV vector)" ('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 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)"	"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"

I. Plaintiffs' Opening Position

The Carter Patent specification expressly defines the term "recombinant AAV vector" in the way proposed by Plaintiffs:

> A "recombinant AAV vector (rAAV vector)" refers to 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).

'535 Patent, col. 9, lines 41-45. The patentee crafted its definition of the term (and thereby the construction of the claim term) by choosing to explicitly exclude the modifier "native" with respect to the inverted terminal repeats and there is nothing in that definition (or elsewhere in the

specification) that requires that "each ITR of the polynucleotide vector is native AAV ITR sequence." Thus, Defendants' effort to limit the claims would be improper, especially because the Carter specification describes the use of modified ITRs that include mutations of wild-type (or native) ITRs.

II. Defendants' Answering Position

All asserted claims of the '535, '717, '888, and '729 Patents recite a "recombinant AAV vector." For the same reasons as explained for the related term of the '054 Patent (*supra* § III(A).A), the Carter specification expressly defines the claimed "rAAV vectors" as containing *native* AAV ITRs. Specifically, the Carter specification defines the term "rAAV vector" as requiring "AAV ITRs" ('535 Patent, col. 9, lines 42-26) and, in turn, defines "AAV ITRs" as requiring *native* AAV ITR (*id.* col. 11, lines 13-16). Dispositively, Plaintiffs *agree* with these definitions. Plaintiffs' proposed construction—to expand the claims to encompass the later-invented *mutated* ITR, is unsupported by anything in the specification, expressly contradicted by it, and should be rejected.

III. Plaintiffs' Reply Position

Remarkably, Novartis tries to inject its "native AAV ITR sequence" argument into the claim term "recombinant AAV vector." As Novartis admits, there is an express definition of this claim term in the Carter patent specification; Plaintiffs have proposed that express definition as the proper construction. Kurtzman Declaration, ¶¶ 39-40. As discussed above, "AAV ITR sequence" means what the parties have agreed to and what the specification reflects; it is not limited to native ITRs and it certainly does not justify the addition of an extraneous limitation into the construction of "recombinant AAV vector."

IV. Defendants' Sur-Reply Position

The parties agree that this term requires "AAV inverted terminal repeat sequences (ITRs)," a term that the parties have proposed for construction and which requires native AAV ITR sequence.

III(B). Disputed Constructions for U.S. Patent No. 9,051,542[17]

A. "Dynamic Light Scattering"

Claim Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"dynamic light scattering" ('542 Patent, claim 5)	"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"	"a technique in physics that can be used to determine a size distribution profile of small particles in suspension or polymers in solution"

I. Plaintiffs' Opening Position

The Wright & Qu '542 Patent

As with all drugs, it is important in gene therapy to deliver a sufficient dose to the patient. But "[t]he solubility of purified [adeno-associated virus] particles is limited, and aggregation of AAV2 particles has been described as a problem." '542 Patent, col. 1, lines 41-43. "In commonly used buffered-saline solutions, significant aggregation occurs at concentrations of 10^{13} particles/mL, and aggregation increases at higher concentrations." *Id.*, col. 1, lines 46-49.

The problem of viral particle aggregation is one of size. Typical AAV particles have a diameter of approximately 26 nanometers (nm), that is, an average radius of 13 nm. *See id.*, col.

[17] In addition to the arguments herein, Defendants reserve the right to challenge disputed terms A, C, and D as indefinite (as applied) during the expert discovery phase of the case.

1, lines 37-38. But if those tiny particles aggregate, they can form much larger clumps that cause a host of problems, ranging from manufacturing losses and inconsistencies in purification, to biodistribution issues, to immunogenicity. '542 Patent, col. 2, lines 9-48. Aggregation gets worse as the concentration of viral particles rises. *Id.*, col. 1, lines 46-49. And for a gene therapy like Zolgensma®, the formulation may require more than 10^{13} (100 trillion) particles per milliliter of solution, making the balance between a sufficient dose and avoiding aggregation a critical concern.

Drs. J. Fraser Wright and Guang Qu discovered a solution to this dilemma, allowing high concentrations of rAAV particles to remain in solution without any significant aggregation. They discovered that by increasing the ionic strength of the solution above 200 mM in the presence of certain multivalent ions, particle aggregation could be avoided even in highly concentrated solutions of AAV particles. Their invention has been an important part of the success of Zolgensma®.

The Zolgensma® Formulation

> According to the Zolgensma® package insert,
>
> ZOLGENSMA is a suspension of an adeno-associated viral vector-based gene therapy for intravenous infusion. ….
>
> ZOLGENSMA has a nominal concentration of 2.0×10^{13} vg/mL. Each vial contains an extractable volume of not less than either 5.5 mL or 8.3 mL and the excipients 20 mM Tris (pH 8.0), 1 mM magnesium chloride ($MgCl_2$), 200 mM sodium chloride (NaCl) and 0.005% poloxamer 188.

Ex. 1, § 11. Zolgensma® must be thawed before use. When thawed, "ZOLGENSMA is a clear to slightly opaque, colorless to faint white liquid, ***free of particles***." *Id.* (emphasis added.)

Construction of "Dynamic Light Scattering"

The parties 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; the only dispute is how specifically the technique should be described. The specification describes the Protein Solutions DynaPro 99 dynamic light scattering method device and specifics for its use ('542 Patent, col. 12, lines 38-39); the device's user manual then clarifies that the technique is based on analyzing temporal fluctuations using the intensity or photon auto-correlation function:

> The light scattered by the sample is collected by a custom optical fiber. The fiber collects wavelets of light, which scatter destructively or constructively, depending on the positions of the illuminated molecules. As the molecules undergo Brownian motion, their relative positions change with time. Small molecules – which diffuse quickly – generate signals that fluctuate rapidly. Conversely, large molecules generate signals that fluctuate slowly. The time dependence of these fluctuations is characterized by ***the intensity auto-correlation function [based in part on] the detected intensity as a function of time***."

Ex. 2, p. 4 (emphasis added). Thus, Plaintiffs believe that the proper construction of dynamic light scattering is "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."

II. Defendants' Answering Position

Technology Overview

The '542 Patent purports to "relate[] to compositions and methods of preparing and storing AAV virions that prevent aggregation." '542 Patent, col. 1, lines 17-19. The patent notes that vector aggregation was a known problem and that the addition of sufficient salt to rAAV compositions was critical for preventing aggregation. *Id.* col. 1, lines 51-55; col. 1, line 65-col. 2,

line 28. In preparing exemplary formulations, the patent employs multiple "Purification Methods" to separate the rAAV virions from unwanted cell lysate components. *Id.* col. 10, line 54-col. 11, line 50. These purified virions are then concentrated into solutions of various ionic strength (a reflection of salt concentration) resulting in the final vector formulation. *Id.* col. 8, lines 6-13. The resulting compositions were assessed for their ability to prevent aggregation following frozen (-20°C and -80°C) and non-frozen (4°C) storage conditions. *Id.* Table 3; col. 9, lines 5-65.[18]

Construction of the Claim Term

The parties essentially agree that the general meaning of the term "dynamic light scattering" (DLS) refers to a technique in physics that can be used to determine a size distribution profile of small particles in suspension or polymers in solution. Plaintiffs' construction, however, incorrectly defines DLS to be a "specific" technique rather than a general one. The art taught that different DLS techniques (*i.e.*, different methods and conditions) can be employed to determine average particle radius values and that different techniques can give different results. *See, e.g.*, Ex. 10. Plaintiffs attempt to avoid this issue in two ways. First, Plaintiffs improperly incorporate the term "specific" into their construction. Second, the tail-end of Plaintiffs' proposed construction improperly attempts to incorporate language regarding the analysis employed using one particular DLS technique. Both attempts to narrow the term should

[18] A person of ordinary skill in the art with respect to the '542 Patent would have possessed at least a BS in biology, chemistry, chemical engineering, biochemistry, pharmaceutical science, or a related discipline, with at least four years of industry, laboratory, and/or clinical experience in formulating or developing dispersions for therapeutic biologics, such as proteins or vectors for gene delivery. Such person may be familiar with, or may consult with someone familiar with, the development and/or administration of viral vectors for gene therapy.

be rejected. The claim does not require any particular DLS technique, and Plaintiffs' proposed language is not found anywhere in the specification or claims.

III. Plaintiffs' Reply Position

Novartis's concerns with Plaintiffs' proposed construction of "dynamic light scattering" come down to two points: first, that Plaintiffs note that it is a "specific technique" for measuring aggregation and, second, that it is defined in terms of the underlying physics. Neither concern has merit.

First, dynamic light scattering ("DLS") is not the only method for determining size distribution in solution or suspension. Other techniques identified in the specification include photon correlation spectroscopy and visual inspection. '542 Patent, col. 2, lines 2-5. The indication that DLS is a "specific technique" is intended only to distinguish those other techniques.

Second, the further definition of the term is based on the fact that DLS is dynamic (considering fluctuations over time) and based on light scattering (generally using the intensity or photon auto-correlation function). Ex. 2, p. 4. Thus, Plaintiffs' proposed construction reflects nothing more than the physics involved in the dynamic light scattering method.

IV. Defendants' Sur-Reply Position

The claim does not require any particular DLS technique and Plaintiffs' attempt to narrow the term should be rejected. *Supra*, p. 56.

B. "Purified"

Claim Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"purified" ('542 Patent, claims 1, 2, 5, 6)	"the state of a product after a completed purification process, not an intermediate that has been subjected only to some refinement"	"having been subjected to a purification procedure, including, for example, ultracentrifugation and/or column chromatography"

I. Plaintiffs' Opening Position

"Purified" is intended to distinguish the "final product" particles of the claimed formulations from intermediates in an ongoing purification process. The prosecution history makes this clear because it was repeatedly the point of distinction over U.S. Patent No. 6,146,874 to Zolotukhin *et al.*

The Examiner argued Zolotukhin (which involves the use of elevated ionic strengths in the preparation of an intermediate) rendered the claims of the application that issued as the '542 Patent obvious. In response, the Applicants distinguished Zolutukhin because the ionic strength of any "purified" rAAV preparation there was not elevated because it was brought down before the preparation could be considered "purified" – at the completion of the purification process:

> [A]pplicants submit Zolotukhin does not teach a composition where the ionic strength of a ***purified*** preparation of rAAV virions [i.e., particles] is greater than 200 mM. Rather, in the passage cited by the Examiner to evidence the teaching of excipients greater than 200 mM ionic strength, the rAAV is in the process of being purified. See, for example, Figure 1 of Zolotukhin where all of the steps using such buffers are purification steps. High salt concentrations are not used in the final preparation. Rather, the final AAV product is formulated in Lactated Ringer's buffer. See, column 12, lines 49-54, where virus is concentrated by centrifugation through a BIOMAX IOOK filter and desalted into Lactated Ringer's. Only after this step is the virus· considered "purified" in the disclosure.

Ex B12 (05/09/12 Amendment), p. 6 (emphasis in original); *see also* 09/21/06 Amendment, p. 5-6; 08/19/08 Amendment, p. 5-6; 12/08/09 Amendment, p. 5-6. Instead of being "purified," the particles in Zolotukhin were in an "intermediate stage" of purification, an iodixanol gradient step:

> Zolotukhin recognizes AAV aggregates with cellular debris, especially proteins present during an ***intermediate stage*** of purification. Further, Zolotukhin actually teaches away from the use of high ionic strength because it describes the use of 1 M NaCl as "unnecessary or unwarranted" in the other steps of the purification process, and it teaches that it is desirable to "remove or reduce the concentration of salt ... prior to use of, or further purification of, the rAAV." See, column 3, line

> 63 to column 4, line 5 of Zolotukhin. Thus, Zolotukhin uses high salt in the first step of the iodixanol gradient to destabilize AAV-lysate protein interactions. High salt concentrations are purposefully eliminated from the remainder of the iodixanol gradient, including the gradient from which the rAAV is collected after centrifugation, because the elimination of high salt is important for subsequent purification steps. See, column 15, lines 22-35 of Zolotukhin.

Ex B12 (02/18/14 Amendment), p. 5-6 (emphasis in original). Based on this distinction between an intermediate and a purified final product, the Examiner withdrew the rejection. Thus, the prosecution history distinguishes between an intermediate and the "purified" product of a completed purification process.

Defendants' proposed construction ignores this clear distinction in the prosecution history. Instead, it only requires the existence of "a purification procedure" and mentions some non-limiting examples. That vague language could apply to Zolotukhin, which would conflict with the prosecution history.

II. Defendants' Answering Position

Based on the intrinsic evidence, a person of ordinary skill in the art would have understood the term "purified" to mean "having been subjected to a purification procedure, including for example, ultracentrifugation and/or column chromatography." Plaintiffs fundamentally agree but their construction attempts to import an unsupported and ambiguous limitation requiring the purification be "complete" and "not an intermediate that has been subjected only to some refinement." That construction is inconsistent with the term's use in the patent and applicants' statements before the Patent Office.

The '542 Patent describes producing rAAV vectors in cell culture, lysing the cells, and then purifying the rAAV vectors to remove contaminants. '542 Patent, col. 10, line 54-col. 11, line 39. The '542 Patent explicitly discloses "Purification Methods 1-3," which refer to (1) double CsCl gradient ultracentrifugation (2) cation exchange chromatography, and (3) cation

exchange chromatography followed by an additional CsCl gradient ultracentrifugation step. *See id.* col. 4, lines 23-32; col. 10, line 54-col. 11, line 39. While the specification recognizes that different purification methods can result in quantitatively and qualitatively different purity profiles (*id.* col. 1, lines 60-64; col. 5, lines 49-56; col. 7, lines 49-52; *see also id.* Figure 2), the use of any of these three general purification methods result in rAAVs which are considered "purified." *E.*g., *id.* col. 10, line 62-col. 11, line 39 ("Vectors are purified by one of these three methods."); col. 4, lines 28-31 ("Vectors are purified by [Purification Methods 1, 2, or 3]…"). Nowhere does the specification or the claims require a particular purity level or provide any indication as to what may confer "completed purification" as opposed to "only [] some refinement."

The prosecution history, including of the parent patent application, Appl'n No. 11/141,996 ("the '996 application"), does not support Plaintiffs' proposed language. *See E.I. du Pont De Nemours & Co. v. Unifrax I LLC*, 921 F.3d 1060, 1070 (Fed. Cir. 2019) (prosecution of parent application relevant to construction). As originally filed, the '996 application contained claims directed to methods of preventing virion aggregation comprising adding one or more excipients to achieve an ionic strength of at least about 200 mM. The Examiner rejected those claims as anticipated by "Zolotukhin" because it disclosed an unpurified lysate (lysed cell culture material) comprising rAAV virions with an ionic strength more than 200mM. Ex. C12, pp. 5-7. Applicants responded by amending all claims to require, among other things, the steps of provision of an rAAV lysate, followed by "purifying rAAV virions from the lysate using ultracentrifugation and/or chromatography" prior to the addition of excipients to the composition. *Id.* pp. 2-3, 8. Applicants argued that the amended claims were patentable over Zolotukhin because it did "not teach a method where the ionic strength of a **purified** preparation

of rAAV virions is raised to at least about 200 mM." *Id.* p. 5 (emphasis in original). Applicants further argued that the Zolotukhin example cited by the Examiner was a "crude preparation [that] had not yet been **subjected to purification steps** as presently claimed." *Id.* Applicants thus made clear that "purification" was accomplished by being "subjected to purification steps" such as ultracentrifugation and/or chromatography.

Consistent with this understanding, the Examiner maintained his rejection and stated that the specification "do[es] not disclose an explicit definition of the term 'purified' applicable for the preparation of rAAV virions" and that "the [] claims are being interpreted by the examiner (for the term 'purified'), as encompassing a rAAV virion preparation that has been obtained through the separation of the virions from the lysate using an ultracentrifugation and/or chromatographic step (irrespective of the degree/quality of the purification achieved)." Ex. C13, pp. 2-3. When later amending all claims to add the underlined language to the phrase "purifying rAAV virions from the lysate using ultracentrifugation and/chromatography, <u>wherein said virions are purified</u> . . . ," applicants stated that "[t]he instant claims have been amended to clarify that purified rAAV are those virions that have been separated from a lysate comprising said virions." Ex. C14, pp. 5-6. This again highlighted that the rAAV vectors are "purified" within the meaning of the claims after a single purification procedure even though additional purification steps might be performed later—in direct contradiction to Plaintiffs' proposed construction.

Plaintiffs attempt to support their construction by mischaracterizing a handful of exchanges in the '542 file history related to the Zolotukhin reference. Plaintiffs argue that, during prosecution, applicants distinguished Zolutukhin as only teaching high ionic strength rAAV intermediates prior to final purification and suggest that "[b]ased on this distinction between an

intermediate and a purified final product, the Examiner withdrew the rejection." *Supra*, p. 58. That is objectively false. Instead, the Examiner maintained the rejections, stating that applicants' claim about the finality of the Zolotukhin composition is:

> duly noted and considered. However, it is noted that **the term "purified" is not specifically defined in the instant disclosure, as being tied to any particular step and/or degree of purification of the AAV particles**, or for that matter number of virions associated with such composition as claims.

Ex. C3, pp. 5-6. Rather than withdraw the Zolotukhin rejections based on the alleged "completeness" or timing of the purification as Plaintiffs contend, the Examiner indicated that such an assertion was unsupported in view of the disclosure's failure to assign a meaning to "purified." *Id.* Only after applicants amended the claims to recite the number of virions associated with the compositions—namely to require that the purified rAAV vector particles in the composition were "at a concentration exceeding $1x10^{13}$ to $6.4x10^{13}$ vg/ml"—did the Examiner withdraw the rejection over Zolutukhin. Ex. C4, pp. 2, 3-8; Ex. C5. That concentration limitation has nothing to do with purity.

III. Plaintiffs' Reply Position

As set forth in Plaintiffs' opening argument, the prosecution history of the '542 patent makes it clear that the applicants were seeking to protect only the product of a completed purification process, not an intermediate that has been subject to some refinement. A person of ordinary skill in the art could scarcely miss the distinction in the prosecution history, not to mention the specification of the patent. But Novartis proposes a construction that is less clear – and less definite – than even the term "purified" with no construction whatsoever.

Novartis does not dispute that the Applicants clearly and repeatedly distinguished Zolotukhin in the application for the '542 Patent, and that distinction was a basis for the withdrawal of the obviousness rejection. Novartis's argument is based exclusively on the parent

application's prosecution, while Plaintiffs' citations were to two amendments in the prosecution of the subsequent application (Application Serial No. 12/661,553) which issued as the '542 patent. In that prosecution, Applicants maintained their position that "Zolotukhin does not teach a composition where the ionic strength of a purified preparation of rAAV virions is greater than 200 mM. Rather, in the passage cited by the Examiner to evidence the teaching of excipients greater than 200 mM ionic strength, the rAAV is in the process of being purified." Ex. B10, p. 6. The Examiner allowed the asserted claims after proposing an amendment to Claim 1 that added the following underlined language: "the purified AAV vector particles <u>are stored</u> in the composition <u>without significant aggregation</u>." Ex. C9, p. 3. The Examiner no doubt came to realize that one does not generally "store" AAV vector particles that are still in the process of being purified, one generally "stores" the finished product. Thus, a person of ordinary skill in the art reviewing the '553 Application would understand the distinction between a "purified" final product and an intermediate product.

Furthermore, Novartis's argument conflicts with its own proposed construction. To dispute Plaintiffs' construction, Novartis relies on the Examiner statement in the parent application that "'purified' is ***not*** specifically defined in the instant disclosure, as being ***tied to any particular step*** and/or degree of purification of the AAV particles." *Supra*, p. 61. But its proposed construction is based on the composition "having been subject to a purification step." Novartis does not identify what that step is with any certainty, providing only non-binding examples. As a result, if Novartis's proposed construction were accepted, the construction would not only run afoul of the Examiner's statement, it would provide no meaningful clarity to one of ordinary skill in the art. And it would also potentially run into the references cited in the prosecution, all of which involve the use of high ionic strength at early purification steps for uses

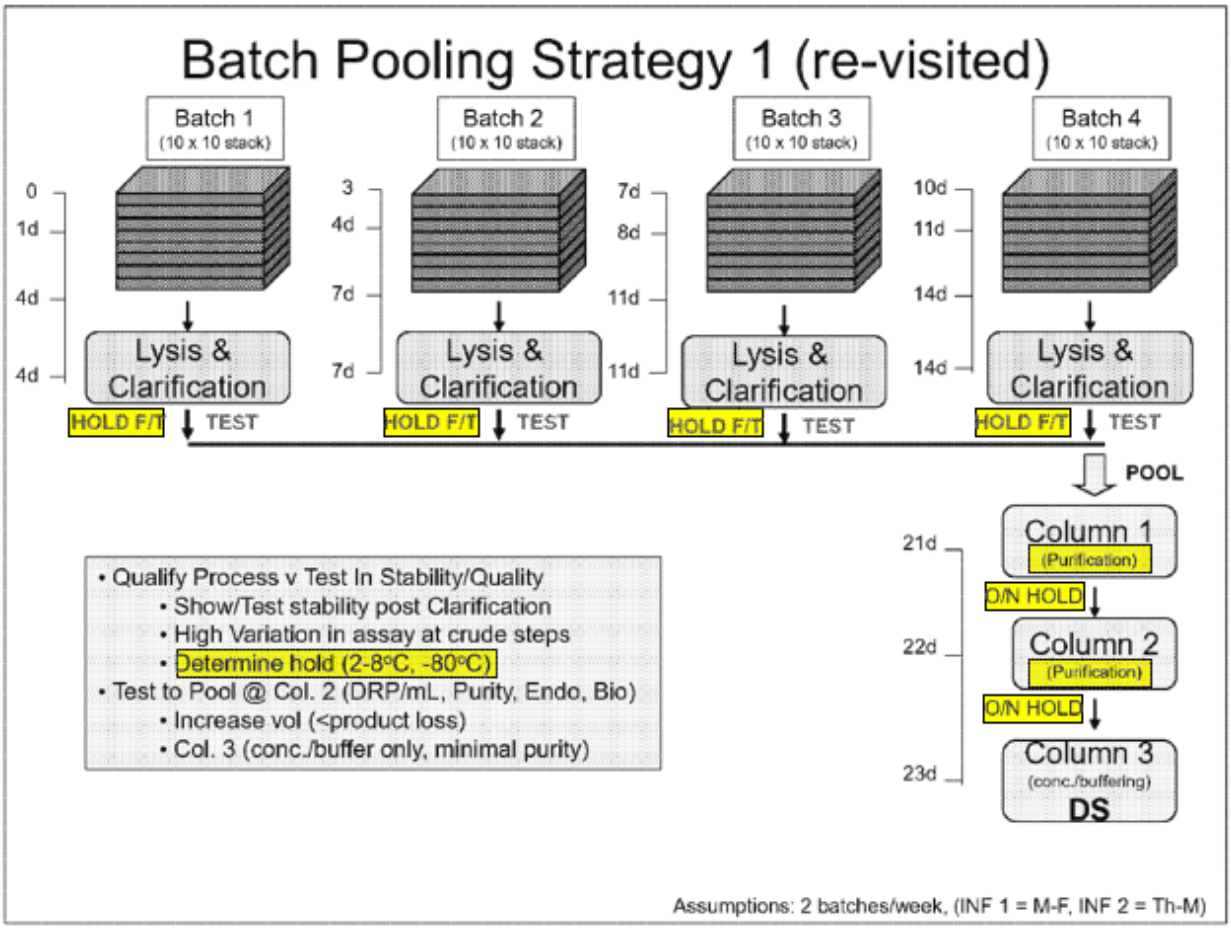
other than storage of a purified composition (such as lysis of the cells in which vectors have been grown or binding and releasing materials from a chromatography column).[19] The materials in those solutions would not be considered "purified" by a person of ordinary skill in the art, but they might be under Novartis's proposed construction. Thus, Novartis's arguments and proposed construction should be rejected.

IV. Defendants' Sur-Reply Position

The '542 prosecution history does not support Plaintiffs. Although applicants *attempted* to distinguish the claimed invention from Zolotukhin by requiring the purification be "complete," the Examiner repeatedly *maintained* the obviousness rejection, stating that applicant's proposed definition of "purified" would run afoul of the specification. *Supra*, pp. 60-61. The position Plaintiffs advocate now was thus *not* "a basis for the withdrawal of the obviousness rejection." *Id.* p. 61.

Nothing supports Plaintiffs' assertion that "[t]he Examiner no doubt came to realize that one does not generally 'store' AAV vector particles that are still in the process of being purified, one generally 'stores' the finished product." *Id.* p. 62. To the contrary, Plaintiffs' and inventor's own documents demonstrate that this is exactly what one of skill *would* do. As shown below, Plaintiffs own strategy included storing the AAV vector particles at 2-8°C or -80°C after each step of purification and prior to obtaining finished product:

[19] Zolotukhin is a good example of the problem created by Novartis's proposed construction – it involves the conventional use of high ionic strength column binding and wash buffers for a heparin affinity chromatography column during the purification of rAAV, not for use in the final purified product. Ex. 20 (U.S. Patent No. 6,146,874), col. 11, lines 24-42. But that step follows an early iodixanol gradient centrifugation step that separates virus particles from cellular debris. *Id.*, col. 10, line 25-col. 11, line 13. To create a purified product, however, Zolotukhin desalted the composition to get rid of the high salt buffer and replace it with an isotonic buffer. *Id.*, col. 12, lines 49-54.



Ex. 26, pp. 311-315. Similarly, inventor Qu investigated aggregation of AAV vectors after each processing step when stored at 4°C, -20°C, or -80°C for up to 12 weeks.

Table 2: Storage and Assays

Sample at Processing Stage	Storage (4°C)	Storage (-20°C)	Storage (-80°C)	Particle Size (week)	Potency Assay
HS elution (6L)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
Q. S. F/T (14L)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
UF (3 L)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
UF (1L)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
UF (500 ml)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
UF (125 ml)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
DF (250 ml)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
DF (125 ml)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
DF (pooled)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*

*: The potency assay needs to be discussed.

Ex. 27, pp. 393-394.

Plaintiffs' argument that Defendants' proposed construction "does not identify what [the purification step] is with any certainty" (*supra*, p. 62) fails too. As the Examiner recognized, the specification does not require "any particular step and/or degree of purification" (Ex. C3, p. 4) and it would be improper to read one into the claims.

Plaintiffs' concern that construing "purified" without inserting their concept of "completeness" will "potentially run into the references cited in prosecution" is no reason to adopt their erroneous construction. Plaintiffs' construction should be rejected.

C. "Significant aggregation"

Claim Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"significant aggregation" ('542 Patent, claims 1, 2, 5, 6)	"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"	Indefinite

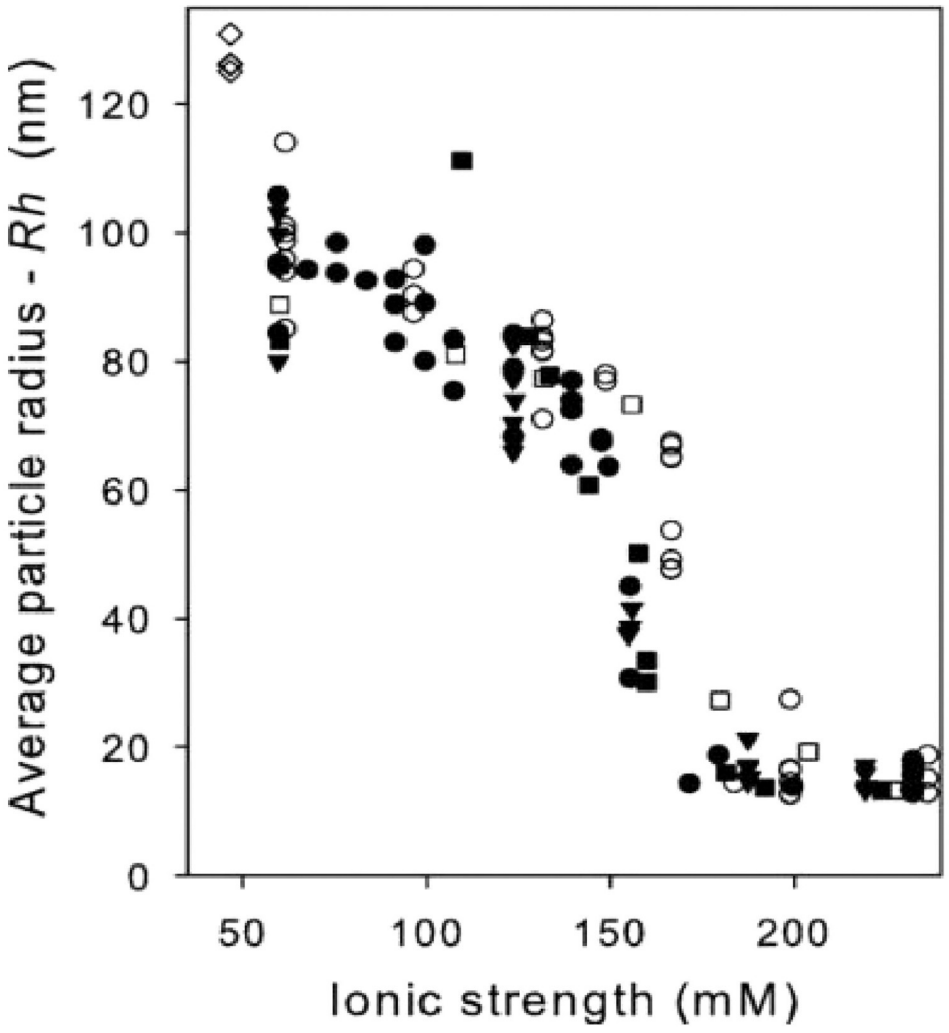
I. Plaintiffs' Opening Position

Viral particle aggregation is a problem of size. When viral particles aggregate into large clumps, those large clumps can cause several problems, including:

- "losses during purification and inconsistencies in testing of purified vector preparations,"
- "influence [on] biodistribution following in vivo administration, and caus[ing] adverse immune responses to vectors following their administration," and
- "[t]esting protocols to characterize purified vectors are also likely to be affected by vector aggregation."

'542 Patent, col. 2, lines 9-10, 15-17, 29-30; *see also id.*, col. 4, lines 42-44 ("AAV2 vector aggregation is frequently observed in concentrated preparations of vectors and can affect purification recovery, and in vivo potency and safety"). Aggregation sufficient to cause any of these problems would be viewed as significant by a person of skill in the art.

The average size of viral particles can be measured in several ways identified in the specification to assess the degree of aggregation. The parties agree that dynamic light scattering is one such way. A detailed example of the use of dynamic light scattering to measure viral particle size is set forth in Example 3. *Id.*, col. 12, lines 37-67. Figure 1B uses dynamic light scattering as a measure of aggregation and shows that the average particle radius at ionic strengths at or above 200 mM (the minimum ionic strength required by the claims) is about 20 nm or less.



Id., Fig. 1B; *id.*, col. 4, lines 14-23. Remembering that the typical AAV particle radius is only approximately 13 nm, the cluster of results below 20 nm at elevated ionic strength shows the

absence of any significant aggregation. The use of dynamic light scattering to confirm the absence of significant aggregation is the subject of representative Claim 5.[20]

Plaintiffs' proposed construction of "significant aggregation," based on the specification, reflects both the methods of detecting aggregation and what would make that aggregation significant: "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." This claim term as used in Claim 1 is definite. Furthermore, Claim 5's reliance on an average particle radius of about 20 nm or less to show the absence of significant aggregation is also definite.

II. Defendants' Answering Position

The term "significant aggregation" is indefinite, as the specification fails to provide the metes and bounds of this term with reasonable certainty. To start, the phrase "without significant aggregation" was first added to the claims as part of a proposed Examiner's Amendment, with no explanation by either the Examiner or applicants as to how the amendment purportedly changed the claim scope. Exs. C9-C10. All previous claims, consistent with the purported invention as described in the specification, were directed to "prevention" of aggregation. *E.g.*, '542 Patent, Abstract; col. 3, lines 5-7; col. 3, lines 16-21.

[20] Dynamic light scattering is not the only way to confirm the absence of significant aggregation. Other means include spectroscopy and visual appearance. '542 Patent, col. 2, lines 4-5. The key in all such measurements is an assessment of the average particle size to exclude large clumps that can cause the many issues linked to significant aggregation.

Although the specification makes passing reference to "significant aggregation," it contains no guidance as to the meaning of the term and fails to explain how to identify it. For example, it states:

> In some embodiments, AAV vectors stored using the methods and compositions of the invention do not exhibit significant aggregation when stored at 4° C. for five days. In other embodiments, AAV vectors that are stored as such compositions do not exhibit significant aggregation after one, five, ten or more freeze-thaw cycles at -20°C. or at -80°C.

Id. col. 3, lines 49-55. This disclosure essentially says there either is or isn't "significant aggregation" but says nothing about what that is or how to measure it. And while the specification indicates that DLS may be used to determine average rAAV particle size and that "no significant aggregation of virions has taken place" (*id.* col. 3, lines 56-60), no threshold is disclosed that would allow one of skill to determine whether a given composition has been stored without "significant aggregation." Similarly, while specification reports that vector recovery following filtration may be used to assess "aggregation," it is silent as to the boundaries of what constitutes "significant aggregation." *Id.* col. 8, lines 6-9; *see, e.g.*, *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1364 (Fed. Cir. 2018) (finding claim term "minimal redundancy" indefinite "[i]n light of the lack of [an] objective boundary or specific examples of what constitutes 'minimal' in the claims, specification, and prosecution history…").

Plaintiffs' proposed construction lacks support in the patent, injects further ambiguity, and should be rejected. Plaintiffs seek to define "significant aggregation" by reciting (i) five potential problems associated with aggregation, and (ii) some potential methods for measuring it. But this language only further confuses the issue, as the specification contains no disclosure regarding whether or which of any of its claimed compositions avoid the purported problems of, for instance, "inconsistencies in testing of purified vector preparations, influence on

biodistribution following in vivo administration, adverse immune responses, or affected testing protocols." *See, e.g.*, '542 Patent, col. 2, lines 9-10. There is also no disclosure correlating the recited methods of measurement with these potential problems. Moreover, the claims are not directed to compositions under any of these conditions (e.g., during testing, administration, etc.); they are directed to compositions for storage.

Plaintiffs' proposed language—that significant aggregation is that which is "sufficient to create a threat of [undesirable consequences]"—injects irresolvable subjectivity into the term. For example, visual appearance sufficient to create a threat of undesirable consequences to who? Under what circumstances? While claims that employ a "term of degree" may be definite when they "provide[] enough certainty to one of skill in the art when read in the context of the invention," (*Interval Licensing*, 766 F.3d at 1370), a term of degree that is "'purely subjective' and depends 'on the unpredictable vagaries of any one person's opinion' is indefinite." *Intell. Ventures I LLC v. T-Mobile USA, Inc.*, 902 F.3d 1372, 1381 (Fed. Cir. 2018).

Plaintiffs point to various places in the specification where potential consequences of aggregation are noted and argue, without support, that these would be "viewed as significant by a person of skill in the art." *Supra*, p. 66. That, of course, is not the definiteness inquiry. The question is whether a skilled artisan would be reasonably certain of what was meant by the term "significant aggregation" and how to determine whether a given composition is encompassed by the claims of the '542 Patent. Enumerating several potential downstream consequences of an undefined term measured by subjective means does not resolve that question.

Plaintiffs' suggestion that, in Figure 1B, "the cluster of results below 20 nm at elevated ionic strength shows the absence of any significant aggregation" misrepresents what the specification teaches. *Supra*, pp. 67-68. To the extent the data in Figure 1B demonstrates

anything, it is that aggregation is *prevented* when average particle size values are less than 20 nm. '542 Patent, col. 9, lines 25-27 ("Rh values >20 nm are deemed to indicate the occurrence of some level of aggregation."); *see also id.* col. 7, lines 20-22 ("FIG. 1B demonstrates that vector aggregation is prevented when ionic strength is ~200 mM or greater…"). The data presented in Figure 1B teaches nothing about where the objective boundary might be for compositions in which aggregation is not prevented but is also not significant.

Plaintiffs' reliance on claim 5 as the source for a potential threshold—an average particle radius of about 20 nm or less—is also misplaced. *Supra*, p. 68. First, "the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314-15 (Fed. Cir. 2005). Second, as with Figure 1B, adding a particle radius limitation that arguably indicates aggregation is prevented says nothing about where the objective boundary might be for compositions in which aggregation is not "significant." Third, Plaintiffs' position is inconsistent with the specification's disclosure that, "[i]n some embodiments, preparations of virions stored according to the methods and compositions of the invention exhibit an average particle radius (Rh) greater than about 15 nm, 20 nm, or 30 nm." '542 Patent, col. 3, lines 60-63.

III. Plaintiffs' Reply Position

Novartis attempts to undercut Plaintiffs' proposed construction of "significant aggregation" by criticizing the fact that Examiner added the claim term and complaining about the clear limits on aggregation set forth in dependent claims. None of these arguments has merit.

Despite Novartis's complaints, the fact that the term "significant aggregation" was added in an Examiner's Amendment increases the certainty that it meets the definiteness requirement. An Examiner is charged with determining whether the broadest reasonable interpretation of the

claim language meets the definiteness requirement, a standard higher than required to be definite in the claim construction process. MPEP § 2173.02. Satisfying that duty is of "utmost importance" for the Examiner, both to identify "the boundaries of the protected subject matter" and to allow determination of whether the claims and specification meet all of the other requirements for patentability. MPEP § 2173. This is not a case where an applicant confused or misled the examiner. Instead, the Examiner carefully crafted the claim language in carrying out his duties. Thus, the fact that the Examiner, not the applicants, added the claim limitation indicating that "significant aggregation" does not occur provides greater surety of definiteness, not less.

Novartis also criticizes the clear standards for assessing aggregation in claims 5 and 6. The two claims provide different methods of ensuring that there is no substantial aggregation. For claim 5, that means "the purified, recombinant AAV vector particles have an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering," less than twice the radius of rAAV particles. '542 Patent, col. 14, lines 34-37; *id.*, col. 1, lines 37-40. That standard is consistent with the specification, which indicates that when "[a]ggregation is assessed by DLS . . . Rh values >20 nm are deemed to indicate the occurrence of some level of aggregation." *Id.*, col. 9, lines 26-28; *see also id.*, col. 3, lines 56-60 ("[P]reparations of virions stored according to the methods and compositions of the invention exhibit an average particle radius (Rh), as measured by dynamic light scattering, indicating that no significant aggregation of virions has taken place."). Similarly, claim 6 requires that "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.*, col. 14, lines 38-41. Again, this is

consistent with the specification's indication that aggregation can be "assessed by measuring vector recovery after filtration through a 0.22 μm filter." *Id.*, col. 8, lines 6-9.

Claim 1's requirement that particles be "stored in the composition without significant aggregation" is similarly clear. As the Examiner saw when he reviewed Figure 1B, ionic strength does not exhibit a gradual, linear relationship to the prevention of aggregation of AAV particles: basically, there is either substantial aggregation or there isn't. *See id.*, Fig 1B. At lower ionic strengths, there is very substantial aggregation with the average size of the aggregates more than fifteen times the size of a single AAV particle; just under 200 mM ionic strength, the aggregate size falls off a cliff to less than the size of two particles. *Id.* So, as the specification indicates, "FIG. 1B demonstrates that vector aggregation is prevented when ionic strength is ~200 mM or greater regardless of which salt is used." *Id.*, col. 7, lines 20-22. That is clearly definite, as the Examiner indicated.

IV. Defendants' Sur-Reply Position

The fact that a claim term was introduced in an examiner's amendment cannot save it from a finding of indefiniteness The specification contains no guidance as to the meaning of "significant aggregation" or how to identify it and neither the Examiner nor applicants provided that explanation during prosecution.

Plaintiffs attempt to obtain the required clarity by ignoring any differences in the various degrees of aggregation. Plaintiffs refer to Figure 1B and state that "there is either substantial aggregation or there isn't" and "at lower ionic strength, there is very substantial aggregation." *Supra*, p. 73. Similarly, Plaintiffs state that claims 5 and 6 "provide different methods of ensuring that there is no substantial aggregation." *Id*. pp. 72-73. These arguments not only introduce two new relative terms of aggregation unsupported by the specification or claims—

"substantial" and "very substantial"—they also mischaracterize the teachings of the patent. Figure 1B demonstrates when aggregation is "prevented" ('542 Patent, col. 7, lines 20-22), and the dependent claims are directed to measuring "some level of aggregation" or "higher" levels of aggregation (*id.* col. 8, lines 46-50; col. 9, lines 25-27).

The specification uses the term "significant aggregation" in only six places, none of which provide metes or bounds for that phrase. *Id.* col. 1, lines 46-49; col. 3, lines 46-60; col. 8, lines 46-50. Elsewhere, the specification variably refers to "some…aggregation" and "extensive aggregation." *Id.* col. 9, lines 25-55. Plaintiffs' blurring of these different terms in an attempt to find definiteness for one of them is contrary to law. *E.g.*, *Horizon Pharma Inc v. D. Reddy's Labs., Inc.*, 839 Fed. Appx. 500, 504 (Fed. Cir. 2021). The term "significant aggregation" is indefinite.

D. "Storage"/"stored"

Claim Term	Plaintiffs' Proposed Construction	Defendants' Proposed Construction
"storage"/"stored" ('542 Patent, claims 1, 2, 5, 6)	"maintenance in a non-frozen state"	"maintenance in a frozen or non-frozen state for a period of time"

I. Plaintiffs' Opening Position

Viewed through the eyes of a person of ordinary skill in the art, both the claims and the specification of the '542 Patent make it clear that "storage" involves a composition that is in solution, i.e., not frozen.[21] Specifically, the stored composition has attributes (including pH, ionic strength, and solubility) that require the composition to be a non-frozen solution. Further, the problem solved by the '542 Patent – aggregation of rAAV particles at high concentrations –

[21] There is no real distinction between Plaintiffs' "maintenance" and Defendants' "maintenance . . . for a period of time." To maintain is to cause or enable a condition or state of affairs to continue, which implies the passage of time during the continuation of the condition.

is a problem that manifests itself in liquid solutions, not frozen compositions. Accordingly, the relevant "storage" is in a liquid state.

Claim 1 of the '542 Patent requires the claimed composition to include AAV vector particles that are "stored . . . without significant aggregation." '542 Patent, col. 14, lines 25-26. The composition has a pH between 7.5 and 8.0; pH is well-known as a scale used to measure the acidity (or basicity) of an aqueous solution (i.e., a liquid). *See*, *e.g.*, Ex. 3 (The American Heritage Science Dictionary), 474 (2005) (definition of pH). Similarly, the claims call out the ionic strength of the composition; ionic strength is a measure of solute concentration in solution. *See*, *supra*, p. 5. Thus, the claims themselves indicate that the purified composition is "stored" for at least part of the time before use in a non-frozen state.

The specification confirms that storage requires maintenance in a non-frozen state. The specification indicates that "an important aspect of vector stability is ***solubility*** during preparation and storage, and vector aggregation is a problem that needs to be fully addressed." '542 Patent, col. 2, lines 62-65 (emphasis added). Solubility is a measure of the miscibility in a liquid solvent. The specification distinguishes the time when the composition may be frozen by indicating that "the present invention, which provides high ionic strength ***solutions*** for use in preparing and storing AAV vectors that maintain high infectivity titer and transduction efficiency, ***even after freeze-thaw cycles***." *Id.,* col. 3, lines 11-15 (emphasis added). Thus, "In some embodiments, AAV vectors stored using the methods and compositions of the invention do not exhibit significant aggregation when stored at 4° C. for five days." *Id.*, col. 3, lines 49-52. Aqueous solutions are liquid when stored at 4° C. The specification therefore confirms that "storage" (and "stored") means "maintenance in a non-frozen state."

II. Defendants' Answering Position

Nothing in intrinsic record provides any basis to construe "storage"/"stored"[22] any differently from its plain and ordinary meaning—maintenance for a period of time, which may be in either a frozen or non-frozen state. Plaintiffs concede there is no difference in the *timing* aspects between the parties' constructions: both parties' constructions recognize that time elapses during storage. *Supra*, p. 74 n.21. Thus, the only dispute is whether storage must be limited to, as Plaintiffs contend, "a non-frozen state." Nothing supports importing that limitation into the claims.

The '542 Patent expressly discloses rAAV vector compositions under frozen storage conditions. For example, the specification states: "[i]n [some] embodiments, AAV vectors that are stored as such compositions do not exhibit significant aggregation after one, five, ten or more freeze-thaw cycles at -20°C and -80°C." '542 Patent, col. 3, lines 52-55. The specification also discloses a AAV2-AADC composition prepared in CF buffer and "stored at -80º C." *Id.* col. 13, lines 17-19. -20°C and -80°C are common laboratory storage conditions to freeze liquid viral compositions and constitute frozen storage. The '542 Patent admits as much in characterizing these as "freeze-thaw cycles." *Id.* col. 13, lines 17-19; *see also id.* col. 2, lines 5-8 (differentiating between "freeze-thaw cycling or non-frozen storage"). Moreover, nothing in the intrinsic record prohibits the "storage" terms from encompassing frozen conditions. To the contrary, the '542 Patent refers to "non-frozen storage" of rAAV virions, implicitly recognizing that "storage" encompasses both frozen and non-frozen conditions. *See id.* col. 2, lines 5-8; col.

[22] "Storage" and "stored" are the noun and past participle forms of the verb "to store" and are being construed equivalently.

9, lines 14-18; *see also id.* col. 3, lines 14-18 (the "invention…provides [] solutions for … storing [r]AAV vectors…even after freeze thaw cycles…").

References on the face of the patent also support Defendants' construction. Croyle 2001 notes that "scientists generally … store the [vector] preparation at −80°C" and further describes preparations "stored at −20 and 4°C for a period of 2 years…" Ex. 11, pp. 1281, 1282. Adadevoh 2002 reports vials of adenovirus reference material that "were removed from storage in an ultra-low freezer (-80° C)…" Ex. 12, p. 67. And a publication by one of the named inventors discusses preserving AAV vector activity "following storage at -20 or -80°C…." Ex. 13, p. 175.

Plaintiffs argue that skilled artisan would understand "storage" to exclude frozen conditions because the rAAV vector aggregation described in the '542 Patent "is a problem that manifests itself in liquid solutions, not frozen compositions." *Supra*, pp. 74-75. Even if true—and Plaintiffs identify nothing in the '542 Patent to support that assertion—the claims on their face are not limited to any particular environment. Plaintiffs' construction would impermissibly import a limitation from the specification into the claims.

Plaintiffs additionally point to the pH, ionic strength, and solubility characteristics of the claimed compositions, arguing that they implicitly support construing storage as limited to non-frozen conditions. *Id*. But Plaintiffs cite to extrinsic evidence and then misrepresent the same. The dictionary definition of "pH" does not require a "liquid" or "aqueous" solution. Those terms do not appear in the reference. *Id.* citing Ex. 3. Even if they did, art cited on the face of the patent demonstrates known methods of measuring the pH of frozen viral compositions. Ex. 11, p. 1287 (discussing "[t]he final frozen pH of a formulation"). As to the ionic strength and solubility limitations, Plaintiffs offer no support for the assertion that those limitations somehow require the composition remains in the liquid state during storage.

III. Plaintiffs' Reply Position

Novartis argues that "storage" is not limited to storage in liquid form and can include frozen storage. The specification makes it clear, however, that the goal of the claimed invention to keep "the purified AAV vector particles . . . stored in the composition without significant aggregation" is accomplished in a solution. Figure 1B – the patent's clearest depiction of ionic strength's prevention of significant aggregation – "demonstrates that vector aggregation is prevented when ionic strength is ~200 mM or greater regardless of which salt is used. These data suggested that the ionic strength (μ) of ***a solution***, a parameter that depends on both solute concentration and charge valency, is the primary factor affecting aggregation." '542 Patent, col. 7, lines 20-25. From this, the patent draws the conclusion that "ionic strength ***of solution*** per se . . . is the relevant physico-chemical parameter." *Id.*, col. 4, lines 57-61; *see also id.*, col. 5, lines 61-65 ("In summary, the use of high ionic strength ***solutions*** during AAV2 vector purification and final formulation . . . are two effective strategies to achieve highly concentrated solutions of AAV2 vectors for use in pre-clinical and clinical studies."). Solutions are liquid, not solid (or frozen); a person of ordinary skill would thus understand the specification as establishing that the "storage" in the claims refers to non-frozen storage.

To the extent any question remained, the specification draws a distinction between storage in liquid form and frozen form by discussing the latter as part of freeze-thaw cycling, not storage. The specification indicates that "AAV stability after storage or freeze-thaw (F/T) cycling is assessed in buffers of the present invention as follows." *Id.*, col. 9, lines 19-20. In that context, the data are reported with regard to "storage at 4°C, as well as . . . one or more F/T cycles at -20 or -80°C." *Id.*, col. 9, lines 45-46. Thus, the specification distinguishes between

"storage" in a liquid state and maintenance through freeze-thaw cycles and the proper construction would limit storage to the liquid (non-frozen) state.

IV. Defendants' Sur-Reply Position

Plaintiffs' attempts to limit the claims to "non-frozen storage" fails. First, that the specification refers to "solutions" (*supra*, p. 78) does not support their proposed construction. A "solution" is a mixture of two or more substances (e.g., buffer and salt) in the same phase, whether liquid or solid. Ex. 28, p. 400; Ex. 29, p. 1716.

Second, Plaintiffs refer to an alleged distinction between storage in liquid form and frozen form based on one portion of the specification which discusses the latter as part of freeze-thaw cycling. *Supra*, p. 78. Plaintiffs ignore, however, other language in that same portion of the specification which refers to "non-frozen storage" and "refrigerated storage," comparing each to stability after freeze-thaw cycling suggesting the applicants knew how to refer to the storage in liquid form if desired. '542 Patent, col. 9, lines 14-24. Even assuming that freeze-thaw cycling did not constitute storage, the '542 Patent expressly discloses rAAV vector compositions under frozen storage conditions. *Supra*, p. 76.

Finally, inventor Qu's own documents contradict Plaintiffs' proposed construction. As shown below, the inventors were concerned with stability of the rAAV vectors after "storage" at 4°C (non-frozen storage) and at -20°C and -80°C (frozen storage). Thus, a skilled artisan would understand "storage" to include both frozen and non-frozen storage.

Table 2: Storage and Assays

Sample at Processing Stage	Storage (4°C)	Storage (-20°C)	Storage (-80°C)	Particle Size (week)	Potency Assay
HS elution (6L)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
Q. S. F/T (14L)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
UF (3 L)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
UF (1L)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
UF (500 ml)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
UF (125 ml)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
DF (250 ml)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
DF (125 ml)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*
DF (pooled)	6 x ~~500~~ ul	6 x ~~500~~ ul	6 x ~~500~~ ul	1.2.3.4.8.12	*

*: The potency assay needs to be discussed.

Ex. 27, pp. 393-394.

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Respectfully submitted,

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