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

DEFENDANTS' FIRST AMENDED INVALIDITY CONTENTIONS REGARDING U.S. PATENT NOS. 6,596,535, 7,125,717, 7,785,888, 7,846,729, 8,093,054, AND 9,051,542

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I. Introduction

Novartis Gene Therapies, Inc., Novartis Pharmaceuticals Corporation, and Novartis AG (collectively, "Novartis" or "Defendants")[1] hereby provide their first amended invalidity contentions ("Contentions") regarding U.S. Patent Nos. 6,596,535 ("the '535 Patent"), 7,125,717 ("the '717 Patent"), 7,785,888 ("the '888 Patent"), 7,846,729 ("the '729 Patent"), 8,093,054 ("the '054 Patent"), and 9,051,542 ("the '542 Patent") (collectively, "the Asserted Patents"), including the attached claim charts and documents produced with Defendants' Initial Invalidity Contentions on July 21, 2022, to Plaintiffs Genzyme Corporation and Aventis Inc. (collectively, "Plaintiffs" or "Genzyme") pursuant to Paragraph 3(h)(i) of the Joint Scheduling Order (D.I. 31) and Paragraph 4(d) of the Delaware Default Standard for Discovery. These Contentions address the patent claims asserted in Plaintiffs' Preliminary Infringement Contentions ("the Asserted Claims") summarized below. Novartis reserves all rights to address additional claims of the Asserted Patents if any such additional claims are subsequently asserted by Genzyme, and nothing herein constitutes a concession or waiver of rights with respect to the invalidity of all claims of the Asserted Patents.

Asserted Patent	Asserted Claims
6,596,535	1-26, 28-29
7,125,717	1-8, 11-17, 20
7,785,888	1-2, 4, 6
7,846,729	1-5, 7-9
8,093,054	1-7, 9, 11-13, 15, 17-27, 30-32, 34, 36
9,051,542	1-2, 5-6

These Contentions are based on information known to Novartis after a diligent and reasonable investigation. In addition to the theories and documents identified herein, Novartis may rely on other theories and documents identified at a later date. Novartis reserves all rights to amend

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

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and/or supplement these Contentions as appropriate under the Local Rules for the United States District Court for the District of Delaware, any other applicable Rule, or the Joint Scheduling Order, or as otherwise permitted by the Court. Novartis also reserves the right to amend or supplement these Contentions after any claim construction opinion issued by the Court or in response to Genzyme's contentions.

The information set forth in these Contentions is provided without waiving: (1) the right to object to the use of any statement for any purpose, in this action or any other, on the grounds of privilege, relevance, materiality, or any other appropriate grounds; (2) the right to object to any request involving or relating to the subject matter of the statements herein; or (3) the right to revise, correct, supplement, or clarify any of the statements provided below at any time. Should Genzyme amend its infringement contentions to assert additional claims or otherwise assert additional claims in this case, Novartis reserves the right to supplement these Contentions. Novartis additionally reserves all rights to challenge the Asserted Claims as unenforceable due to inequitable conduct, or as invalid under § 102(f), in view of further discovery in this action. Any application of prior art or other evidence to the Asserted Claims is not, and should not be viewed as, an admission that any claim meets the requirements of 35 U.S.C. § 112 or any other section of Title 35.

Discovery is ongoing in this action. Accordingly, Novartis reserves the right to supplement these Contentions with information gathered in discovery and invalidity theories flowing therefrom. Novartis has not yet received relevant discovery, including documents from Genzyme or the named inventors of the Asserted Patents, relating to the claims or defenses in this action. For example, Genzyme has produced few (if any) documents evidencing the conception or reduction to practice of any purported invention claimed in the Asserted Patents. Novartis has not had the opportunity to take any deposition in this action, including the depositions of the named

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inventors. Further, the parties currently dispute the construction of certain terms of the Asserted Claims, and the Court has not yet construed any terms of the Asserted Claims. Novartis reserves its rights to modify, amend, and/or supplement its Contentions as discovery progresses, in response to, among other things, information learned in fact or expert discovery, including identification of additional prior art, Genzyme or its experts' positions on infringement, claim construction or invalidity, the Court's rulings, including on claim construction, and in the event Genzyme is permitted to assert any additional claims or sets forth additional or revised infringement theories, in accordance with the Joint Scheduling Order, the Local Rules for the United States District Court for the District of Delaware, the Federal Rules of Civil Procedure, and/or any other applicable authority as this action progresses and additional information is obtained.

Nothing herein should be construed as an admission that Novartis agrees with Genzyme's reading of the Asserted Claims or any implied construction of the Asserted Claims by Genzyme in its Preliminary Infringement Contentions. Neither should anything herein be construed as an adoption by Novartis of any express or implied construction of the Asserted Claims, nor should anything in these Contentions be construed to limit Novartis's right to independently and alternatively address claim construction of the Asserted Claims in accordance with the Joint Scheduling Order. Novartis's Contentions are not an admission by Novartis that Novartis's Zolgensma® (onasemnogene abeparvovec-xioi) gene therapy product ("the Accused Product") and the uses thereof are covered by any asserted claim or claim element. Genzyme continues to have the burden of proof on infringement. To the extent that prior art cited for a particular limitation discloses functionality or structure that is the same or similar in some respects to the alleged functionality or structure of the Accused Product and the uses thereof as set forth in

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Genzyme's Preliminary Infringement Contentions, Novartis does not concede that those claim limitations are in fact met by the Accused Product and the uses thereof.

These Contentions are based on the limited information provided by Genzyme in its Preliminary Infringement Contentions, which fail to show how Novartis can be liable for direct or indirect infringement of the Asserted Claims. Despite obligations under the Local Rules and the Joint Scheduling Order, Genzyme's Preliminary Infringement Contentions fail to provide sufficient detail concerning the meaning and scope of the Asserted Claims and how the claim language in fact applies to the activities of Novartis. Genzyme's Preliminary Infringement Contentions identify as a purported basis for infringement only 35 U.S.C. §§ 271(a) and/or (b), and only literal infringement, to the exclusion of any separate reasoning or rationale regarding infringement under the doctrine of equivalents. Novartis accordingly reserves the right to amend and/or supplement these Contentions, including the right to identify additional information concerning the prior art identified herein as well as additional prior art if Genzyme changes or supplements its Preliminary Infringement Contentions, advocates particular claim construction positions, identifies additional theories of infringement, including theories under the doctrine of equivalents or other sections of Title 35, and/or the Court construes the claims.

Novartis is currently unaware of the extent, if any, to which Genzyme will contend that limitations of the Asserted Claims are not disclosed in the prior art identified by Novartis. To the extent that Genzyme makes such contentions, Novartis may identify and rely on additional prior art.

It should be recognized that a person of ordinary skill in the art would generally read a prior art reference as a whole and in the context of other publications, literature, and general knowledge in the field. To understand and interpret any specific statement or disclosure in a prior

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art reference, a person of ordinary skill in the art would rely upon other information including other publications and general scientific knowledge in the field.

Novartis may rely on any of the patents or publications deriving from applications in the respective claimed priority chains of the Asserted Patents, materials listed on the face of the Asserted Patents and related patents, admitted prior art references in the specifications of the Asserted Patents and related patents, the prosecution histories of the Asserted Patents and related patents, references cited in any proceedings related to the Asserted Patents or related patents, both before the United States Patent and Trademark Office (USPTO) (including the Patent Trial and Appeal Board) and in other jurisdictions, expert or fact testimony provided on behalf of Genzyme in any such proceedings, any references known to Genzyme or any affiliated party and the references cited in any invalidity contentions that have been or will be submitted in any action or proceedings involving the Asserted Patents or related patents. Novartis may also rely on expert testimony, inventor(s)'s admissions, and any additional prior art located or developed during the course of discovery. Novartis may rely on any of the materials in these Contentions to demonstrate a motivation to combine and a reasonable expectation of success. Novartis may also rely on expert testimony to further explain the prior art and to, for example, demonstrate a motivation to combine and a reasonable expectation of success. Novartis may also rely on uncited portions of the identified prior art, references cited within the identified prior art, other references (irrespective of whether such references themselves qualify as prior art) to show the state of the art, and/or expert testimony to provide context to, or aid in, understanding the cited portions of the identified prior art.

Documents thus far produced by Genzyme do not evince any secondary consideration of nonobviousness that would lead to a conclusion that the Asserted Claims would not have been

obvious to a person of ordinary skill in the art. In the event that Genzyme contends that there are any secondary considerations of nonobviousness, Novartis will respond. Further, Genzyme must establish the requisite nexus between any alleged secondary consideration and the Asserted Claims. Novartis is not aware of any evidence that would prove the required nexus of any alleged secondary considerations and the Asserted Claims. Nevertheless, even if there were any evidence of a nexus between any alleged secondary considerations and the Asserted Claims (there is none), any such alleged secondary considerations would not rebut the strong *prima facie* evidence of obviousness here.

II. Legal Standards

A. Invalidity Under 35 U.S.C. § 102: Anticipation

Under 35 U.S.C. § 102(a) (pre-AIA), a patent claim is invalid if the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent. Under § 102(b) (pre-AIA), a patent claim is invalid if "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States."

A patent can be invalid under other provisions of § 102 (pre-AIA) if, for example, the invention was described in an application for patent published under § 122(b) by another filed in the United States before the invention by the applicant for patent (§ 102(e)) or "the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it" (§ 102(g)(2)). A patent applicant is not entitled to a patent if "he did not himself invent the subject matter sought to be patented," *i.e.*, he derived the invention from another. 35 U.S.C § 102(f). "To show derivation, the party asserting invalidity must prove both prior conception of the invention by another and communication of that conception to the patentee." *Gambro Lundia AB v. Baxter*

Healthcare Corp., 110 F.3d 1573, 1576 (Fed. Cir. 1997). "One cannot claim or reproduce the invention of another and obtain a patent on that 'invention.'" *Auxilium Pharm., Inc. v. Watson Labs., Inc.*, No. 12-3084, 2014 WL 9859224, at *29 (D.N.J. Dec. 16, 2014) (internal citations omitted); *see also In re Certain Consol. Roflumilast Cases*, No. 15-3375, 2017 WL 3816542, at *1 (D.N.J. Aug. 31, 2017) (granting defendants' leave to file amended invalidity contentions to assert invalidity under 35 U.S.C. § 102(f) for derivation and improper inventorship based on the contention that the invention was derived from the work of another and "none of the named inventors contributed to the conception of the subject matter of the [p]atents").

Anticipation of a patent requires a "single prior art reference [that] discloses, either expressly or inherently, each limitation of the claim." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). Therefore, even if a prior art reference does not expressly recite each limitation of a claim, the claim may be anticipated. *Id.* An inherent disclosure is present where "the natural result flowing from the operation as taught would result in the performance of the questioned function." *King Pharm., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010). If practice of the prior art inevitably produces the claimed feature, it is not required that a person of ordinary skill in the art recognize the inherency. *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1373 (Fed. Cir. 2007); *Abbott Labs. v. Baxter Pharm. Prods. Inc.*, 471 F.3d 1363, 1368 (Fed. Cir. 2006) ("inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure."). Moreover, an anticipation analysis "indisputably allows for some flexibility" such as considering whether a person of ordinary skill in the art would "at once envisage" the combination of the claimed invention. *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1069-70 (Fed. Cir. 2017); *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381-82 (Fed. Cir. 2015).

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B. Invalidity Under 35 U.S.C. § 103: Obviousness

Under 35 U.S.C. § 103 (pre-AIA), a patent claim is invalid "if the differences between the subject matter . . . patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." The obviousness analysis factors include: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the prior art and the claimed subject matter; and (4) any objective evidence of nonobviousness, also known as secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). To "determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue," a court should "look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). A patent may be obvious if, *inter alia*, there was a "known problem for which there was an obvious solution encompassed by the patent's claims" or the combination of the patent's claims was "obvious to try." *Id.* at 419-421. "[I]nherency may supply a missing claim limitation in an obviousness analysis." *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194-95 (Fed. Cir. 2014). If the natural result flowing from practicing the teachings of a reference would result in the claimed attribute, the reference renders the attribute obvious, even without expressly reciting it. *Id.* at 1194 (citing and quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). A patent applicant cannot render an obvious approach nonobvious merely by using that approach and claiming the expected but previously unstated result. *See id.*

C. Invalidity Under 35 U.S.C. § 112: Written Description

A patent's specification must contain a written description of the claimed invention. 35 U.S.C. § 112, first paragraph. To meet the written description requirement, the specification must

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reasonably convey that the inventor(s) in fact invented what is claimed. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). The assessment of compliance with the written description requirement is "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id*.

In determining whether the specification provides adequate written description support, products that post-date the patent's priority date, including an accused infringing product, can be taken into consideration. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374-75 (Fed. Cir. 2017); *see also AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300-01 (Fed. Cir. 2014). A "mere wish or plan for obtaining the claimed invention is not adequate written description." *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1335 (Fed. Cir. 2021) (citing *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011)) (internal quotation omitted).

When a patent claims a genus, a sufficient description of a genus requires disclosure of "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.* (citing *Centocor*, 636 F.3d at 1350). The requirement applies equally to both claims directed to a genus of compounds and claims directed to methods of using the genus. *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004). "[G]eneric claim language appearing *in ipsis verbis* in the original specification does not satisfy the written description requirement if it fails to support the scope of the genus claimed," regardless of whether the genus claimed is a genus of compounds or a genus of conditions. *Ariad*, 598 F.3d at 1350 (citing *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002).

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D. Invalidity Under 35 U.S.C. § 112: Enablement

A patent's specification must describe how to make and use the claimed invention as to enable a person of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and use the same. 35 U.S.C. § 112, first paragraph. "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010) (quoting *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997)).

Undue experimentation is evaluated under the *Wands* factors, which include (1) the breadth of the claims, (2) the predictability or unpredictability of the art, (3) the amount of direction or guidance, (4) the presence or absence of working examples, (5) the quantity of experimentation necessary, (6) the nature of the invention, and (7) the relative level of skill of those in the art. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). When practicing the full scope of the claims entails making and screening each of at least tens of thousands of candidate compounds in an iterative manner, the claims are not enabled as a matter of law. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1386 (Fed. Cir. 2013).

"[A]n enablement determination is made *retrospectively*, *i.e.*, by looking back to the filing date of the patent application and determining whether undue experimentation *would have been* required to make and use the claimed invention at that time." *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371-72 (Fed. Cir. 1999). In determining whether the full scope of a claim is enabled or not, it is also appropriate to consider whether categories of embodiments within the claim are enabled. *See, e.g., Trs. of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018) (holding a claim invalid for not enabling one of six embodiments falling within the scope of the claim); *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1257 (Fed. Cir. 2004)

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(claims encompassing undisclosed chimeric antibodies required undue experimentation). Additionally, "[w]hile functional claim limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language." *Amgen Inc. v. Sanofi*, 987 F.3d 1080, 1087 (2021).

E. Invalidity Under 35 U.S.C. § 112: Indefiniteness

Under 35 U.S.C. § 112, second paragraph, a patent "is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig. Instruments, Inc.*, 572 U.S. 898, 901 (2014). A patent must be "precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them. Otherwise there would be a zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims." *Id*. at 909-10. Patent claims are invalid for indefiniteness when a claim term may be determined by multiple methods, the testing results of which "will necessarily fall within or outside the claim scope depending on the . . . method chosen." *Honeywell Intern. v. ITC*, 341 F.3d 1332, 1341 (Fed. Cir. 2003). Where a patent fails to specify which of available alternative tests to use for measuring compliance with a claim limitation, and different tests can have different results, the claims are indefinite. *HZNP Meds. LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 698 (Fed. Cir. 2019).

F. Invalidity for Obviousness-Type Double Patenting

Nonstatutory obviousness-type double patenting is based on a judicially created doctrine grounded in public policy to prevent both the unjustified timewise extension of the right to exclude granted by a patent and to "prevent multiple infringement suits by different assignees asserting essentially the same patented invention." *In re Hubbell*, 709 F.3d 1140, 1145 (Fed. Cir. 2013).

Obviousness-type double patenting exists where the conflicting claims are not identical, but at least one challenged claim is not patentably distinct from the reference claim(s) because the challenged claim is either anticipated by, or would have been obvious over, the reference claim(s). *See, e.g.*, *In re Berg*, 140 F.3d 1428 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046 (Fed. Cir. 1993); *In re Langi*, 759 F.2d 887 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937 (CCPA 1982); *In re Vogel*, 422 F.2d 438 (CCPA 1970); and *In re Thorington*, 418 F.2d 528 (CCPA 1969).

The substantive obviousness-type double patenting analysis involves two steps. "[f]irst, the court 'construes the claim[s] in the [challenged] patent and the claim[s] in the [reference] patent and determines the differences.' Second, the court 'determines whether those differences render the claims patentably distinct.'" *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1385 (Fed. Cir. 2010) (quoting *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008)); *see also Abbvie Inc. v. Mathilda & Terence Kennedy Inst. Of Rheumatology Tr.*, 764 F.3d 1366, 1374 (Fed. Cir. 2014). If the challenged claim is not patentably distinct from the reference claim, the challenged claim is invalid. *See Sun Pharm.*, 611 F.3d at 1385.

A "claim to a method of using a composition is not patentably distinct from an earlier claim to the identical composition in a patent disclosing the identical use." *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008) (quoting *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1385–86 (Fed. Cir. 2003)). A limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003).

The safe harbor protection against obviousness-type double patenting provided by 35 U.S.C. § 121 does not apply to continuation applications. In *Amgen Inc. v. F. Hoffman-La Roche*

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Ltd., 580 F.3d 1340 (Fed. Cir. 2009), the Federal Circuit held that a patent issuing on an original application that was subject to a restriction requirement could be used as a reference against a continuation of the same application, even though the continuation could have been filed as a divisional. *Id.* at 1352-53. The Federal Circuit explained that "[t]he statute on its face applies only to divisional applications, and a continuation application . . . is not a divisional application." *Id.* at 1353.

III. Accompanying Production to Rule 4(d) Disclosures

A. The '535, '717, '888, '729, and '054 Patents

The earliest application to which the '535, '717, '888, '729, and '054 patents claim priority is U.S. Provisional Application No. 60/160,080, filed on August 9, 1999. Genzyme asserts that the '535, '717, '888, '729, and '054 patents are entitled to the benefit of a priority date of August 9, 1999. The references listed below constitute prior art to the '535, '717, '888, '729, and '054 patents, or otherwise constitute evidence showing the state of the prior art, aiding in understanding the prior art, the knowledge of a person of ordinary skill in the art, and/or the scope of the Asserted Claims. Novartis also incorporates by reference all prior-art references cited within the '535, '717, '888, '729, and '054 patents and their file histories. Novartis reserves the right to identify or rely on additional or different references based on Genzyme's contentions and/or arguments as to any other priority date of the '535, '717, '888, '729, and '054 patents.

- Bartlett J., et al., *Genetics and Biology of Adeno-Associated Virus*, VIRAL VECTORS: GENE THERAPY AND NEUROSCIENCE APPLICATIONS 55 (1995) ("Bartlett (1995)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064109-64127)

- Berns K., et al., *Biology of Adeno-associated Virus*, ADENO-ASSOCIATED VIRUS (AAV) VECTORS IN GENE THERAPY 1 (1996) ("Berns (1996)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064184-64279)

- Carter B., *Variant and Defective Interfering Parvoviruses*, THE PARVOVIRUSES 209 (1984) ("Carter (1984)") is prior art under 35 U.S.C. §§102(a) and (b). (NVS-ZOL-00063957-63977)

- Carter B., et al., *Development of Adeno-associated Virus Vectors for Gene Therapy of Cystic Fibrosis*, ADENO-ASSOCIATED VIRUS (AAV) VECTORS IN GENE THERAPY 120 (1996) ("Carter (1996)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064040-64065)

- Dong J., et al., *Quantitative Analysis of the Packaging Capacity of Recombinant Adeno-Associated Virus*, 7 HUMAN GENE THERAPY 2101 (1996) ("Dong (1996)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00063266-63282)

- Ferrari F., et al., *Second-Strand Synthesis Is a Rate-Limiting Step for Efficient Transduction by Recombinant Adena-Associated Virus Vectors*, 70 J. OF VIROLOGY 3227 (1996) ("Ferrari (1996)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064137-64145)

- Ferrari F., et al., *New developments in the generation of Ad-free, high-titer rAAV gene therapy vectors*, 3 NATURE MEDICINE 1295 (1997) ("Ferrari (1997)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00063978-63980)

- Fisher, K., et al., *Transduction with Recombinant Adeno-Associated Virus for Gene Therapy Is Limited by Leading-Strand Synthesis*, 70 J. OF VIROLOGY 520 (1996) ("Fisher (1996)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064280-64296)

- Hermens, W., et al., *Comparison of the performance of an adeno- and adeno-associated viral vector encoding the growth cone protein B-50/GAP-43: A preliminary study*, VIRAL VECTORS: TOWARDS APPLICATION IN NEUROREGENERATION RESEARCH 149 (1997) ("Hermens (1997)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064022-64039)

- Hörster, A., et al., *Recombinant AAV-2 harboring gfp-antisense/ribozyme fusion sequences monitor transduction, gene expression, and show anti-HIV-1 efficacy*, 6 GENE THERAPY 1231 (1999) ("Hörster (1999)") is prior art under 35 U.S.C. § 102(a). (NVS-ZOL-00063707-63714)

- Kaplitt M., et al., *Transfer and Expression of Potentially Therapeutic Genes into the Mammalian Central Nervous System in Vivo Using Adeno-Associated Viral Vectors*, GENE THERAPY AND NEUROSCIENCE APPLICATIONS 193 (1995) ("Kaplitt (1995)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00063788-63813)

- Mamounas M., et al., *Increased titer of recombinant AAV vectors by gene transfer with adenovirus coupled to DNA-polylysine complexes*, 2 GENE THERAPY 429 (1995) ("Mamounas (1995)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00063446-63449)

- McCarty D., et al., *Self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis*, 8 GENE THERAPY 1248 (2001) ("McCarty (2001)"). (NVS-ZOL-00064297-64303)

- McCarty D., et al, *Adeno-associated virus terminal repeat (TR) mutant generates self-complementary vectors to overcome the rate-limiting step to transduction in vivo*, 10 GENE THERAPY 2112 (2003) ("McCarty (2003)"). (NVS-ZOL-00063981-63987)

- McCarty D., *Self-complementary AAV Vectors; Advances and Applications*, 16 MOLECULAR THERAPY 1648 (2008) ("McCarty (2008)"). (NVS-ZOL-00000149-157)

- Muzyczka N., *Use of Adeno-Associated Virus as a General Transduction Vector for Mammalian Cells*, 158 CURRENT TOPICS IN MICROBIOLOGY & IMMUNOLOGY 97 (1992) ("Muzyczka (1992)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00063723-63755)

- Phillips M., et al., *Prolonged reduction of high blood pressure with an in vivo, nonpathogenic, adeno-associated viral vector delivery of AT1-R mRNA antisense*, 1 HYPERTENSION 374 (1997) ("Phillips (1997)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064016-64021)

- Samulski R., et al., *A Recombinant Plasmid from Which an Infectious Adeno-Associated Virus Genome Can Be Excised In Vitro and Its Use To Study Viral Replication*, 61 J. OF VIROLOGY 3096 (1987) ("Samulski (1987)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00063957-63381)

- Su H., et al., *Selective Killing of APP-Positive Hepatocellular Carcinoma Cells by Adena-Associated Virus Transfer of the Herpes Simplex Virus Thymidine Kinase Gene*, 7 HUMAN GENE THERAPY 463 (1996) ("Su (1996)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00063946-63956)

- Welch P., et al., *Ribozyme gene therapy for hepatitis C virus infection*, 10 CLINICAL & DIAGNOSTIC VIROL. 163 (1998) ("Welch (1998)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064128-64136)

- Wong K., et al., *Adeno-associated Virus Based Vectors As Antivirals*, ADENO-ASSOCIATED VIRUS (AAV) VECTORS IN GENE THERAPY 145 (1996) ("Wong (1996)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00063756-63787)

- Xiao X., et al., *Production of High-Titer Recombinant Adena-Associated Virus Vectors in the Absence of Helper Adenovirus*, 72 J. OF VIROLOGY 2224 (1998) ("Xiao (1998)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064175-64183)

- Zolotukhin S., et al., *A Humanized" Green Fluorescent Protein cDNA Adapted for High-Level Expression in Mammalian Cells*, 70 J. OF VIROLOGY 4646 (1996) ("Zolotukhin (1996)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00063581-63595)

- PCT Int. App. Pub. No. WO 95/13392 (filed Nov. 3, 1994) is prior art under 35 U.S.C. §§ 102(a), (b), and (e). (NVS-ZOL-00064066-64102)

- PCT Int. App. Pub. No. WO 95/28493 (filed Apr. 13, 1995) is prior art under 35 U.S.C. §§ 102(a), (b), and (e). (NVS-ZOL-00063382-63445)
- PCT Int. App. Pub. No. WO 95/28948 (filed Apr. 24, 1995) is prior art under 35 U.S.C. §§ 102(a), (b), and (e). (NVS-ZOL-00063596-63706)
- PCT Int. App. Pub. No. WO 97/17458 (filed Nov. 8, 1996) is prior art under 35 U.S.C. §§ 102(a), (b), and (e). (NVS-ZOL-00063504-63580)
- PCT Int. App. Pub. No. WO 97/32018 (filed Feb. 27, 1997) is prior art under 35 U.S.C. §§ 102(a), (b), and (e). (NVS-ZOL-00063283-63381)
- PCT Int. App. Pub. No. WO 99/11764 (filed Sept. 4, 1998) is prior art under 35 U.S.C. § 102(a). (NVS-ZOL-00063814-63917)
- PCT Int. App. Pub. No. WO99/47691 (filed Mar. 18, 1999) is prior art under 35 U.S.C. § 102(a). (NVS-ZOL-00063450-63503)
- U.S. Patent No. 7,465,583 (issued Dec. 16, 2008) ("'583 patent"). (NVS-ZOL-00063988-64015)
- U.S. Patent No. 7,790,154 (issued Sep. 7, 2010) ("'154 patent"). (NVS-ZOL-00064146-64174)
- U.S. Patent No. 8,361,457 (issued Jan. 29, 2013) ("'457 patent"). (NVS-ZOL-00063918-63945)

B. The '542 Patent

The earliest applications to which the '542 patent claims priority are U.S. Provisional Application No. 60/575,997, filed on June 1, 2004, and U.S. Provisional Application No. 60/575,997, filed on December 22, 2004. Genzyme asserts that the '542 patent is entitled to the benefit of a priority date of June 1, 2004 and/or December 22, 2004. The references listed in the preceding section and the references listed below constitute prior art to the '542 patent, or otherwise constitute evidence showing the state of the prior art, aiding in understanding the prior art, the knowledge of a person of ordinary skill in the art, and/or the scope of the Asserted Claims. Novartis also incorporates by reference all prior-art references cited within the '542 patent and its

file history. Novartis reserves the right to identify or rely on additional or different references based on Genzyme's contentions and/or arguments as to any other priority date of the '542 patent.

- Arakawa, T. & Timasheff, S.N., *Mechanism of protein salting in and salting out by divalent-cation salts balance between hydration and salt binding*, 23 BIOCHEMISTRY 5912 (1984) ("Arakawa (1984)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064434-64445)

- Clark, K.R., *Recent advances in recombinant adeno-associated virus vector production*, 61 KIDNEY INTL. S-9 (2002) ("Clark (2002)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064327-64333)

- Croyle, M.A. et al., *Development of formulations that enhance physical stability of viral vectors for gene therapy*, 8 GENE THER. 1281 (2001) ("Croyle (2001)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00192548-192557)

- Gao. G. et al., *Novel adeno-associated viruses from rhesus monkeys as vectors for human gene therapy* 99 PNAS 11854 (2002) ("Gao(2002)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064423-64428)

- Gao, G. et al., *Adeno-associated viruses undergo substantial evolution in primates during natural infections* 100 PNAS 6081 (2003) ("Gao(2003)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064397-64402)

- Gatlin, L.A., et al., *Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parenteral Products*, *in* INJECTABLE DRUG DEVELOPMENT: TECHNIQUES TO REDUCE PAIN AND IRRITATION 401 (Gupta, P.K. & Brazeau, G.A., eds.) (1999) ("Gatlin (1999)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064304-64326)

- Huang J., et al., *Aggregation of AAV Vectors, its Impact on Liver-directed Gene Transfer and Development of Vector Formulations to Prevent and Dissolve Aggregation and Enhance Gene Transfer Efficiency*, 1 MOLECULAR THERAPY S286 (2000) ("Huang (2000)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064410-64422)

- Johnson, F.B., et al., *Effect of Environmental pH on Adenovirus-Associated Virus*, 150 PROC. SOC. EXP. BIOL. MED. 585 (1975) ("Johnson (1975)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064389-64396)

- Laughlin et al., *Cloning of infectious adeno-associated virus genomes in bacterial plasmids*, 23 GENE 65 (1983) ("Laughlin (1983)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064446-64454)

- Mingozzi F. et al., *Improved Hepatic Gene Transfer by Using an Adeno-Associated Virus Serotype 5 Vector*, 76 J. VIROL. 10487 (2002) ("Mingozzi (2002)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00192529-192534)

- Mount, J.D. et al., *Sustained phenotypic correction of hemophilia B dogs with a factor IX null mutation by liver-directed gene therapy*, 99 BLOOD 2670 (2002) ("Mount (2002)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064403-64409)

- Potter. M. et al., *[24] Streamlined Large-Scale Production of Recombinant Adeno-Associated Virus (rAAV) Vectors, in* METHODS IN ENZYMOLOGY VOLUME 346 GENE THERAPY METHODS 413 (Phillips, M. I., ed.) (2002) ("Potter (2002)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00192535-192547)

- Sommer J.M., et al., *Quantification of Adeno-Associated Virus Particles and Empty Capsids by Optical Density Measurement*, Mol. Ther., 7(1):122-128 (2003) ("Sommer (2003)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064382-64388)

- Vanderberghe L., et al., *AAV Clades: Their ability to Recombine and Cross Species-Barriers* 9 MOLECULAR THERAPY S35 (2004) ("Vanderberghe (2004)") is prior art under 35 U.S.C. § 102(a). (NVS-ZOL-00064334)

- Wright J., et al., *Recombinant adeno-associated virus: Formulation challenges and strategies for a gene therapy vector*, 6 CURRENT OPINION IN DRUG DISCOVERY & DEVELOPMENT 174 (2003) ("Wright (2003)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064429-64433)

- Wu, P. et al., *Mutational Analysis of the Adeno-Associated Virus Type 2 (AAV2) Capsid Gene and Construction of AAV2 Vectors with Altered Tropism* 74 J. VIROL. 8635 (2000) ("Wu (2000)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064740-64752)

- Ye, X. et al., *Regulated Delivery of Therapeutic Proteins After in Vivo Somatic Cell Gene Transfer* 283 SCIENCE 88-91 (1999) ("Ye (1999)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064494-64497)

- PCT Int. App. Pub. No. WO99/41416 (filed Feb. 12, 1999) ("Frei (1999)") is prior art under 35 U.S.C. §§ 102(a) and (b). (NVS-ZOL-00064335-64362)

- PCT Int. App. Pub. No. WO01/66137 (filed Mar. 6, 2001) ("Evans (2001)") is prior art under 35 U.S.C. §§ 102(a), (b), and (e). (NVS-ZOL-00064672-64739)

- PCT Int. App. Pub. No. WO03/039459 (filed Oct. 31, 2002) ("Liu (2003)") is prior art under 35 U.S.C. §§ 102(a), (b), and (e). (NVS-ZOL-00064504-64671)

- PCT Int. App. Pub. No. WO03/046142 (filed Nov. 26, 2002) ("Lochrie (2003)") is prior art under 35 U.S.C. §§ 102(a) and (e). (NVS-ZOL-00064455-64493)

- U.S. Patent No. 6,261,823 (issued Jul. 17, 2001) ("Tang (2001)") is prior art under 35 U.S.C. §§ 102(a), (b), and (e). (NVS-ZOL-00064498-64503)

IV. Invalidity Contentions As To The ’535 Patent

A. The ’535 Patent Claims Are Invalid for Anticipation and/or Obviousness

Each Asserted Claim of the ’535 patent is invalid for anticipation and/or obviousness. In addition to the information set forth below, a chart identifying where specifically in each item of prior art each limitation of each Asserted Claim of the ’535 patent is found is attached as Appendix A, which is incorporated herein. Pinpoint citations to material in the prior art are exemplary of the disclosures and teachings of the prior art. Those citations should not be construed as limiting the disclosure of any prior art or as reflecting the only section of a prior art reference disclosing a particular limitation or teaching.

1. Independent Claim 1

The ’535 patent admits that by August 9, 1999, the use of an rAAV vector comprising a single-stranded heterologous nucleotide sequence was well-known. *See, e.g.*, ’535 patent at 3:19-25 (“The native AAV genome has been used as the basis of vector systems for the delivery and expression of heterologous genes in host cells such as mammalian cells, such as for gene therapy.”) (*citing* Muzyczka (1992) *Curr. Top. Microbiol. Immunol.* 158:97-129; Carter, B. J. (1992) *Curr. Op. Biotechnol.* 3:535-539; and Flotte et al. (1995) *Gene Therapy* 2:357-362). The ’535 patent further admits that “[r]ecombinant AAV (RAAV) vectors, based on the native AAV genome, are generally produced by deletion of rep and/or cap sequences and [their] replacement by a heterologous sequence. Thus, rAAV vectors generally comprise a single-stranded DNA molecule comprising a heterologous gene sequence or sequences flanked by at least one AAV ITR, and typically by two AAV ITRs, one at each end.” *Id.* at 3:25-31.

The ’535 patent further admits that by August 9, 1999, it was well-known that “efficient, productive packaging in an AAV virus particle is limited to vectors having approximately the size

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of an AAV genome (i.e., approximately 4.7 kb) or smaller" and that by August 9, 1999, those skilled in the art had already used smaller rAAV genomes. *Id.* at 3:39-41; *id.* at 44-51 (*citing* Dong et al. (1996) *Hum. Gene Therapy* 7:2101-2112 for teaching the use of "rAAV genomes having sizes between 2 kb and 6 kb"); *see also Id.* at 9:64-65 ("The maximum size vector that can be packaged to yield an infectious viral particle is approximately 5.2 kb."); *id.* at 15:54-58 ("In the case of an rAAV vector of the invention, its length may be less than about. . . .5.5."). Indeed, by August 9, 1999, the use of rAAV vectors of approximately half size was well-known and described in numerous prior art references. *See, e.g.*, Hörster (1999); Muzyczka (1992); Hermens (1997); Dong (1996).

Hörster (1999) describes the use of "fusion constructs between the indicators luciferase and gfp and the HIV-1-directed antisense sequence AR6 or ribozyme Rz12." Hörster (1999) at 1232. Hörster (1999) describes 12 fusion constructs comprising single stranded heterologous nucleotide sequences. *Id.* at 1232. Hörster (1999) discloses approximately half size rAAV vector fragments comprising heterologous sequences encoding luciferase, gfp, AR6, and/or Rz12 flanked by ITRs in Figures 1 and 3. *Id.* at 1232-33.

Muzyczka (1992) describes the use of rAAV vectors "containing the *dl*3-94/neo genome (50% of wild type size)" and "the neomycin phosphotransferase gene." Muzyczka (1992) at 112-13. The *dl*3-94/neo genome (50% of wild type size, *i.e.*, an approximately half size vector) "were found to consist predominantly of particles that had the density of AAV particles containing a wild type complement of DNA. When the DNA in these particles was examined it was found to consist of three kinds of molecules. The predominant DNA molecule was an inverted dimer of the *dl*3-94/neo genome. Such molecules occur as a natural consequence of the AAV DNA replication

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mechanism and have been described in studies of spontaneously occurring deletions or AAV defective interfering (DI) genomes." *Id.* at 112-13 (citations omitted).

Hermens (1997) describes the generation of an rAAV virus with a vector "containing an expression cassette for B-50/GAP-43." Hermens (1997) at 153. Hermens describes the B-50/GAP-43 open reading frame (ORF) as "cloned into pcDNAI/Amp5.0 (Invitrogen). This resulted in pcDNAB-50 containing a CMV-B-50-A+ expression cassette. Subsequently, from a plasmid designated psub201 (a recombinant plasmid from which an infectious AAV genome can be excised Samulski, et al., 1987) the AAV-coding sequences are replaced by the CMV-B-50-A+ expression cassette (2.1 kb) of pcDNAB-50. This resulted in plasmid psub201B-50." *Id.*

Dong (1996) describes rAAV vectors "from 2 kb to 6 kb in size" that carry "a chloramphenicol acetyltransferase (CAT) reporter gene." Dong (1996) at 2101. Dong (1996) also describes that "on the Southern blot of virion DNA, only [the] sample from the 1.9-kb vector contained DNA that appeared twice as large as single stranded DNA on an alkaline gel (Fig. 5, lane 2, DS). When the vector DNAs were isolated from infected cells in the absence of adenovirus-mediated double-strand conversion, the majority of the 1.9-kb vectors were in double-stranded form, and none was observed in any of the larger vectors." *Id.* at 2107-08.

The '535 patent admits that by August 9, 1999, it was well-known that the AAV life cycle involves the generation of "a self-complementary double-stranded molecule that is covalently closed at one end" called "the replicative form (RF)." '535 patent at 2:11-15; *see also* Carter (1984) at 212 ("These molecules consist of complementary strands which are covalently joined at one terminus by a hairpin structure formed by virtue of the palindromic terminal sequence 126 nucleotides in length."). The '535 patent further admits that by August 9, 1999, it was well-known that "formation of the RF is required for transcription of viral proteins (or, in the case of

recombinant AAV, the transcription of heterologous sequences such as a transgene) to occur, since cellular RNA polymerizing systems require a double-stranded template." '535 patent at 2:40-45; *see also* Carter (1984) at 219 ("Also, as shown in Fig. 2, the RF structure is the configuration that would be expected during replication of AAV DNA."). The '535 patent also admits that when a recombinant viral vector has a sequence complexity that is approximately one half its length, "a vector is able to form a 'snapback' molecule which is double stranded along most or all of its length, thus analogous to the RF produced during AAV infection." '535 patent at 15:25-33; *see also id.* at 18:46-50 ("Upon replication, the half-size genome is copied into a complementary DNA strand that is covalently attached to its template at one end (see FIGS. 1 and 3), forming a structure that will 'snap back' into a hairpin duplex."); *id.* at 34:1-7 ("Alkaline gel analysis, shown in Fig. 7A, indicates that preparations of virus particles having vector genomes that were made from a half-size plasmid contain DNA molecules that have a single-stranded length that is the same as a native AAV genome (second lane from left). This is what would be expected if 'snap-back'-type RF molecules have been packaged in these virus particles."); Carter (1984) at 216, 222 (indicating that DNA 1.41b, "which appeared to be mainly hairpin molecules," had a "mean molecular size estimated from gel electrophoresis of about 50% of genome length"). The '535 patent further admits that vectors of the alleged invention:

> [C]an be produced by constructing a parvovirus vector, such as an rAAV vector, that has a size approximately one-half of a native genome and allowing such a vector to replicate in a host cell. . . . Upon replication, the half-size genome is copied into a complementary DNA strand that is covalently attached to its template at one end (see FIGS. 1 and 3), forming a structure that will "snap back" into a hairpin duplex. . . . These recombinant parvovirus vectors comprise an ITR sequence between the heterologous sequences (i.e., an ITR sequence flanked on both sides by heterologous sequences)."

'535 patent at 18:40-58; *see also* Carter (1984) at 212 "Some variant genomes have a conformation similar to that of certain intracellular replicating forms of parvovirus DNA. These molecules

consist of complementary strands which are covalently joined at one terminus by a hairpin structure formed by virtue of the [ITR]. These molecules at a neutral pH spontaneously renature with zero-order kinetics to form duplex structures.”). As the ’535 patent depicts in Figs. 1 and 3, “the heterologous sequence [generated from such half-sized vectors] forms base pairs essentially along its entire length, thus analogous to an AAV replicative form.” ’535 patent at 5:10-12.

Literature dated after August 9, 1999, e.g., McCarty (2008), supports the admissions of the ’535 patent by disclosing that such self-complimentary rAAV vectors “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 dimeric inverted repeat will be no larger than the normal AAV packaging capacity (~4,700 nucleotides).” McCarty (2008) at 1649. McCarty (2008) further recognizes that “[a]lthough this further restricts the transgene carrying capacity of an already small viral vector, it offers a substantial premium in the efficiency, and speed of onset, of transgene expression because dsDNA conversion is independent of host-cell DNA synthesis and vector concentration.” *Id.* at 1649 (*citing* McCarty (2001), Gene Ther 8:1248-54).

Thus, each of Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996) teach the approximately half size vector comprising a region which forms intrastrand base pairs such that expression of a coding region of a heterologous sequence is enhanced. *See e.g.*, Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996).

Accordingly, the disclosure in Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996) of rAAV vectors comprising a heterologous sequence and having a length that is approximately half size inherently anticipate and/or render obvious (alone or in combination) claim 1 of the ’535 patent because, as the ’535 patent admits, such vectors necessarily and

inevitably contain "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."

2. Dependent Claims 2-26 and 28-29

The dependent claims of the '535 patent are additionally invalid over the prior art, at least based on the references and combinations set forth in Appendix A. As set forth in Appendix A, the prior art discloses, expressly or inherently, each and every limitation of the dependent claims, including the claimed features of the rAAV vector (claims 2, 3, 4, 5), a host cell comprising the vector (claims 6, 8, and 10) which is mammalian (claims 7, 9, and 11), an rAAV particle comprising the rAAV vector (claims 12, 13, 14, and 15), a composition of rAAV particles (claims 16, 18, and 20) which has a pharmaceutically acceptable excipient (17, 19, and 21), the claimed method for preparing the rAAV (claims 22, 23, 24, 25 and 26), and a population of rAAV vectors and particles produced according to such methods (claims 28 and 29). A person of ordinary skill in the art would have been motivated to pursue the combinations listed in Appendix A with a reasonable expectation of success in achieving the asserted dependent claims. For example, as the '535 patent admits, "[r]ecombinant vectors based on parvovirus, such as adeno-associated virus (AAV), show promise for gene therapy." '535 patent at 1:27-28. The '535 patent also admits that the dependent claim limitations related to producing an rAAV particle with the rAAV vector were known in the art. *See e.g.,* '535 patent at 3:37-38 ("rAAV vectors can be encapsidated into AAV virus particles to form recombinant adeno-associated viruses (rAAV)."). The '535 patent also admits that the dependent claim limitations directed to rep function, cap function, and helper functions were well known in the art. *See e.g.,* '535 patent at 2:54-59 ("Helper functions involved

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in the replication of the [replicative form] can be provided by co-infection of AAV-infected cells with adenoviruses, herpesviruses or poxviruses. Carter (1990) supra. Alternatively, cells may contain integrated genes, viral or otherwise, that supply helper function."). The prior art listed in Appendix A is directed to, *e.g.*, rAAV vectors capable of forming intrastrand base pairs that enhance expression, methods of producing particles that contain these rAAV vectors, and compositions of rAAV vector particles. A person of ordinary skill in the art, as of August 19, 1999, would have been familiar with this prior art and would have been motivated to combine these teachings, and the others set forth in Appendix A, with a reasonable expectation of success, thereby rendering obvious dependent claims 2-26 and 28-29.

B. The '535 Patent Claims Are Invalid under 35 U.S.C. § 112

In addition, or in the alternative, Novartis contends that the Asserted Claims of the '535 patent do not satisfy one or more requirements of 35 U.S.C. § 112. Novartis identifies the below grounds upon which the Asserted Claims of the '535 patent are invalid based on lack of written description under 35 U.S.C. § 112, first paragraph, lack of enablement under 35 U.S.C. § 112, first paragraph, and indefiniteness under 35 U.S.C. § 112, second paragraph.

1. Invalidity under 35 U.S.C. § 112, First Paragraph for Inadequate Written Description

As discussed *supra*, a patent's specification must contain a written description of the claimed invention. 35 U.S.C. § 112, ¶ 1. The description must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*) (citations omitted). In other words, the specification must reasonably convey that the inventor had possession of the claimed subject matter as of the filing date. *Id.*

To satisfy the written description requirement for a claimed genus, a specification must describe the claimed invention in such a way that a person of ordinary skill in the art would understand that the entire genus that is being claimed has been invented, and not just a single species of the genus. *Carnegie Mellon Univ. v. Hoffman-La Roche, Inc.*, 541 F.3d 1115, 1124 (Fed. Cir. 2008). In particular, when attempting to claim a functionally-defined genus, "a sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.* at 1350 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)). "A vague functional description and an invitation for further research does not constitute written disclosure . . . ." *Id.* at 1356. And "if the art is unpredictable, then disclosure of more species is necessary to adequately show possession of the entire genus." *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1125 (Fed. Cir. 2004). While it is "not fatal" that members of a genus are not disclosed in a patent, the specification should provide other means of identifying which members of the genus would interact with other variable elements. *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330 (Fed. Cir. 2021).

The Asserted Claims of the '535 patent are invalid under 35 U.S.C. § 112, ¶ 1, because the claimed genus of vectors is neither supported by a representative number of species nor by a disclosure of structural features common to the members of the claimed genus responsible for the claimed functions that would allow a person of ordinary skill in the art to visualize or recognize the other members of the genus. As explained in detail below, the specification of the '535 patent does not reasonably convey to a person of ordinary skill in the art that the inventor had possession of the vast—nearly limitless—genus of rAAV vectors used in the Asserted Claims. The claims use

structural and functional language in an attempt to claim a vast genus of vectors that achieve a particular result. Yet, the rAAV vectors claimed are not limited, for example, by serotype of AAV, gene of interest, or amount of intrastrand base paring (which is functionally defined as "enhanc[ing]" expression). Further, Plaintiffs dispute Defendants' proposed claim constructions, which are consistent with the disclosures in the intrinsic evidence and provide that each ITR of the claimed rAAV vectors is native AAV ITR sequence. By contrast, under Plaintiffs' proposed claim constructions, the claimed rAAV vectors are not limited, for example, by the number, location, and sequence of ITR(s). Rather, the Asserted Claims purport to define the rAAV vectors by functional properties, such as their ability to enhance expression of a heterologous sequence relative to vectors that lack sufficient intrastrand base pairing to enhance said expression. A person of ordinary skill in the art would have understood the purported scope of the claimed genus is exceedingly broad, unknown and unknowable, and consequently would require an expansive and random search for all of the different options of vectors that may or may not work.[2] *See Brenner v. Manson*, 383 U.S. 519, 536 (1966) ("a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

A "representative number of species" means that the species which are adequately described are representative of the entire genus. *Carnegie Mellon*, 541 F.3d at 1124. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. *Id.* For inventions in unpredictable arts, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one

[2] Further, because the term "enhanced" as used in the Asserted Claims is indefinite (*infra*, Section IV.B.3.), a person of ordinary skill in the art would not be able to determine the purported scope of the claimed genus of vectors with reasonable certainty. Likewise, the term "lacks sufficient intrastrand base pairing" as used in the Asserted Claims is indefinite (*id.*), further highlighting that the purported scope of the claimed genus cannot be determined with reasonable certainty.

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species within the genus. *Id.* The genus of vectors claimed in the ’535 patent is not supported by a representative number of species. Despite the vast scope of the claimed genus, the ’535 patent contains only minimal guidance and examples regarding what rAAV vectors would possess this function of enhanced expression. Indeed, the ’535 patent provides just one exemplary structure (a half-sized vector containing a particular heterologous gene and wherein each ITR of the vector is native AAV ITR sequence) that purportedly accomplishes the claimed function of enhanced expression. It also fails to inform a person of ordinary skill in the art about the amount of overall intrastrand base pairing necessary to achieve the required enhanced expression. More specifically, the specification fails to provide any specific details as to the structural features relating to the base pairing requirements set forth in the Asserted Claims. Yet subsequent research has shown that the location and amount of base pairing influences the amount of expression.

In determining whether the specification provides adequate written description support, products that post-date the patent’s priority date, including an accused infringing product, can be taken into consideration. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374-75 (Fed. Cir. 2017). In particular, evidence showing that a claimed genus does not disclose a representative number of species may include post-filing evidence of species that fall within the claimed genus but are not disclosed by the patent. *Id.* at 1374. Despite the minimal teachings in the specification of the ’535 patent outlined above, the claims purport to cover all structures (and iterations thereof)—including later-developed vectors containing mutated ITRs, which merited their own patent protection (*see, e.g.*, McCarty (2001); McCarty (2003); McCarty (2008); U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457)—that accomplish the “enhanced expression” function.

The ’535 patent also fails to disclose structural features common to members of the genus that are responsible for the claimed functions such that one of skill in the art could visualize or

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recognize the members of the claimed genus of rAAV vectors, as explained in detail below. "[F]unctionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus." *AbbVie Deutschland GmbH & Co. KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014); *see also Juno*, 10 F.4th at 1337 (disclosure of two working embodiments "does not provide information sufficient to establish that a skilled artisan would understand how to identify the species of scFvs capable of binding to the limitless number of targets as the claims require.").

For at least the reasons discussed herein, and outlined in more detail for specific claim limitations below, the Asserted Claims of the '535 patent are invalid under 35 U.S.C. § 112, ¶ 1 for failing to satisfy the written description requirement.

a. Independent Claim 1

i. "a single-stranded heterologous nucleotide sequence comprising a region which forms intrastrand base pairs . . . wherein the region which forms intrastrand base pairs is in a coding region"

The purported scope of the claims of the '535 patent is broad with respect to the limitations reciting "a single-stranded heterologous nucleotide sequence comprising a region which forms intrastrand base pairs . . . wherein the region which forms intrastrand base pairs is in a coding region," as recited in independent claim 1, relative to the limited examples and disclosure in the specification. More specifically, the specification fails to provide any specific details as to the structural features relating to the base pairing requirements set forth in the claims.

The claims of the '535 patent purport to encompass a vast array of rAAV formats. For example, the "heterologous nucleotide sequence" is expressly defined in the '535 patent

specification to purportedly encompass any "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." *Id.* at 9:29-35. The coding region is expressly defined in the '535 patent specification as "a 'coding region' of a heterologous sequence" and "is a sequence of contiguous nucleotides which gives rise in a host cell to a transcription and/or translation product." *Id.* at 10:19-22. The '535 patent specification further states that "[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." *Id.* at 10:33-37. Thus, the purported scope of the heterologous nucleotide sequences encompassed by independent claim 1 (and its dependent claims) is limitless.

In contrast to the broad purported scope of claim 1, the '535 patent specification teaches only one purported working example of an rAAV vector comprising a nucleotide sequence comprising a coding region for green fluorescent protein (GFP). *See* Examples 1-3, 5-8, 10-12.[3] This is the sole exemplary heterologous sequence comprising a coding region in the specification. Other than GFP, the specification does not provide any additional examples of other coding regions falling within the purported scope of the claims that possess the claimed functional elements (e.g., intrastrand base pairing in the coding region). Yet, the claims purport to cover an unlimited number of heterologous sequences of unlimited size and function (or no function at all) and coding regions

[3] The '535 patent also teaches an example (Example 13) of an rAAV vector encoding a fusion protein of tumor necrosis factor receptor (TNFR) and an immunoglobulin constant region (Fc) produced "according to the Examples above." '535 patent at 37:61-65 (Example 13). However, the TNFR-Fc example appears to be prophetic and does not describe whether or how the vector encoding TNFR-Fc is designed to give rise to intrastrand base pairing. Example 5 describes an rAAV vector encoding human alkaline phosphatase and bacterial neomycin resistance gene used as a control, but it does not appear to possess intrastrand base pairing in the coding region and thus does not exemplify the claims. *Id.* at 31:64-32:2.

of a variety of lengths from 5 to more than 500 nucleotides in length. *Id.* at 10:33-37. Given the substantial structural variation purportedly encompassed by the functionally-defined genus, the ’535 patent specification does not disclose a representative number of species that achieves the claimed result sufficient to support the claimed genus of all single-stranded heterologous nucleotide sequences comprising a region which forms intrastrand base pairs wherein the region which forms intrastrand base pairs is in a coding region. Furthermore, there is no structural feature of the nucleotide sequence that would be common to members of the genus because the claims purport to cover any nucleotide sequence, and the specification does not describe any correlation between any nucleotide sequence structure and the functional requirements of the claimed genus.

Thus, claim 1 of the ’535 patent lacks written description support for “a single-stranded heterologous nucleotide sequence comprising a region which forms intrastrand base pairs . . . wherein the region which forms intrastrand base pairs is in a coding region” because a person of ordinary skill in the art would not reasonably believe that the ’535 patent inventor had possession of the claimed genus of any heterologous nucleotide sequence comprising a region which forms intrastrand base pairs, wherein the region which forms intrastrand base pairs is in a coding region.

ii. “a [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”

The ’535 patent uses functional language to describe a desired result for the vectors purportedly encompassed by independent claim 1 and claims dependent thereon. Specifically, claim 1 recites “a [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 . . . ." *Id.* at claim 1 (emphasis added). The '535 patent states that "[i]t is understood that, for purposes of this invention, a recombinant viral vector containing a sequence or region that forms intrastrand base pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the degree of intrastrand base pairing." *Id.* at 10:60-65. The specification further teaches that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:65-11:1. The '535 patent describes that "[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." *Id.* at 10:33-37. In some embodiments, "the total amount of sequence that forms intrastrand base pairs (which could be in one or more regions) is greater than about 125 nucleotides, greater than about 250 nucleotides, greater than about 500 nucleotides, and/or greater than about 1,000 nucleotides." *Id.* at 15:8-13. Under the circumstances where a coding region is 5 nucleotides and the extent of intrastrand base pairing is 25%, the amount of intrastrand base pairing could be as little as 1 or 2 nucleotides. As discussed above, the '535 patent exemplifies a single rAAV vector that purportedly achieved intrastrand base pairing across the entire coding region. Applicant did not possess rAAVs having 25% intrastrand base pairing across a 5-nucleotide coding region, i.e., fewer than 2 nucleotides, and having enhanced expression. Nor did the applicant possess any coding regions having lengths other than the length of GFP and any other percentage of base pairing other than 100%. Indeed, even today, AAV vectors that are too short or too long cannot package and express

efficiently. For example, "stuffer" sequences are sometimes used to lengthen AAV vectors and enhance expression in certain systems.

The '535 patent attempts to claim every rAAV vector that would achieve the desired result. The specification states that an "[a]n 'AAV inverted terminal repeat (ITR)' sequence . . . is an approximately 145-nucleotide sequence that is present at both termini of the *native* single-stranded AAV genome." '535 patent at 11:14-17 (emphasis added). The specification also explains that *native* ITR sequences, i.e., from a native AAV2 genome, were used in the purported working examples. *Id.* at 16:3-5. Non-native ITR sequences were never tested or even constructed, according to the patent specification.

To the extent the '535 patent claims are construed to encompass *non-native* ITR sequences, the '535 patent claims are invalid for lack of written description, because the claimed genus of vectors comprising any modified, mutated, or non-native ITR is unsupported by the disclosure of the patent specification, which includes only a single purported working example wherein each ITR of the vector is native AAV ITR sequence from AAV2. As noted above, in determining whether the specification provides adequate written description support, products that post-date the patent's priority date, including an accused infringing product, can be taken into consideration. *Amgen Inc. v. Sanofi*, 872 F.3d at 1374-75. Here, to the extent the '535 patent claims are construed to encompass non-native ITR sequences, the claims improperly purport to cover all structures (and iterations thereof) (including later-developed structures like those described in McCarty (2001), McCarty (2003) and McCarty (2008) containing a mutated ITR that was not yet invented at the time of filing the '535 patent, and which merited its own patent protection (U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457)) that accomplish the "enhanced expression" function.

Yet, the ’535 patent specification provides only one structure (a half-sized vector containing a particular heterologous gene and wherein each ITR of the vector is native AAV ITR sequence) that purportedly accomplishes the claimed function of enhanced expression. The single purported working example compares expression from an rAAV vector encoding GFP which has “half-complexity” with expression of GFP from an rAAV vector that possesses no intrastrand base pairing. *See, e.g., id.* at 37:23-27. The specification explains that a “half-complexity” vector is one that forms a “snapback” molecule and is double-stranded along most or all of its length. *Id.* at 15:25-33; *see also id.* at 7:64-8:5 (“rAAV vectors which contained two copies of [GFP] in opposite orientation, and were accordingly able to form a double-stranded molecule due to intrastrand base pairing, displayed significantly higher expression levels (as indicated by percentage of cells expressing reporter gene) in 293 and HeLa cells compared to another vector which was not able to form intrastrand base pairing of the GFP gene.”).

Thus, the single purported working example in the specification discloses an rAAV vector with 100% intrastrand base pairing in the rAAV vector whose expression is “enhanced” over an rAAV vector with no intrastrand base pairing. The ’535 patent inventor acknowledged as much during prosecution of the application that led to the ’535 patent when arguing to overcome a rejection under 35 U.S.C. § 112, ¶ 1 for lack of written description regarding the “enhanced expression” limitation. *See* GENZ_NOV_00002135 (“In fact, data in Example 8 indicated that the *entire* genome of such vectors [that have significantly enhanced expression of GFP] is base-paired”) (emphasis added); *see also* GENZ_NOV_00002136 (“Example 8 shows an entire genome of an rAAV vector is base-paired”).

This one purported working example does not amount to a disclosure of a representative number of species corresponding to the purported scope of the claimed functional genus of rAAV

vectors with enhanced expression. The specification does not provide any examples of enhanced expression with amounts of intrastrand base pairing less than 100% in the coding region or examples of enhanced expression over comparator vectors that possess at least some intrastrand pairing. Given that the purported scope of claim 1 and its dependent claims cover substantial variation within the genus of permissible intrastrand base pairing for both the first and second rAAV vectors in the claim, the specification does not disclose a representative number of species sufficient to support the claimed genus.

Nor was there any established correlation between vector base pairing structure and function (sufficient to enhance expression). This is abundantly clear from the lack of guidance provided by the ’535 patent’s incredibly broad (to the point of meaningless) disclosure regarding the level of intrastrand base pairing that can lead to enhanced expression. Indeed, as the ’535 patent admits, this was a particularly unpredictable field. *See, e.g.*, ’535 patent at 4:36-39 (“there can be difficulties in obtaining sufficient levels of expression of heterologous sequences from rAAV vectors and viruses containing such vectors”). Thus, significantly more disclosure was required for a person of ordinary skill in the art to conclude that the inventor possessed the full scope of the functionally defined genus recited in the claims.

For at least these reasons, claim 1 of the ’535 patent (and its dependent claims) lacks written description support for “a [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” because a person of ordinary skill in the art would not reasonably believe that the ’535 patent inventor had possession of the claimed genus.

b. Dependent Claims 2-26 and 28-29

The dependent claims of the ’535 patent merely recite additional features that provide no meaningful narrowing of independent claim 1, and the dependent claims therefore lack written description for the same reasons set forth above for claim 1, as well as for the additional reasons discussed below.

i. Dependent Claim 2

Claim 2 depends from claim 1 and further recites the rAAV vector, “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 all or most of its length.” Other than the size of the sequence complexity of the heterologous sequence, claim 2 does not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as “along all or most of its length”), and, under Plaintiffs’ proposed claim constructions, provides no meaningful limits regarding the number, location, and sequence of ITR(s), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. The ’535 patent specification broadly states “the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%.” *Id.* at 10:65-11:1. Yet, the specification fails to provide any information as to where (if anywhere) in this exceptionally broad range intrastrand base pairing would be considered to be along “most” of the length of the heterologous nucleotide sequence and would accomplish the claimed function of enhanced expression. Thus, for at least the reasons explained herein and above for claim 1, a person of

ordinary skill in the art would not reasonably have understood that the ’535 patent inventor had possession of the genus of claim 2.

ii. Dependent Claim 3

Claim 3 depends from claim 2 and further recites the rAAV vector, “comprising an ITR flanked on both sides by heterologous sequences.” Other than the presence of an ITR, claim 3 does not further limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, or amount of intrastrand base paring (which is vaguely described as “along all or most of its length”), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Further, under Plaintiffs’ proposed claim constructions, the ’535 patent specification provides no limitation as to where the ITR in dependent claim 3 should be located in the rAAV vector or what the sequence of the ITR should be, so long as it is flanked on both sides by heterologous sequences of indeterminate structure.

Thus, for at least the reasons explained herein and above for claims 1 and 2, a person of ordinary skill in the art would not reasonably have understood that the ’535 patent inventor had possession of the genus of claim 3.

iii. Dependent Claim 4

Claim 4 depends from claim 1 and further recites the rAAV vector, wherein the coding region forms a double-stranded structure “along most or all of its length.” Other than the vague description of the amount of intrastrand base pairing “along most or all of its length,” claim 4 does not further limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type or length of heterologous sequence, or the number, location, and sequence of ITR(s) (under Plaintiffs’

proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. The ’535 patent specification broadly states “the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%.” *Id.* at 10:65-11:1. Yet, the specification fails to provide any information as to where (if anywhere) in this exceptionally broad range intrastrand base pairing would be considered to be along “most” of the length of the heterologous nucleotide sequence and would accomplish the claimed function of enhanced expression. Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the ’535 patent inventor had possession of the genus of claim 4.

iv. Dependent Claim 5

Claim 5 depends from claims 1, 2, 3 or 4 and further recites “wherein the vector is capable of being packaged in an AAV particle.” Claim 5 does not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as “along all or most of its length”), or the number, location, and sequence of ITR(s) (under Plaintiffs’ proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1-4, a person of ordinary skill in the art would not reasonably have understood that the ’535 patent inventor had possession of the genus of claim 5.

v. Dependent Claims 6, 8, and 10

Claim 6 depends from claim 1, claim 8 depends from claim 5, and claim 10 depends from claims 2, 3, or 4. These claims all recite a host cell comprising the rAAV vector. The specification broadly provides that "[a] 'host cell' is a cell which has been or can be a recipient for a vector(s) of this invention and the progeny thereof." *Id.* at 12:42-43. Thus, claims 6, 8, and 10 purport to encompass an unknown and unknowable number of host cell types. The single vector exemplified in the specification was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other cells (*see, e.g.*, *id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any host cell. Moreover, claims 6, 8, and 10 do not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type or length of heterologous sequence, amount of intrastrand base paring (which is functionally defined as "enhanc[ing]" expression), or the number, location, and sequence of ITR(s) (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1-5, a person of ordinary skill in the art would not reasonably have understood that the '535 patent inventor had possession of the genus of claims 6, 8, and 10.

vi. Dependent Claims 7, 9, and 11

Claim 7 depends from claim 6, claim 9 depends from claim 8, and claim 11 depends from claim 10. These claims all recite that the host cell comprising the rAAV vector is a mammalian cell. As recited in the specification, the purported scope of the claims covers any mammalian cell type, including both mammalian cell lines and primary cells, as well as stem cells. *Id.* at 26:51-58;

28:39-41. Thus, claims 7, 9, and 11 purport to encompass an unknown and unknowable number of mammalian host cell types. The single vector exemplified in the specification was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other mammalian cells (*see, e.g.*, *id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any mammalian cell. Moreover, claims 7, 9, and 11 do not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), or the number, location, and sequence of ITR(s) (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1, 6, 8, and 10, a person of ordinary skill in the art would not reasonably have understood that the '535 patent inventor had possession of the genus of claims 7, 9, and 11.

vii. Dependent Claims 12-15

Claim 12 depends from claim 1, claim 13 depends from claim 5, claim 14 depends from claim 2, and claim 15 depends from claims 3 or 4. These claims all recite a recombinant AAV particle comprising the rAAV vector. Claims 12-15 do not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type or length of heterologous sequence, amount of intrastrand base paring (which is functionally defined as "enhanc[ing]" expression), or the number, location, and sequence of ITR(s) (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-

size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1-5, a person of ordinary skill in the art would not reasonably have understood that the ’535 patent inventor had possession of the genus of claims 12-15.

viii. Dependent Claims 16, 18, and 20

Claim 16 depends from claim 1, claim 18 depends from claim 5, and claim 20 depends from claims 2, 3, or 4. These claims all recite a composition comprising the rAAV vector. Claims 16, 18, and 20 do not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type or length of heterologous sequence, amount of intrastrand base paring (which is functionally defined as “enhanc[ing]” expression), or the number, location, and sequence of ITR(s) (under Plaintiffs’ proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1-5, a person of ordinary skill in the art would not reasonably have understood that the ’535 patent inventor had possession of the genus of claims 16, 18, and 20.

ix. Dependent Claims 17, 19, and 21

Claim 17 depends from claim 14,[4] claim 19 depends from claim 18, and claim 21 depends from claim 20. These claims all recite that the composition comprising the rAAV vector further comprises a pharmaceutically acceptable excipient. None of these claims meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus

[4] As discussed below, claim 17 is invalid under 35 U.S.C. § 112, fourth paragraph for being an improper dependent claim.

of which is not limited by any serotype of AAV, gene of interest, type or length of heterologous sequence, amount of intrastrand base paring (which is functionally defined as "enhanc[ing]" expression), or the number, location, and sequence of ITR(s) (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1, 14, 18, and 20, a person of ordinary skill in the art would not reasonably have understood that the '535 patent inventor had possession of the genus of claims 17, 19, and 21.

x. Dependent Claim 22

Claim 22 depends from claim 5 and further recites a method for preparing the rAAV vector wherein the method comprises incubating a host cell under conditions that allow AAV replication and encapsidation, wherein the host cell comprises (a) an rAAV vector comprising a heterologous nucleotide sequence and one or more 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. The specification broadly provides that "[a] 'host cell' is a cell which has been or can be a recipient for a vector(s) of this invention and the progeny thereof." *Id.* at 12:42-43. Thus, claim 22 purports to encompass an unknown and unknowable number of host cell types. The single vector exemplified in the specification was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other cells (*see, e.g., id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any host cell. Moreover, claim 22 does not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of

heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), or the number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1 and 5, a person of ordinary skill in the art would not reasonably have understood that the '535 patent inventor had possession of the genus of claim 22.

xi. Dependent Claim 23

Claim 23 depends from claim 22 and further recites wherein the rep and cap functions are provided by a rep-cap cassette that is stably integrated in the host cell genome. Claim 23 does not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), or the number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Nor does claim 23 provide any further detail as to what the host cell is. The single vector exemplified in the specification was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other cells (*see, e.g.*, *id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any host cell. Thus, for at least the reasons explained herein and above for claims 1 and 22, a person of ordinary skill in the art would not reasonably have understood that the '535 patent inventor had possession of the genus of claim 23.

xii. Dependent Claim 24

Claim 24 depends from claim 22 and further recites wherein the rep and cap functions are provided by a plasmid. Claim 24 does not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), or the number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Nor does claim 24 provide any further detail as to what the host cell is. The single vector exemplified in the specification was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other cells (*see, e.g., id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any host cell. Thus, for at least the reasons explained herein and above for claims 1 and 22, a person of ordinary skill in the art would not reasonably have understood that the '535 patent inventor had possession of the genus of claim 24.

xiii. Dependent Claim 25

Claim 25 depends from claim 22 and further recites wherein the rAAV vector is provided in a plasmid. Claim 25 does not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), or the number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a

heterologous nucleotide sequence containing a coding region for a detectable marker. Nor does claim 25 provide any further detail as to what the host cell is. The single vector exemplified in the specification was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other cells (*see, e.g., id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any host cell. Thus, for at least the reasons explained herein and above for claims 1 and 22, a person of ordinary skill in the art would not reasonably have understood that the ’535 patent inventor had possession of the genus of claim 25.

xiv. Dependent Claim 26

Claim 26 depends from claim 22 and further recites wherein the rAAV vector is stably integrated into the host cell genome. Claim 26 does not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as “along all or most of its length”), or the number, location, or sequence of ITRs (under Plaintiffs’ proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Nor does claim 26 provide any further detail as to what the host cell is. The single vector exemplified in the specification was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other cells (*see, e.g., id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any host cell. Thus, for at least the reasons explained herein and above for claims 1 and 22, a person of ordinary skill in the art would not reasonably have understood that the ’535 patent inventor had possession of the genus of claim 26.

xv. Dependent Claim 28

Claim 28 depends from claim 22 and further recites a population of rAAV particles produced according to the method of claim 22. Claim 28 does not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), or the number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Nor does claim 28 provide any further detail as to what the host cell is. The single vector exemplified in the specification was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other cells (*see, e.g., id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any host cell. Thus, for at least the reasons explained herein and above for claims 1 and 22, a person of ordinary skill in the art would not reasonably have understood that the '535 patent inventor had possession of the genus of claim 28.

xvi. Dependent Claim 29

Claim 29 depends from claim 22 and further recites a population of rAAV vectors produced according to the method of claim 22. Claim 29 does not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), or the number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-

size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Nor does claim 29 provide any further detail as to what the host cell is. The single vector exemplified in the specification was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other cells (*see, e.g., id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any host cell. Thus, for at least the reasons explained herein and above for claims 1 and 22, a person of ordinary skill in the art would not reasonably have understood that the ’535 patent inventor had possession of the genus of claim 29.

2. Invalidity under 35 U.S.C. § 112, First Paragraph for Lack of Enablement

“To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.” *ALZA Corp. v. Andrx Pharms.*, LLC., 603 F.3d 935, 940 (Fed. Cir. 2010) (quoting *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997)). An essential question for an enablement analysis is “whether the scope of enablement of [a claim] is as broad as the scope of the claim.” *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212 (Fed. Cir. 1991). The applicant must disclose a range of embodiments that is adequate in relation to the breadth of the patent right being sought. *See, e.g., In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (finding scope of claims that encompassed any and all vaccines in any animal toward any RNA virus not enabled when only a single working example was provided).

The need to engage in “an iterative, trial-and-error process to practice the claimed invention,” where the specification provides “only a starting point, a direction for further research,” precludes a finding of enablement. *ALZA*, 603 F.3d at 941. Where the skilled artisan “would need to assay each of at least tens of thousands of candidates” and the specification offered

"no guidance or predictions about particular substitutions" that would lead to other effective members, genus claims are not enabled based on undue experimentation. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385-86 (Fed. Cir. 2013). "[T]he enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those requirements, especially where predictability and guidance fall short. In particular, it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim." *Amgen Inc. v. Sanofi Aventisub LLC*, 987 F.3d 1080, 1086 (Fed. Cir. 2021). Thus, "[w]hile functional claim limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language." *Id.* at 1087; *see also id.* ("[T]he use of broad functional claim limitations raises the bar for enablement . . . .")

As discussed *supra*, the claims of the '535 patent are broadly defined by structural and functional elements. Determining which combination of structures in the claimed rAAV vectors would result in enhanced expression of a desired gene (i.e., by supporting increased base pairing) would require an iterative, trial-and-error process that would amount to undue experimentation, due to the vast genus of rAAV vectors claimed. Indeed, for example, the inventor states that the intrastrand complementarity "may be any of a number of sizes," therefore including an unlimited spectrum of sizes, without providing any supporting detail or information regarding which sizes will accomplish the claimed function beyond those having 100% complementarity. *See* '535 patent at 14:64-15:13. Further, during prosecution, the inventor acknowledged that "[t]he specification teaches that intrastrand base pairing may be anywhere along the heterologous sequence, and may or may not be within a coding region of a heterologous sequence." GENZ_NOV_00002136.

Again, this lack of specificity would require an iterative, trial-and-error process to determine which combination of structures in the claimed rAAV vectors would result in enhanced expression of a desired gene.

Undue experimentation is evaluated under the Wands factors, which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). An evaluation of the experimentation required under the *Wands* factors follows.

a. Independent Claim 1

i. Factors 1 and 2: Quantity of Experimentation Necessary and Amount of Direction or Guidance Presented

As discussed above, independent claim 1 of the ’535 patent (and its dependent claims) involves a vast genus of rAAV vectors that must meet certain functional limitations. Determining which combination of structures in a specific vector would result in enhanced expression (i.e., by supporting increased intrastrand base pairing) would require an excessive amount of experimentation across all heterologous sequences and lengths to yield sufficient intrastrand base pairing and purportedly enhanced expression. Further, post-filing date studies have shown that small changes to the structure of rAAV vectors could significantly impact the functionality of the vectors. The ’535 patent does not provide sufficient direction or guidance across the broad purported scope of unlimited heterologous sequences and vector lengths purportedly encompassed by the genus of rAAV vectors in independent claim 1 and its dependent claims.

Independent claim 1 of the ’535 patent (and its dependent claims) presents a vast array of rAAV formats. The claimed vectors use *any* serotype of rAAV particle, and *any* serotype of rAAV

vector, which are not required to be derived from the same serotype. In contrast, the only serotype of rAAV particles used in the purported working example in the specification is rAAV serotype 2 particles. ’535 patent at 16:3-5. While the specification states that “it is fully expected that the same principles derived from analysis of AAV2 will be applicable to other AAV serotypes, since it is known that the various serotypes are quite closely related, both functionally and structurally, even at the genetic level,” (*id.* at 16:6-10), such a statement is merely expressing a hypothesis and invitation for further research by a person of ordinary skill in the art to use other AAV serotypes. Courts have found the claims were not enabled when the amount of experimentation “would take a substantial amount of time and effort,” and the “only ways for a person of ordinary skill to discover undisclosed claimed embodiments would be through either ‘trial and error, by making changes to the disclosed antibodies and then screening those antibodies for the desired binding and blocking properties,’ or else ‘by discovering the antibodies de novo’ according to a randomization-and-screening ‘roadmap.’” *Amgen*, 987 F.3d at 1088 (citing *Amgen Inc. v. Sanofi*, No. 14-1317, 2019 WL 4058927, *11–*12 (D. Del. Aug. 28, 2019).

The claims purport to encompass an rAAV vector comprising *any* nucleotide sequence comprising a coding region. In contrast, the rAAV vector used in the purported working example only encodes green fluorescent protein. *Id.* at Fig. 5. Further, the claims purport to encompass a genus of rAAV vectors that set no limits on the amount of intrastrand base pairing in the coding region. Rather, the rAAV vector is defined functionally as possessing enhanced expression relative to a second rAAV vector that lacks an undefined amount of “sufficient” intrastrand base pairing to enhance expression. The patent states that the intrastrand complementary “may be any of a number of sizes,” therefore including an entirely unlimited spectrum of sizes, without providing any supporting detail or information regarding workable ranges. *See* ’535 patent, 14:64–15:13.

The only embodiment exemplified in the patent is described as a vector that is base paired "along most or all of its length." *Id.* at 15:29-33. No guidance is provided for any levels of base pairing less than 100% that can achieve the claimed enhanced expression.

Moreover, the '535 patent provides very little guidance as to how a person of ordinary skill in the art should determine whether enhanced expression is present. For example, the claims do not indicate when expression is to be assessed. In the Examples, an increased percentage of fluorescent cells, as measured at two different time points (48 or 72 hours) post-infection, is shown for cells infected with the 100% intrastrand base paired rAAV vector compared to a second vector with no intrastrand base pairing. *Id.* at 32:25-33:17; 36:41-37:27. However, while some time presumably must pass for expression to reach a detectable level, it is possible that as time passes the expression may decrease. Conversely, it is possible that, as enough time passes, the control vector that "lacks sufficient intrastrand base pairing to enhance expression" may exhibit increased expression of a transgene so that it is not possible to determine a significant difference between expression levels of the vectors. The patent provides no guidance regarding how one skilled in the art would test for the claimed enhanced expression at either of these time points.

Moreover, it is evident from at least Figure 6F of the '535 patent, that the examples described in the specification used a lambda stuffer sequence in the control vector. The lambda stuffer was known to negatively impact expression. Thus, the examples described in the specification may have utilized a control that artificially suppressed expression due to the use of a lambda stuffer, thereby inflating the level of "enhanced expression" observed for the test vector. As a result, it is impossible for a person of ordinary skill in the art to determine, based on the examples provided in the specification, what characteristics of the claimed rAAV vectors, e.g.,

amount of intrastrand base pairing, would be required to enhance expression over a vector that "lacks sufficient intrastrand base pairing."

The '535 patent disclosure further provides little to no guidance regarding determining intrastrand base pairing that is "sufficient" to enhance expression or what it means to "lack[] sufficient intrastrand base pairing" to enhance expression of the heterologous sequence. With regard to the length of the requisite level of intrastrand base pairing, the specification teaches that a region of intrastrand complementarity can be anywhere from as little as 5 to greater than 1000 nucleotides. *Id.* at 10:33-37. The specification also states that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about *any* of the following: 25%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:65-11:1 (emphasis added). Yet, the only purported working example discloses an rAAV vector with close to 100% intrastrand base pairing in the rAAV vector and whose expression is "enhanced" over an rAAV vector with no intrastrand base pairing. Moreover, it is likely the purported working example is inoperative, in whole or in part.

Further, to the extent the '535 patent claims are construed to encompass *non-native* ITR sequences, the '535 patent claims are invalid for lack of enablement, because experimentation across the full scope of rAAV vectors comprising any modified, mutated, or non-native ITR would require a substantial amount of time and effort, particularly in view of the limited disclosures in the patent specification (disclosing a single purported working example of an rAAV having intrastrand base pairing, *i.e.*, a half-size vector wherein each ITR of the vector is native AAV ITR sequence and comprising a heterologous nucleotide sequence containing a coding region for a detectable marker). Indeed, substantial time and effort was required to generate, experimentally test, and ascertain the functionality of later-developed vectors containing a mutated ITR, which

subsequently received its own patent protection (*see, e.g.*, McCarty (2008); McCarty (2003); McCarty (2001); U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457).

Due to the lack of direction and very limited guidance presented in the specification of the ’535 patent, the Asserted Claims of the ’535 patent require a high degree of trial and error in determining which combination of structures in the patented technology would be conducive to supporting increased base pairing and thus enhance expression of a desired gene compared to a vector lacking sufficient base pairing. In other words, undue experimentation will be required to practice the full scope of the Asserted Claims.

ii. Factor 3: Presence or Absence of Working Examples

With regard to functionally-defined genus claims in unpredictable arts, the Federal Circuit has “refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim.” *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As discussed above, *see supra*, there is a single purported working example of an rAAV vector which shows “enhanced expression” in the ’535 patent, and that example is limited to use of a half-size AAV GFP vector that has nearly 100% base pairing and shows enhanced expression compared to an rAAV vector that lacks any base pairing.[5] Moreover, it is likely the purported working example is inoperative, in whole or in part. This single purported working example does not amount to a demonstration

[5] As discussed *supra*, the TNFR-Fc example (Example 13) appears to be prophetic and does not describe any details regarding whether the vector encoding TNFR-Fc is designed to give rise to intrastrand base pairing. Similarly, Example 5 describes an rAAV vector encoding human alkaline phosphatase and bacterial neomycin resistance genes used as controls, but this vector does not appear to possess intrastrand base pairing in the coding region and thus do not exemplify the claims. *Id.* at 31:64-32:2.

with reasonable specificity of how to make and use other potential embodiments across the full scope of the Asserted Claims.

iii. Factors 4-6: Nature of the Invention, State of the Prior Art, and Relative Skill of Those in the Art

The nature of the claimed invention is an rAAV vector with a heterologous sequence with a coding region that forms intrastrand base pairs sufficient to enhance expression of the sequence as compared to an rAAV vector which lacks sufficient intrastrand base pairing to enhance said expression. As the ’535 patent admits, the state of the art was such that the field was still in its early stages at the time of filing (1999). *See, e.g.*, ’535 patent at 1:27-35 (“Recombinant vectors based on parvovirus, such as adeno-associated virus (AAV), show promise for gene therapy. However, obtaining efficient, sufficient levels of expression of a transgene in various cell types has presented problems. Some cell types are impermissive in the sense that initiation of transcription or translation of the transgene is inefficient, with expression accordingly very slow to initiate, if it initiates at all.”). Thus, before the invention could be practiced, it would be necessary to make and screen each candidate rAAV vector for sufficient intrastrand base pairing in its heterologous sequence to enhance expression of said sequence. And although the level of skill in the art was relatively high at the time of filing (1999), skill alone cannot stand in for a total absence of guidance in the specification.

iv. Factor 7: Predictability or Unpredictability of the Art

As the ’535 patent specification admits, this was a particularly unpredictable field at the time of filing (1999). *See, e.g.*, ’535 patent at 4:36-39 (“there can be difficulties in obtaining sufficient levels of expression of heterologous sequences from rAAV vectors and viruses containing such vectors”). This unpredictability would have been compounded by the breadth of the claims, which read on all heterologous sequences (e.g., RNA) and all vector lengths. In

particular, as discussed above, the lower size limit of the vectors described in the ’535 patent would have been wholly inoperable. Further, minor changes to characteristics of the rAAV vector, including size, rAAV serotype, etc. could potentially result in significant, unpredictable changes to the level of intrastrand base pairing and expression of the heterologous sequence. Without testing, a person of ordinary skill in the art could not have predicted whether a given rAAV vector within the vast genus of rAAV vectors claimed would contain sufficient intrastrand base pairing to enhance expression compared to an equally undefined second vector, let alone meet any of the other claim limitations.

v. Factor 8: Breadth of the Claims

Independent claim 1 of the ’535 patent (and its dependent claims) is extremely broad and contains several limitations that are unbounded and/or defined only by broad functional requirements, as explained at length above. *See supra*, Sections IV.B.1 and IV.B.2.a.i. Given the breadth of disclosure, a person of ordinary skill in the art would require significant experimentation to devise a construct that meets the functional limitations in the claims of the ’535 patent, i.e., that has sufficient intrastrand base pairing such that expression of a heterologous sequence is enhanced relative to a construct that lacks sufficient intrastrand base pairing to enhance expression.

As discussed above, the specification merely invites the person of ordinary skill in the art to perform his or her own experimentation to determine the amount of intrastrand base pairing that would work to “enhance expression” for any given coding region and rAAV serotype in order to meet the limitations of the Asserted Claims. As a result, an undue amount of experimentation would be required for a person of ordinary skill in the art to make and use the alleged invention of the Asserted Claims of the ’535 patent.

b. Dependent Claims 2-26 and 28-29

As explained above with respect to the lack of written description, the dependent claims of the ’535 patent further recite features that provide no meaningful limitation as to claim scope, as the dependent claims still purport to encompass a nearly limitless universe of nearly all types of serotype of AAV, gene of interest, amount of intrastrand base paring (which is functionally defined as “enhanc[ing]” expression), and, under Plaintiffs’ proposed claim constructions, provide no meaningful limits regarding the number, location, and sequence of ITR(s). For at least the same reasons set forth in Sections IV.B.1 and IV.B.2.a., the asserted dependent claims are invalid for lack of enablement.

3. Invalidity under 35 U.S.C. § 112, Second Paragraph for Indefiniteness

Under 35 U.S.C. § 112, ¶ 2, a patent “is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” *Nautilus, Inc. v. Biosig. Instruments, Inc.*, 572 U.S. 898, 901 (2014). A patent must be “precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them. Otherwise there would be a zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims.” *Id.* at 909-910 (internal quotations and citations omitted).

i. “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 1 of the ’535 patent and its dependent claims require, among other things, an 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 [a] 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. "Enhanced" in this context is indefinite, as the specification fails to explain (1) how much intrastrand base pairing is required to result in "enhanced" expression, (2) at what point in time the expression should be measured, and (3) how much expression amounts to "enhanced" expression. The specification only provides generalized statements regarding the required "enhanced" expression, but enhanced expression purportedly resulting from intrastrand base pairing is not expressly defined in the patent specification and purportedly encompasses any enhancement, measured by any means, at any point in time relative to any other rAAV that has a different and undefined amount of intrastrand base pairing.

With regard to intrastrand base pairing, the '535 specification fails to elaborate on what position or quantity of intrastrand base pairing will achieve the "enhanced" expression, making it impossible to know how one is potentially infringing. For example, the patent explains that "a recombinant viral vector containing a sequence or region that forms intrastrand base-pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the *degree* of intrastrand base pairing. *Id.* at 10:60-65 (emphasis added). The patent further explains that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%. 95%, 98%, 99%." *Id.* at 10:65-11:1. The patent also explains that "[t]he region(s) of intrastrand complementarity . . . in the recombinant viral vector 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." *Id.* at 14:49-57 (emphasis added). The patent further teaches 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.* at 14:63-65 (emphasis added). These sweeping statements do not put the public on notice of what the claimed invention is—i.e., how much intrastrand base pairing would be needed in specific vectors to arrive at enhanced expression.

Next, with regard to the temporal aspect of measuring expression, the '535 patent specification does not define what time points should be used to measure such a rate. The single purported working example (Example 6) which measures differences in rates of expression only conducts this measurement at 48 and 72 hours and only provides the rate of expression for the GFP expression in the half-sized vector, not the control vector. A person of ordinary skill in the art would know that expression levels will vary over time. Thus, a person of ordinary skill in the art could potentially infringe at one point in time, but not another.

With regard to how much expression amounts to "enhanced" expression, the patent again provides little guidance. The '535 specification teaches that intrastrand base-pairing contributes to increased levels and/or increased rate of heterologous sequence expression, *id.* at 7:61-64, and defines "expression" as follows:

"Expression" includes transcription and/or translation. Methods of detecting transcription, such as Northern analysis, and translation, such as Western analysis or ELISA, are well known in the art. These methods also permit measuring differing levels of transcription and/or translation, whether that difference is between or among different vectors, different times, different host cells, etc. *Id.* at 13:22-28.

Based on this definition, a person of ordinary skill in the art would not know whether "enhanced expression" relates to the rate of expression, e.g., the speed, or the level of expression, e.g., the amount. Further, from this definition, a person of ordinary skill in the art would be unable to determine whether to detect transcription, translation, or both, and what method or methods by which said expression should be assessed. The different measurement techniques disclosed in the '535 specification possess different sensitivity levels which could yield different results when measuring expression from the same rAAV vector. The Federal Circuit has held patent claims invalid for indefiniteness where a claim term may be determined by multiple methods, the testing results of which "will necessarily fall within or outside the claim scope depending on the . . . method chosen." *Honeywell Intern. v. ITC*, 341 F.3d 1332, 1341 (Fed. Cir. 2003).

Moreover, the purported comparator against which expression levels are measured, i.e., a second rAAV vector that "lacks sufficient intrastrand base pairing," is not clearly defined in the specification. The single purported working example in the specification discloses an rAAV vector with close to 100% intrastrand base pairing in the rAAV vector and whose expression is "enhanced" over an rAAV vector with no intrastrand base pairing. Ultimately, the claim limitation is circular, whereby an undefined sufficiency of base pairing and expression in a first rAAV is relative to an undefined insufficiency of base pairing and expression in a second rAAV (whose insufficiency is relative to the first rAAV).

ii. "along most or all of its length"

Claims 2-5, 8-11, 13-15, 17-26, and 28-29 of the '535 patent require, among other things, an rAAV vector comprising a heterologous sequence wherein either the heterologous sequence or the coding region forms a double-stranded structure "along most or all of its length." Requiring constructs that form a double-stranded structure along most or all of the length of the heterologous

sequence or coding region is indefinite, as the specification fails to explain the circumstances under, and characteristics by which, "most or all" of the heterologous sequence or coding region is double-stranded in order to accomplish the claimed function of enhanced expression.

The patent states that "a recombinant viral vector containing a sequence or region that forms intrastrand base-pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the degree of intrastrand base pairing." '535 patent at 10:61-65. Despite that a person of ordinary skill in the art would understand "most" to mean "more than half," the patent provides no other guidance regarding the circumstances or characteristics of the claimed double-stranded structure, instead stating broadly 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.* at 14:63-65 (emphasis added). The patent broadly provides that "[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." *Id.* at 10:33-37. Further, the patent broadly states that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:65-11:1. The patent specification and claims provide no guidance as to what circumstances or characteristics of the "most or all" double-stranded structure are necessary or sufficient to accomplish the claimed function of enhanced expression, e.g., where and how much intrastrand base pairing must occur (ranging from 50-100% of 5 to 500+ nucleotides anywhere in the coding region or any number of nucleotides in the heterologous sequence) and whether or what conditions must be satisfied to enhance expression (e.g., type of cell, type of AAV, type of nucleotide, intracellular conditions, extracellular conditions, etc.).

These overbroad claims reciting forming a double-stranded structure along most or all of the length of a nucleotide sequence or coding region do not put the public on notice of what the claimed invention is, thus making it impossible to know whether one is potentially infringing. *See, e.g., Nautilus*, 572 U.S. at 901.

iii. "conditions that allow"

Claims 22-26 and 28-29 of the '535 patent require, among other things, a method for preparing an rAAV vector wherein the method comprises incubating a host cell under "conditions that allow" AAV replication and encapsidation. Incubating a host cell under "conditions that allow" AAV replication and encapsidation as part of a method of preparing an rAAV vector is indefinite, as the specification fails to explain what these "conditions" should be, other than conditions that do not prevent such events from occurring.

The patent provides three exemplary approaches to packaging AAV, including that "[o]ne exemplary technique of this third approach is outlined in [WO 95/13365 (Targeted Genetics Corporation and Johns Hopkins University) . . . In a preferred embodiment, an AAV packaging plasmid comprising the rep gene operably linked to a heterologous promoter is introduced into the cell, and then the cell is incubated under conditions that allow replication and packaging of the rAAV vector sequence into particles." '535 patent at 22:15-47. The patent specification and claims provide no guidance as to what these conditions are that would allow replication and packaging of the rAAV vector sequence into particles. These overbroad claims reciting "conditions that allow" AAV replication and encapsidation do not put the public on notice of what the claimed invention is—i.e., what the parameters of these "conditions" are, thus making it impossible to know whether one is potentially infringing. *See, e.g., Nautilus*, 572 U.S. at 901.

For at least these reasons, the Asserted Claims of the '535 patent are invalid under 35 U.S.C. § 112 as indefinite.

4. Invalidity under 35 U.S.C. § 112, Fourth Paragraph

Under 35 U.S.C. § 112, ¶ 4, a claim in dependent form "shall contain a reference to a claim previously set forth and then specify a *further limitation of the subject matter claimed*." 35 U.S.C. § 112, ¶ 4 (emphasis added).

a. Dependent Claim 17 is an improper dependent claim

Claim 17 is invalid for being an improper dependent claim because it does not further limit the claim from which it depends. Claim 17 depends from claim 14, and recites "[t]he composition of claim 14, further comprising a pharmaceutical acceptable excipient." However, claim 14 does not recite a composition and instead recites "[a] recombinant AAV particle comprising the rAAV vector of claim 2." Because claim 17 does not further limit the purported scope of the AAV recited in claim 14, it is invalid under 35 U.S.C. § 112, ¶ 4.

V. Invalidity Contentions As To The '717 Patent

A. The '717 Patent Claims Are Invalid for Anticipation and/or Obviousness

Each Asserted Claim of the '717 patent is invalid for anticipation and/or obviousness. In addition to the information set forth below, a chart identifying where specifically in each item of prior art each limitation of each Asserted Claim of the '717 patent is found is attached as Appendix B, which is incorporated herein. Pinpoint citations to material in the prior art are exemplary of the disclosures and teachings of the prior art. Those citations should not be construed as limiting the disclosure of any prior art or as reflecting the only section of a prior art reference disclosing a particular limitation or teaching.

1. Independent Claims 1 and 2

The '717 patent admits that by August 9, 1999, the use of an rAAV vector comprising a single-stranded heterologous nucleotide sequence was well-known. *See, e.g.*, '717 patent at 3:17-

23 ("The native AAV genome has been used as the basis of vector systems for the delivery and expression of heterologous genes in host cells such as mammalian cells, such as for gene therapy.") (*citing* Muzyczka (1992) *Curr. Top. Microbiol. Immunol.* 158:97-129; Carter, B. J. (1992) *Curr. Op. Biotechnol.* 3:535-539; and Flotte et al. (1995) *Gene Therapy* 2:357-362). The '717 patent further admits that "[r]ecombinant AAV (rAAV) vectors, based on the native AAV genome, are generally produced by deletion of rep and/or cap sequences and [their] replacement by a heterologous sequence. Thus, rAAV vectors generally comprise a single-stranded DNA molecule comprising a heterologous gene sequence or sequences flanked by at least one AAV ITR, and typically by two AAV ITRs, one at each end." '717 patent at 3:23-29.

The '717 patent further admits that by August 9, 1999, it was well-known that "efficient, productive packaging in an AAV virus particle is limited to vectors having approximately the size of an AAV genome (i.e., approximately 4.7 kb) or smaller" and that by August 9, 1999, those skilled in the art had already used smaller rAAV genomes. *Id.* at 3:37-39; 42-49 (*citing* Dong et al. (1996) *Hum. Gene Therapy* 7:2101-2112 for teaching the use of "rAAV genomes having sizes between 2 kb and 6 kb"); *see also id.* at 9:64-65 ("The maximum size vector that can be packaged to yield an infectious viral particle is approximately 5.2 kb."); *id.* at 15:56-60 ("In the case of an rAAV vector of the invention, its length may be less than about. . . .5.5."). Indeed, by August 9, 1999, the use of rAAV vectors of approximately half size was well-known and described in numerous prior art references. *See, e.g.*, Hörster (1999); Muzyczka (1992); Hermens (1997); Dong (1996).

The '717 patent further admits that it was well-known that co-infection with a helper virus engendered safety concerns and identified methods known in the art to remove or inactivate the helper virus. *See e.g.*, '717 patent at 4:16-23 ("infection of the host cell with a helper virus may be

undesirable because of safety concerns related to other properties of helper viruses and helper functions"); *id.* at 25:29-39 ("Optionally, rAAV virus preparations can be further processed to enrich for rAAV particles, deplete helper virus particles, or otherwise render them suitable for administration to a subject. See Atkinson et al. for exemplary techniques (WO 99/11764). Purification techniques can include isopynic gradient centrifugation, and chromatographic techniques. Reduction of infectious helper virus activity can include inactivation by heat treatment or by pH treatment as is known in the art. Other processes can include concentration, filtration, diafiltration, or mixing with a suitable buffer or pharmaceutical excipient.").

Hörster (1999) describes the use of "fusion constructs between the indicators luciferase and gfp and the HIV-1-directed antisense sequence AR6 or ribozyme Rz12." Hörster (1999) at 1232. Hörster (1999) describes 12 fusion constructs comprising single stranded heterologous nucleotide sequences. *Id.* at 1232. Hörster (1999) discloses approximately half size rAAV vector fragments comprising heterologous sequences encoding luciferase, gfp, AR6, and/or Rz12 flanked by ITRs in Figures 1 and 3. *Id.* at 1232-33. Hörster (1999) also describes producing infectious rAAV particles using a system that "provides all necessary helper functions for rAAV particle formation by plasmid-coded genes thereby avoiding the use of infectious adenovirus." *Id.* at 1233. Hörster (1999) describes using "wtAAV, AAV-gfp and AAV-gfp-AR6-particles of varying infective doses of up to a MOI of 125 to transduce HeLaP4/CCR5 cells." *Id.* at 1234. Hörster (1999) also describes that "[t]ransduced cells showed *gfp* expression according to the MOI used." *Id.* at 1234.

Muzyczka (1992) describes the use of rAAV vectors "containing the *dl*3-94/neo genome (50% of wild type size)" and "the neomycin phosphotransferase gene." Muzyczka (1992) at 111-12. The *dl*3-94/neo genome (50% of wild type size, *i.e.*, an approximately half size vector) "were

found to consist predominantly of particles that had the density of AAV particles containing a wild type complement of DNA. When the DNA in these particles was examined it was found to consist of three kinds of molecules. The predominant DNA molecule was an inverted dimer of the *dl*3-94/neo genome. Such molecules occur as a natural consequence of the AAV DNA replication mechanism and have been described in studies of spontaneously occurring deletions or AAV defective interfering (DI) genomes." *Id.* at 113 (citations omitted). Muzyczka (1992) describes in Figure 6 "[g]rowth of an AAV recombinant virus stock. Human cells are transfected with the AAV recombinant plasmid and a complementing plasmid which is defective for packaging but supplies the wild type AAV gene products. The cells are also infected with adenovirus (*Ad*) to supply helper function. The virus stock produced contains both adenovirus and the AAV recombinant virus. Adenovirus is inactivated by heat or removed by density gradient centrifugation." *Id.* at 112. Myzyczka (1992) also describes that the rAAV vectors "proved to be capable of efficiently transducing foreign DNA into human cells." *Id.* at 111.

Hermens (1997) describes the generation of an rAAV virus with a vector "containing an expression cassette for B-50/GAP-43." Hermens (1997) at 153. Hermens (1997) describes the B-50/GAP-43 open reading frame (ORF) as "cloned into pcDNAI/Amp5.0 (Invitrogen). This resulted in pcDNAB-50 containing a CMV-B-50-A+ expression cassette. Subsequently, from a plasmid designated psub201 (a recombinant plasmid from which an infectious AAV genome can be excised Samulski, et al., 1987) the AAV-coding sequences are replaced by the CMV-B-50-A+ expression cassette (2.1 kb) of pcDNAB-50. This resulted in plasmid psub201B-50." *Id.* at 153. Hermens (1997) describes "the application of an alternative viral vector, based on adeno-associated virus, has been shown to direct long-term expression of a foreign gene in the brain without noticeable toxicity." *Id.* at 149. Hermens (1997) describes that "[s]ince AAV is heat stable

the heating step results in the elimination of heat labile infectious adenovirus," or alternatively, inactivating the helper virus (Ad) by "[f]ollowing centrifugation at 1500 g for 20 min at 4°C to remove the cell debris, the supernatant was heated at 56°C for 30 min." *Id.* at 153-54.

Dong (1996) describes rAAV vectors "from 2 kb to 6 kb in size" that carry "a chloramphenicol acetyltransferase (CAT) reporter gene." Dong (1996) at 2101. Dong (1996) also describes that "on the Southern blot of virion DNA, only [the] sample from the 1.9-kb vector contained DNA that appeared twice as large as single stranded DNA on an alkaline gel (Fig. 5, lane 2, DS). When the vector DNAs were isolated from infected cells in the absence of adenovirus-mediated double-strand conversion, the majority of the 1.9-kb vectors were in double-stranded form, and none was observed in any of the larger vectors." *Id.* at 2107-08. Dong (1996) describes that "AAV particles carrying vectors ranging from 1,918 to 5,113 nucleotides in size transferred CAT genes into HeLa cells. This demonstrated that vectors up to 5.1 kb in size were packaged into AAV virions, and consequently transduced into target cells." *Id.* at 2104. Dong (1996) also describes how "adenoviruses were heat-inactivated at 65°C for 30 min." *Id.* at 2103.

The '717 patent admits that by August 9, 1999, it was well-known that the AAV life cycle involves the generation of "a self-complementary double-stranded molecule that is covalently closed at one end" called "the replicative form (RF)." '717 patent at 2:11-15; *see also Carter* (1984) at 212 ("These molecules consist of complementary strands which are covalently joined at one terminus by a hairpin structure formed by virtue of the palindromic terminal sequence 126 nucleotides in length."). The '717 patent further admits that by August 9, 1999, it was well-known that "formation of the RF is required for transcription of viral proteins (or, in the case of recombinant AAV, the transcription of heterologous sequences such as a transgene) to occur, since cellular RNA polymerizing systems require a double-stranded template." '717 patent at 2:40-45;

see also Carter (1984) at 219 ("Also, as shown in Fig. 2, the RF structure is the configuration that would be expected during replication of AAV DNA."). The '717 patent also admits that when a recombinant viral vector has a sequence complexity that is approximately one half its length, "a vector is able to form a 'snapback' molecule which is double stranded along most or all of its length, thus analogous to the RF produced during AAV infection." '717 patent at 15:31-34; *see also id.* at 18:47-51 ("Upon replication, the half-size genome is copied into a complementary DNA strand that is covalently attached to its template at one end (see FIGS. 1 and 3), forming a structure that will 'snap back' into a hairpin duplex."); *id.* at 34:26-32 ("Alkaline gel analysis, shown in Fig. 7A, indicates that preparations of virus particles having vector genomes that were made from a half-size plasmid contain DNA molecules that have a single-stranded length that is the same as a native AAV genome (second lane from left). This is what would be expected if 'snap-back'-type RF molecules have been packaged in these virus particles."); Carter (1984) at 216, 222 (indicating that DNA 1.41b, "which appeared to be mainly hairpin molecules," had a "mean molecular size estimated from gel electrophoresis of about 50% of genome length"). The '717 patent further admits that vectors of the alleged invention:

> [C]an be produced by constructing a parvovirus vector, such as an rAAV vector, that has a size approximately one-half of a native genome and allowing such a vector to replicate in a host cell. . . . Upon replication, the half-size genome is copied into a complementary DNA strand that is covalently attached to its template at one end (see FIGS. 1 and 3), forming a structure that will "snap back" into a hairpin duplex. . . . These recombinant parvovirus vectors comprise an ITR sequence between the heterologous sequences (i.e., an ITR sequence flanked on both sides by heterologous sequences)."

'717 patent at 18:41-59; *see also* Carter (1984) at 212 "Some variant genomes have a conformation similar to that of certain intracellular replicating forms of parvovirus DNA. These molecules consist of complementary strands which are covalently joined at one terminus by a hairpin structure formed by virtue of the [ITR]. These molecules at a neutral pH spontaneously renature

with zero-order kinetics to form duplex structures.”). As the ’717 patent depicts in Figs. 1 and 3, “the heterologous sequence [generated from such half-sized vectors] forms base pairs essentially along its entire length, thus analogous to an AAV replicative form.” ’717 patent at 5:8-10.

Literature dated after August 9, 1999, e.g., McCarty (2008), supports the admissions of the ’717 patent by disclosing that such self-complimentary rAAV vectors “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 dimeric inverted repeat will be no larger than the normal AAV packaging capacity (~4,700 nucleotides).” McCarty (2008) at 1649. McCarty (2008) further recognizes that “[a]lthough this further restricts the transgene carrying capacity of an already small viral vector, it offers a substantial premium in the efficiency, and speed of onset, of transgene expression because dsDNA conversion is independent of host-cell DNA synthesis and vector concentration.” *Id.* (*citing* McCarty (2001), Gene Ther 8:1248-54).

Thus, each of Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996) teach the approximately half size vector comprising a region which forms intrastrand base pairs such that expression of a coding region of a heterologous sequence is enhanced. *See e.g.*, Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996). Moreover, the prior art discloses methods for introducing a polynucleotide into, and expressing a polynucleotide coding region in, a cell, comprising contacting the cell with an rAAV particle comprising an rAAV vector, in the absence of an AAV helper virus, under conditions that allow uptake of the rAAV vector and expression of the coding region. *See e.g.*, Hörster (1999), Muzyczka (1992), Hermens (1997), Dong (1996), Berns (1996), Carter (1996), Kaplitt (1995), Bartlett (1995), Xiao (1998), Ferrari (1996), Ferrari (1997), Samulski (1987), WO9911764 (1997), Phillips (1997), Welch (1998), Su (1996), Zolotukhin (1996), WO9732018 (1996), Mamounas (1995), Fisher (1996), WO9947691 (1999),

WO9717458 (1995), and WO9528493 (1994). A person of ordinary skill in the art would have been motivated to combine such teachings with a reasonable expectation of success to meet the claim limitations of claims 1 and 2.

Accordingly, the disclosure in Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996) of a method for introducing a polynucleotide into, and expressing a polynucleotide coding region in, a cell, essentially in the absence of an AAV helper virus, with rAAV vectors comprising a heterologous sequence, with one or more ITRs flanking said heterologous sequence, and having a length that approximately a half size vector, inherently anticipate and/or render obvious (alone or in the combinations identified in Appendix B) claims 1 and 2 of the ’717 patent because, as the ’717 patent admits, such methods using such vectors necessarily and inevitably contain “a single-stranded heterologous nucleotide sequence comprising a 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.”

2. Dependent Claims 3-8, 11-17, and 20

The dependent claims of the ’717 patent are additionally invalid over the prior art, at least based on the references and combinations set forth in Appendix B. As set forth in Appendix B, the prior art discloses, expressly or inherently, each and every limitation of the dependent claims, including the claimed features of the rAAV vector and method (claims 3-8 and 12-17), including wherein the cell is mammalian (claims 11 and 20). A person of ordinary skill in the art would have been motivated to pursue the combinations listed in Appendix B with a reasonable expectation of success in achieving the asserted dependent claims. For example, as the ’717 patent admits, “[r]ecombinant vectors based on parvovirus, such as adeno-associated virus (AAV), show promise for gene therapy.” ’717 patent at 1:29-30. The ’717 patent also admits that the dependent claim

limitations related to introducing a polynucleotide into a mammalian host cell under conditions that allow uptake of the rAAV vector were known in the art. *See e.g., id.* at 3:17-20 ("The native AAV genome has been used as the basis for vector systems for the delivery and expression of heterologous genes in host cells such as mammalian cells, such as for gene therapy."). The prior art listed in Appendix B is directed to, *e.g.*, rAAV vectors capable of forming intrastrand base pairs that enhance expression and methods of using such vectors for introducing and expressing a polynucleotide coding region into a cell. A person of ordinary skill in the art, as of August 19, 1999, would have been familiar with this prior art and would have been motivated to combine these teachings, and the others set forth in Appendix B, with a reasonable expectation of success, thereby rendering obvious dependent claims 3-8, 11-17, and 20.

B. The '717 Patent Claims Are Invalid under 35 U.S.C. § 112

In addition, or in the alternative, Novartis contends that the Asserted Claims of the '717 patent do not satisfy one or more requirements of 35 U.S.C. § 112. Novartis identifies the below grounds upon which the Asserted Claims of the '717 patent are invalid based on lack of written description under 35 U.S.C. § 112, first paragraph, lack of enablement under 35 U.S.C. § 112, first paragraph, and indefiniteness under 35 U.S.C. § 112, second paragraph.

1. Invalidity under 35 U.S.C. § 112, First Paragraph for Inadequate Written Description

As discussed *supra*, a patent's specification must contain a written description of the claimed invention. 35 U.S.C. § 112, ¶ 1. The description must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*) (citations omitted). In other words, the specification must reasonably convey that the inventor had possession of the claimed subject matter as of the filing date. *Id.*

To satisfy the written description requirement for a claimed genus, a specification must describe the claimed invention in such a way that a person of ordinary skill in the art would understand that the entire genus that is being claimed has been invented, and not just a single species of the genus. *Carnegie Mellon Univ. v. Hoffman-La Roche, Inc.*, 541 F.3d 1115, 1124 (Fed. Cir. 2008). In particular, when attempting to claim a functionally-defined genus, "a sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.* at 1350 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)). "A vague functional description and an invitation for further research does not constitute written disclosure . . . ." *Id.* at 1356. And "if the art is unpredictable, then disclosure of more species is necessary to adequately show possession of the entire genus." *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1125 (Fed. Cir. 2004). While it is "not fatal" that members of a genus are not disclosed in a patent, the specification should provide other means of identifying which members of the genus would interact with other variable elements. *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330 (Fed. Cir. 2021).

The Asserted Claims of the '717 patent are invalid under 35 U.S.C. § 112, ¶ 1, because the claimed method comprises using a genus of vectors that is neither supported by a representative number of species nor by a disclosure of structural features common to the members of the genus responsible for the claimed functions that would allow a person of ordinary skill in the art to visualize or recognize the other members of the genus. As explained in detail below, the specification of the '717 patent does not reasonably convey to a person of ordinary skill in the art that the inventor had possession of the vast—nearly limitless—genus of rAAV vectors used in the

methods of the Asserted Claims. The claims use structural and functional language in an attempt to claim methods comprising a vast genus of vectors that achieve a particular result. Yet, the rAAV vectors claimed are not limited, for example, by serotype of AAV, gene of interest, or amount of intrastrand base paring (which is functionally defined as "enhanc[ing]" expression). Further, Plaintiffs dispute Defendants proposed claim constructions, which are consistent with the disclosures in the intrinsic evidence and provide that each ITR of the claimed rAAV vectors is native AAV ITR sequence. By contrast, under Plaintiffs' proposed claim constructions, the claimed rAAV vectors are not limited, for example, by the number, location, and sequence of ITR(s). Rather, the Asserted Claims purport to define the rAAV vectors by functional properties, such as their ability to enhance expression of a coding region of a heterologous sequence relative to vectors that lack sufficient intrastrand base pairing to enhance said expression. A person of ordinary skill in the art would have understood the purported scope of the claimed methods comprising this genus is exceedingly broad, unknown and unknowable, and consequently would require an expansive and random search for all of the different options of vectors that may or may not work.[6] *See Brenner v. Manson*, 383 U.S. 519, 536 (1966) ("a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

A "representative number of species" means that the species which are adequately described are representative of the entire genus. *Carnegie Mellon*, 541 F.3d at 1124. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. *Id.* For inventions in unpredictable arts, adequate written description

[6] Further, because the term "enhanced" as used in the Asserted Claims is indefinite (*infra*, Section V.B.3.), a person of ordinary skill in the art would not be able to determine the purported scope of the claimed genus of vectors with reasonable certainty. Likewise, the term "lacks sufficient intrastrand base pairing" as used in the Asserted Claims is indefinite (*id.*), further highlighting that the purported scope of the claimed genus cannot be determined with reasonable certainty.

of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. *Id.* The genus of vectors required by the methods claimed in the ’717 patent is not supported by a representative number of species. Despite the vast scope of the claimed genus, the ’717 patent contains only minimal guidance and examples regarding what rAAV vectors would possess this function of enhanced expression. Indeed, the ’717 patent provides just one exemplary structure (a half-sized vector containing a particular heterologous gene and wherein each ITR of the vector is native AAV ITR sequence) that purportedly accomplishes the claimed function of enhanced expression. It also fails to inform a person of ordinary skill in the art about the amount of overall intrastrand base pairing necessary to achieve the required enhanced expression. More specifically, the specification fails to provide any specific details as to the structural features relating to the base pairing requirements set forth in the Asserted Claims. Yet subsequent research has shown that the location and amount of base pairing influences the amount of expression.

In determining whether the specification provides adequate written description support, products that post-date the patent’s priority date, including an accused infringing product, can be taken into consideration. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374-75 (Fed. Cir. 2017). In particular, evidence showing that a claimed genus does not disclose a representative number of species may include post-filing evidence of species that fall within the claimed genus but are not disclosed by the patent. *Id.* at 1374. Despite the minimal teachings in the specification of the ’717 patent outlined above, the claims purport to cover all structures (and iterations thereof)—including later-developed vectors containing mutated ITRs, which merited their own patent protection (*see, e.g.*, McCarty (2001); McCarty (2003); McCarty (2008); U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457)—that accomplish the “enhanced expression” function.

The ’717 patent also fails to disclose structural features common to members of the genus that are responsible for the claimed functions such that one of skill in the art could visualize or recognize the members of the claimed genus of rAAV vectors, as explained in detail below. “[F]unctionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus.” *AbbVie Deutschland GmbH & Co. KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014); *see also Juno*, 10 F.4th at 1337 (disclosure of two working embodiments “does not provide information sufficient to establish that a skilled artisan would understand how to identify the species of scFvs capable of binding to the limitless number of targets as the claims require.”).

For at least the reasons discussed herein, and outlined in more detail for specific claim limitations below, the Asserted Claims of the ’717 patent are invalid under 35 U.S.C. § 112, ¶ 1 for failing to satisfy the written description requirement.

a. Independent Claims 1 and 2

i. “a single-stranded heterologous nucleotide sequence comprising a coding region which forms intrastrand base pairs”

The purported scope of the claims of the ’717 patent is broad with respect to the limitations reciting “a single-stranded heterologous nucleotide sequence comprising a coding region which forms intrastrand base pairs,” as recited in independent claims 1 and 2,[7] relative to the limited examples and disclosure in the specification. More specifically, the specification fails to provide

[7] Independent claim 2 of the ’717 patent differs slightly in this particular limitation in that it says “a single-stranded heterologous nucleotide sequence comprising *the* coding region which forms intrastrand base pairs.” (Emphasis added.)

any specific details as to the structural features relating to the base pairing requirements set forth in the claims.

The claims of the ’717 patent purportedly encompass a vast array of rAAV formats. For example, the “heterologous nucleotide sequence” is expressly defined in the ’717 patent specification to purportedly encompass any “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.” *Id.* at 9:29-35. The coding region is expressly defined in the ’717 patent specification as “a ‘coding region’ of a heterologous sequence” and “is a sequence of contiguous nucleotides which gives rise in a host cell to a transcription and/or translation product.” *Id.* at 10:19-22. The ’717 patent specification further states that “[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides.” *Id.* at 10:33-37. Thus, the purported scope of the heterologous nucleotide sequences encompassed by independent claims 1 and 2 (and their dependent claims) is limitless.

In contrast to the broad purported scope of claims 1 and 2, the ’717 patent specification teaches only one purported working example of an rAAV vector comprising a nucleotide sequence comprising a coding region for green fluorescent protein (GFP). *See* Examples 1-3, 5-8, 10-12.[8] This is the sole exemplary heterologous sequence comprising a coding region provided in the

[8] The ’717 patent also teaches an example (Example 13) of an rAAV vector encoding a fusion protein of tumor necrosis factor receptor (TNFR) and an immunoglobulin constant region (Fc) produced “according to the Examples above.” ’717 patent at 37:61-65 (Example 13). However, the TNFR-Fc example appears to be prophetic and does not describe whether or how the vector encoding TNFR-Fc is designed to give rise to intrastrand base pairing. Example 5 describes an rAAV vector encoding human alkaline phosphatase and bacterial neomycin resistance gene used as a control, but it does not appear to possess intrastrand base pairing in the coding region and thus does not exemplify the claims. *Id.* at 32:13-18.

specification. Other than GFP, the specification does not provide any additional examples of other coding regions falling within the purported scope of the claims that possess the claimed functional elements (e.g., intrastrand base pairing in the coding region). Yet, the claims purport to cover an unlimited number of heterologous sequences of unlimited size and function (or no function at all) and coding regions of a variety of lengths from 5 to more than 500 nucleotides in length. *Id.* at 10:33-37. Given the substantial structural variation purportedly encompassed by the functionally-defined genus, the ’717 patent specification does not disclose a representative number of species that achieves the claimed result sufficient to support the claimed genus of all single-stranded heterologous nucleotide sequences comprising a coding region which forms intrastrand base pairs. Furthermore, there is no structural feature of the nucleotide sequence that would be common to members of the genus because the claims purport to cover any nucleotide sequence, and the specification does not describe any correlation between any nucleotide sequence structure and the functional requirements of the claimed genus.

Thus, claims 1 and 2 of the ’717 patent (and their dependent claims) lack written description support for “a single-stranded heterologous nucleotide sequence comprising a coding region which forms intrastrand base pairs” because a person of ordinary skill in the art would not reasonably believe that the ’717 patent inventor had possession of the claimed genus of any heterologous nucleotide sequence comprising a coding region which forms intrastrand base pairs.

ii. "wherein the rAAV vector comprises a single-stranded heterologous nucleotide sequence comprising a 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"

The '717 patent uses functional language to describe a desired result for the vectors used in the methods purportedly encompassed by independent claims 1 and 2 and claims dependent thereon. Specifically, claims 1 and 2 recite "wherein the rAAV vector comprises a single-stranded heterologous nucleotide sequence comprising a 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." *Id.* at claims 1 and 2 (emphasis added). The '717 patent states that "[i]t is understood that, for purposes of this invention, a recombinant viral vector containing a sequence or region that forms intrastrand base pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the degree of intrastrand base pairing." *Id.* at 10:59-64. The specification further teaches that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:64-67. The '717 patent describes that "[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." *Id.* at 10:33-37. In some embodiments, "the total amount of sequence that forms intrastrand base pairs (which could be in one or more regions) is greater than about 125 nucleotides, greater than about 250 nucleotides, greater than about 500 nucleotides, and/or greater than about 1,000 nucleotides." *Id.* at 15:10-15. Under the circumstances where a coding region is 5 nucleotides and the extent of

intrastrand base pairing is 25%, the amount of intrastrand base pairing could be as little as 1 or 2 nucleotides. As discussed above, the ’717 patent exemplifies a single rAAV vector that purportedly achieved intrastrand base pairing across the entire coding region. Applicant did not possess rAAVs having 25% intrastrand base pairing across a 5-nucleotide coding region, i.e., fewer than 2 nucleotides, and having enhanced expression. Nor did the applicant possess a heterologous sequence having any length other than the length of GFP and any other percentage of base pairing other than 100%. Indeed, even today, AAV vectors that are too short or too long cannot package and express efficiently. For example, “stuffer” sequences are sometimes used to lengthen AAV vectors and enhance expression in certain systems.

The ’717 patent attempts to claim methods that utilize every rAAV vector that would achieve the desired result. The specification states that an “[a]n ‘AAV inverted terminal repeat (ITR)’ sequence . . . is an approximately 145-nucleotide sequence that is present at both termini of the *native* single-stranded AAV genome.” ’717 patent at 11:13-16 (emphasis added). The specification also explains that *native* ITR sequences, i.e., from a native AAV2 genome, were used in the purported working examples. *Id.* at 16:5-7. Non-native ITR sequences were never tested or even constructed, according to the patent specification.

To the extent the ’717 patent claims are construed to encompass *non-native* ITR sequences, the ’717 patent claims are invalid for lack of written description, because the claimed genus of vectors comprising any modified, mutated, or non-native ITR is unsupported by the disclosure of the patent specification, which includes only a single purported working example wherein each ITR of the vector is native AAV ITR sequence from AAV2. As noted above, in determining whether the specification provides adequate written description support, products that post-date the patent’s priority date, including an accused infringing product, can be taken into consideration.

Amgen Inc. v. Sanofi, 872 F.3d at 1374-75. Here, to the extent the ’717 patent claims are construed to encompass non-native ITR sequences, the claims improperly purport to cover the use of all rAAV vector structures (and iterations thereof) (including later-developed structures like those described in McCarty (2001), McCarty (2003) and McCarty (2008) containing a mutated ITR that was not yet invented at the time of filing the ’717 patent, and which merited its own patent protection (U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457)) that accomplish the “enhanced expression” function.

Yet, the ’717 patent specification provides only one structure (a half-sized vector containing a particular heterologous gene wherein each ITR of the vector is native AAV ITR sequence) that purportedly accomplishes the claimed function of enhanced expression. The single purported working example compares expression from an rAAV vector encoding GFP which has “half-complexity” with expression of GFP from an rAAV vector that possesses no intrastrand base pairing. *See, e.g.*, *id.* at 37:24-28. The specification explains that a “half-complexity” vector is one that forms a “snapback” molecule and is double-stranded along most or all of its length. *Id.* at 15:27-35; *see also id.* at 7:65-8:5 (“rAAV vectors which contained two copies of [GFP] in opposite orientation, and were accordingly able to form a double-stranded molecule due to intrastrand base pairing, displayed significantly higher expression levels (as indicated by percentage of cells expressing reporter gene) in 293 and HeLa cells compared to another vector which was not able to form intrastrand base pairing of the GFP gene.”).

Thus, the single purported working example in the specification discloses an rAAV vector with 100% intrastrand base pairing in the rAAV vector whose expression is “enhanced” over an rAAV vector with no intrastrand base pairing. The ’717 patent inventor acknowledged as much during prosecution of a patent application in the family when arguing to overcome a rejection

under 35 U.S.C. § 112, ¶ 1 for lack of written description regarding the "enhanced expression" limitation. *See* GENZ_NOV_00002135 ("In fact, data in Example 8 indicated that the *entire* genome of such vectors [that have significantly enhanced expression of GFP] is base-paired") (emphasis added); *see also* GENZ_NOV_00002136 ("Example 8 shows an entire genome of an rAAV vector is base-paired").

This one purported working example does not amount to a disclosure of a representative number of species corresponding to the purported scope of the claimed methods that utilize a functionally-defined genus of rAAV vectors with enhanced expression. The specification does not provide any examples of enhanced expression with amounts of intrastrand base pairing less than 100% in the coding region or examples of enhanced expression over comparator vectors that possess at least some intrastrand pairing. Given that the purported scope of claims 1 and 2 and their dependent claims cover substantial variation within the genus of permissible intrastrand base pairing for both the first and second rAAV vectors in the claims, the specification does not disclose a representative number of species sufficient to support the claimed genus.

Nor was there any established correlation between vector base pairing structure and function (sufficient to enhance expression). This is abundantly clear from the lack of guidance provided by the '717 patent's incredibly broad (to the point of meaningless) disclosure regarding the level of intrastrand base pairing that can lead to enhanced expression. Indeed, as the '717 patent admits, this was a particularly unpredictable field. *See, e.g.*, '717 patent at 4:34-37 ("there can be difficulties in obtaining sufficient levels of expression of heterologous sequences from rAAV vectors and viruses containing such vectors"). Thus, significantly more disclosure was required for a person of ordinary skill in the art to conclude that the inventor possessed the full scope of the functionally defined genus recited in the claims.

For at least these reasons, claims 1 and 2 of the ’717 patent (and their dependent claims) lack written description support for “wherein the rAAV vector comprises a single-stranded heterologous nucleotide sequence comprising a 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” because a person of ordinary skill in the art would not reasonably believe that the ’717 patent inventor had possession of the vast genus required by the claimed methods.

iii. “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” and “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”

The purported scope of the claims of the ’717 patent is broad with respect to the limitations reciting a “method for introducing a polynucleotide into a cell,” as recited in independent claim 1, and a “method for expressing a polynucleotide coding region in a cell,” as recited in independent claim 2, relative to the limited examples and disclosure provided in the specification. More specifically, the specification fails to provide any definition of the term “cell,” but instead describes “[t]ypes of cells into which the polynucleotides of the invention can be introduced” as including, but not limited to “eucaryotic cells, procaryotic cells and Archaea. Eucaryotic cells include animal cells, plant cells, yeast cells and, in a preferred embodiment, mammalian cells, more preferably,

human cells, mammalian, including human, cells include cell lines as well as primary cells, such as primary foreskin fibroblasts." '717 patent at 26:54-61.

The claims of the '717 patent thus purport to encompass a broad genus of any cell type, including at least the genus of cells described in the specification, which includes Archaea, prokaryotic, and eukaryotic cells. '717 patent at 26:54-61. Thus, the purported scope of the cells encompassed by independent claims 1 and 2 (and their dependent claims) is limitless.

In contrast to the broad purported scope of claims 1 and 2, the '717 patent specification teaches only two purported working examples of cell types transduced with an rAAV vector: 293 cells, which are a human embryonic kidney cell line and HeLa cells (both mammalian, not prokaryotic or Archaea). *See id.* at 7:65-8:5; Examples 3, 5-10; Tables 1-3, 5. These are the sole exemplary cell types discussed in the specification. Other than these two mammalian cell types, the specification does not provide any examples of prokaryotic cells or Archaea that fall within the purported scope of the claims, or what conditions would allow uptake of the rAAV vector into such cell types or whether enhanced expression from of the coding region in an rAAV vector can be achieved in such cell types. Given the substantial variation purportedly encompassed by the genus, the '717 patent specification does not disclose a representative number of species that achieves the claimed result sufficient to support the claimed genus of all cell types. Furthermore, there is no structural feature of the cells that would be common to members of the genus because the claims purport to cover any cell type, and the specification does not describe any correlation between any structure and the functional requirements of the claimed genus of cells.

Thus, claims 1 and 2 of the '717 patent (and their dependent claims) lack written description support for "a cell" because a person of ordinary skill in the art would not reasonably believe that the '717 patent inventor had possession of the claimed genus of any cell type.

iv. "wherein the rAAV vector comprises one or more inverted terminal repeat (ITR) sequences flanking said heterologous sequence"

The purported scope of the claims of the '717 patent is broad with respect to the limitations reciting a "wherein the rAAV vector comprises one or more inverted terminal repeat (ITR) sequences flanking said heterologous sequence," as recited in independent claims 1 and 2, relative to the limited examples and disclosure provided in the specification. More specifically, claims 1 and 2 of the '717 patent (and their dependent claims) purport to encompass using an rAAV vector with only one ITR. The claims purport to encompass methods wherein the rAAV vector "comprises *one* or more inverted terminal repeat (ITR) sequence flanking said heterologous sequence." *Id.* at claims 1 and 2 (emphasis added).

In contrast, the purported working examples in the '717 patent specification describe use of a single half-size vector wherein each ITR of the vector (e.g., at both termini) is native AAV ITR sequence from AAV2. The '717 patent specification does not exemplify whether rAAV vectors of the invention with a single ITR can produce the "enhanced expression" result required by the claims. Indeed, post-filing date studies have shown that use of only a single ITR in the types of rAAV vectors claimed would be inoperable. Thus, claims 1 and 2 of the '717 patent (and their dependent claims) lack written description support for "wherein the rAAV vector comprises one or more inverted terminal repeat (ITR) sequences flanking said heterologous sequence" because a person of ordinary skill in the art would not reasonably believe that the '717 patent inventor had possession of, e.g., rAAV vectors having the claimed *one* ITR sequence and which also possess the recited functional property of enhanced expression.

b. Dependent Claims 3-8, 11-17, and 20

The dependent claims of the '717 patent merely recite additional features that provide no meaningful narrowing of independent claims 1 and 2, and the dependent claims therefore lack

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written description support for the same reasons set forth above for claims 1 and 2, as well as for the additional reasons discussed below.

i. Dependent Claims 3 and 12

Claim 3 depends from claim 1 and claim 12 depends from claim 2. These claims further recite 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 all or most of its length. Other than the size of the sequence complexity of the heterologous sequence, claims 3 and 12 do not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), or the number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. The '717 patent specification broadly states "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:64-67. Yet, the specification fails to provide any information as to where (if anywhere) in this exceptionally broad range intrastrand base pairing would be considered to be along "most" of the length of the heterologous nucleotide sequence and would accomplish the claimed function of enhanced expression. Thus, for at least the reasons explained herein and above for claims 1 and 2, a person of ordinary skill in the art would not reasonably have understood that the '717 patent inventor had possession of the genus of claims 3 and 12.

ii. Dependent Claims 4, 6, 13, and 15

Claim 4 depends from claim 3, claim 6 depends from claim 5, claim 13 depends from claim 12, and claim 15 depends from claim 14. These claims all recite wherein the double-stranded structure is formed within the cell. Claims 4, 6, 13, and 15 do not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), or the number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1, 3, 5, 12, and 14, a person of ordinary skill in the art would not reasonably have understood that the '717 patent inventor had possession of the genus of claims 4, 6, 13, and 15.

iii. Dependent Claims 5 and 14

Claim 5 depends from claim 1 and claim 14 depends from claim 2. These claims further recite wherein the coding region forms a double-stranded structure "along most or all of its length." Other than the vague description of the amount of intrastrand base pairing "along most or all of its length," claims 5 and 14 do not further limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type or length of heterologous sequence, or the number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. The '717 patent specification broadly states "the extent of intrastrand base pairing need not be

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100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:64-67. Yet, the specification fails to provide any information as to where (if anywhere) in this exceptionally broad range intrastrand base pairing would be considered to be along "most" of the length of the heterologous nucleotide sequence and would accomplish the claimed function of enhanced expression. Thus, for at least the reasons explained herein and above for claims 1 and 2, a person of ordinary skill in the art would not reasonably have understood that the '717 patent inventor had possession of the genus of claims 5 and 14.

iv. Dependent Claims 7 and 16

Claim 7 depends from claim 1 and claim 16 depends from claim 2. These claims further recite the rAAV vector, "comprises an ITR flanked on both sides by heterologous sequences." Other than describing the relative location of an ITR, claims 7 and 16 do not further limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, or amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Further, under Plaintiffs' proposed claim constructions, the '717 patent specification provides no meaningful limitation as to where the ITR should be located in the rAAV vector or what the sequence of the ITR should be, so long as it is flanked on both sides by heterologous sequences of indeterminate structure. Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the '717 patent inventor had possession of the genus of claim 7.

v. Dependent Claims 8 and 17

Claim 8 depends from claim 1 and claim 17 depends from claim 2. These claims further recite wherein the heterologous sequence encodes a protein of therapeutic interest. The patent specification does not define a "protein of therapeutic interest," and merely states broadly that "the terms 'therapeutic gene', 'target polynucleotide', 'transgene', 'gene of interest', 'heterologous sequence' and the like generally refer to a sequence or sequences to be transferred using a vector." *Id.* at 12:50-53. Thus, claims 8 and 17 read on an incredibly broad genus of structurally-undefined proteins that are instead defined entirely by their generic functional property of delivery using a vector. Moreover, claims 8 and 17 do not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), or the number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker, which is not described as being of therapeutic interest. Thus, for at least the reasons explained herein and above for claims 1 and 2, a person of ordinary skill in the art would not reasonably have understood that the '717 patent inventor had possession of the genus of claims 8 and 17.

vi. Dependent Claims 11 and 20

Claim 11 depends from claim 1 and claim 20 depends from claim 2. These claims further recite the cell is a mammalian cell. Claims 11 and 20 do not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length"), or the

number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, claims 11 and 20 purport to encompass an unknown and unknowable number of mammalian cells and methods of introducing a polynucleotide, and expressing a polynucleotide coding region, in such cells, including mammalian cell types and whether such mammalian cells and methods are in an *in vitro*, *in vivo*, laboratory testing, or clinical administration setting. Neither the claim nor specification provides any further detail as to what the mammalian cell is. As recited in the specification, the purported scope of the claims covers any mammalian cell type, including both mammalian cell lines and primary cells, as well as stem cells. *Id.* at 26:54-61; 28:42-44. This vector was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other mammalian cells (*see, e.g., id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any mammalian cell. Thus, for at least the reasons explained herein and above for claims 1 and 2, a person of ordinary skill in the art would not reasonably have understood that the '717 patent inventor had possession of the genus of claims 11 and 20.

2. Invalidity under 35 U.S.C. § 112, First Paragraph for Lack of Enablement

"To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *ALZA Corp. v. Andrx Pharms.*, LLC., 603 F.3d 935, 940 (Fed. Cir. 2010) (quoting *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997)). An essential question for an enablement analysis is "whether the scope of enablement of [a claim] is as broad as the scope of the claim."

Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212 (Fed. Cir. 1991). The applicant must disclose a range of embodiments that is adequate in relation to the breadth of the patent right being sought. *See, e.g.*, *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (finding scope of claims that encompassed any and all vaccines in any animal toward any RNA virus not enabled when only a single working example was provided).

The need to engage in "an iterative, trial-and-error process to practice the claimed invention," where the specification provides "only a starting point, a direction for further research," precludes a finding of enablement. *ALZA*, 603 F.3d at 941. Where the skilled artisan "would need to assay each of at least tens of thousands of candidates" and the specification offered "no guidance or predictions about particular substitutions" that would lead to other effective members, genus claims are not enabled based on undue experimentation. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385-86 (Fed. Cir. 2013). "[T]he enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those requirements, especially where predictability and guidance fall short. In particular, it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim." *Amgen Inc. v. Sanofi Aventisub LLC*, 987 F.3d 1080, 1086 (Fed. Cir. 2021). Thus, "[w]hile functional claim limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language." *Id.* at 1087; *see also id.* ("[T]he use of broad functional claim limitations raises the bar for enablement . . . .")

As discussed *supra*, the claims of the '717 patent are broadly defined by structural and functional elements. Determining which combination of structures in the claimed methods

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utilizing rAAV vectors would result in enhanced expression of a desired gene (i.e., by supporting increased base pairing) would require an iterative, trial-and-error process that would amount to undue experimentation, due to the vast genus of rAAV vectors purportedly encompassed by the methods claimed. Indeed, for example, the inventor states that the intrastrand complementarity "may be any of a number of sizes," therefore including an unlimited spectrum of sizes, without providing any supporting detail or information regarding which sizes will accomplish the claimed function beyond those having 100% complementarity. *See* '717 patent at 14:65-15:15. Further, during prosecution of a patent in this family, the inventor acknowledged that "[t]he specification teaches that intrastrand base pairing may be anywhere along the heterologous sequence, and may or may not be within a coding region of a heterologous sequence." GENZ_NOV_00002136. Again, this lack of specificity would require an iterative, trial-and-error process to determine which combination of structures in the claimed rAAV vectors would result in enhanced expression of a desired gene.

Undue experimentation is evaluated under the Wands factors, which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). An evaluation of the experimentation required under the *Wands* factors follows.

a. Independent Claims 1 and 2

i. Factors 1 and 2: Quantity of Experimentation Necessary and Amount of Direction or Guidance Presented

As discussed above, independent claims 1 and 2 of the '717 patent (and their dependent claims) comprise contacting any cell type (or any mammalian cell type in the case of claims 11

and 20) with an rAAV particle. The claims purport to encompass introducing a polynucleotide or expressing a polynucleotide coding region in any cell type. In contrast, the purported working examples in the ’717 patent specification describe contacting two immortalized human cell lines (HEK 293 cells and HeLa cells). *See, e.g.*, Examples 7 and 11 (using HeLa cell lines), Example 6 (using human 293 cells, a HEK cell line). Based on results with just two cell types (one of which the specification teaches is considered inefficient at expressing rAAV vectors, i.e., HeLa cells), the specification extrapolates broadly that “[c]ell types that were traditionally considered impermissive in the sense of inefficient expression (whether due to time course and/or levels of expression) of parvovirus vectors are now practical, useable, hosts.” *Id.* at 8:12-15. Further, as discussed above, the ’717 patent specification describes “[t]ypes of cells into which the polynucleotides of the invention can be introduced” as including, but not limited to “eucaryotic cells, procaryotic cells and Archaea.” ’717 patent at 26:54-56. However, post-filing date studies have shown that expression of the types of rAAV vectors claimed in a prokaryotic cell would be inoperable. Thus, the ’717 patent does not provide sufficient direction or guidance across the limitless scope of cell types in independent claims 1 and 2 and their dependent claims.

Independent claims 1 and 2 of the ’717 patent (and their dependent claims) further purport to encompass using an rAAV vector with only one ITR. The claims purport to encompass methods wherein the rAAV vector “comprises *one* or more inverted terminal repeat (ITR) sequence flanking said heterologous sequence.” *Id.* at claims 1 and 2 (emphasis added). In contrast, the purported working examples in the ’717 patent specification describe use of a single half-size vector wherein each ITR of the vector (e.g., at both termini) is native AAV ITR sequence from AAV2. The ’717 patent specification does not exemplify whether rAAV vectors of the invention with, e.g., a single ITR can produce the “enhanced expression” result required by the claims.

Indeed, post-filing date studies have shown that use of only a single ITR in the types of rAAV vectors claimed would be inoperable. Thus, the ’717 patent does not provide sufficient direction or guidance to enable the use of, e.g., a single ITR.

Independent claims 1 and 2 (and their dependent claims) further involve methods requiring a vast genus of rAAV vectors that must meet certain functional limitations. Determining which combination of structures in a specific vector would result in enhanced expression (i.e., by supporting increased intrastrand base pairing) would require an excessive amount of experimentation across all heterologous sequences and lengths to yield sufficient intrastrand base pairing and purportedly enhanced expression. Further, post-filing date studies have shown that small changes to the structure of rAAV vectors could significantly impact the functionality of the vectors. The ’717 patent does not provide sufficient direction or guidance across the broad purported scope of unlimited heterologous sequences and vector lengths purportedly encompassed by the genus of rAAV vectors in independent claims 1 and 2 and their dependent claims.

Independent claims 1 and 2 of the ’717 patent (and their dependent claims) present a vast array of rAAV formats. The claimed methods involve vectors using *any* serotype of rAAV particle, and *any* serotype of rAAV vector, which are not required to be derived from the same serotype. In contrast, the only serotype of rAAV particles used in the purported working example in the specification is rAAV serotype 2 particles. ’717 patent at 16:5-7. While the specification states that “it is fully expected that the same principles derived from analysis of AAV2 will be applicable to other AAV serotypes, since it is known that the various serotypes are quite closely related, both functionally and structurally, even at the genetic level,” (*id.* at 16:7-11), such a statement is merely expressing a hypothesis and invitation for further research by a person of ordinary skill in the art to use other AAV serotypes. Courts have found that claims were not enabled when the amount of

experimentation "would take a substantial amount of time and effort," and the "only ways for a person of ordinary skill to discover undisclosed claimed embodiments would be through either 'trial and error, by making changes to the disclosed antibodies and then screening those antibodies for the desired binding and blocking properties,' or else 'by discovering the antibodies de novo' according to a randomization-and-screening 'roadmap.'" *Amgen*, 987 F.3d at 1088 (citing *Amgen Inc. v. Sanofi*, No. 14-1317, 2019 WL 4058927, *11–*12 (D. Del. Aug. 28, 2019).

The claims purport to encompass an rAAV vector comprising *any* nucleotide sequence comprising a coding region. In contrast, the rAAV vector used in the purported working example only encodes green fluorescent protein. *Id.* at Fig. 5. Further, the claims purport to encompass a genus of rAAV vectors that set no limits on the amount of intrastrand base pairing in the coding region. Rather, the rAAV vector is defined functionally as possessing enhanced expression relative to a second rAAV vector that lacks an undefined amount of "sufficient" intrastrand base pairing to enhance expression. The patent states that the intrastrand complementarity "may be any of a number of sizes," therefore including an entirely unlimited spectrum of sizes, without providing any supporting detail or information regarding workable ranges. *See* '717 patent, 14:65–15:15. The only embodiment exemplified in the patent is described as a vector that is base paired "along most or all of its length." *Id.* at 15:27-35. No guidance is provided for any levels of base pairing less than 100% that can achieve the claimed enhanced expression.

Moreover, the '717 patent provides very little guidance as to how a person of ordinary skill in the art should determine whether enhanced expression is present. For example, the claims do not indicate when expression is to be assessed. In the Examples, an increased percentage of fluorescent cells, as measured at two different time points (48 or 72 hours) post-infection, is shown for cells infected with the 100% intrastrand base paired rAAV vector compared to a second vector

with no intrastrand base pairing. *Id.* at 32:45-33:57; 36:42-37:29. However, while some time presumably must pass for expression to reach a detectable level, it is possible that as time passes the expression may decrease. Conversely, it is possible that, as enough time passes, the control vector that "lacks sufficient intrastrand base pairing to enhance expression" may exhibit increased expression of a transgene so that it is not possible to determine a significant difference between expression levels of the vectors. The patent provides no guidance regarding how one skilled in the art would test for the claimed enhanced expression at either of these time points.

Moreover, it is evident from at least Figure 6F of the '717 patent, that the examples described in the specification used a lambda stuffer sequence in the control vector. The lambda stuffer was known to negatively impact expression. Thus, the examples described in the specification may have utilized a control that artificially suppressed expression due to the use of a lambda stuffer, thereby inflating the level of "enhanced expression" observed for the test vector. As a result, it is impossible for a person of ordinary skill in the art to determine, based on the examples provided in the specification, what characteristics of the rAAV vectors in the claimed methods, e.g., amount of intrastrand base pairing, would be required to enhance expression over a vector that "lacks sufficient intrastrand base pairing."

The '717 patent disclosure further provides little to no guidance regarding determining intrastrand base pairing that is "sufficient" to enhance expression or what it means to "lack[] sufficient intrastrand base pairing" to enhance expression of the heterologous sequence. With regard to the length of the requisite level of intrastrand base pairing, the specification teaches that a region of intrastrand complementarity can be anywhere from as little as 5 to greater than 1000 nucleotides. *Id.* at 10:33-37. The specification also states that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about *any* of the following: 25%, 40%, 50%,

60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:64-67 (emphasis added). Yet, the only purported working example discloses an rAAV vector with close to 100% intrastrand base pairing in the rAAV vector and whose expression is "enhanced" over an rAAV vector with no intrastrand base pairing. Moreover, it is likely the purported working example is inoperative, in whole or in part.

Further, to the extent the '717 patent claims are construed to encompass *non-native* ITR sequences, the '717 patent claims are invalid for lack of enablement, because experimentation across the full scope of rAAV vectors comprising any modified, mutated, or non-native ITR would require a substantial amount of time and effort, particularly in view of the limited disclosures in the patent specification (disclosing a single purported working example of an rAAV having intrastrand base pairing, *i.e.*, a half-size vector wherein each ITR of the vector is native AAV ITR sequence and comprising a heterologous nucleotide sequence containing a coding region for a detectable marker). Indeed, substantial time and effort was required to generate, experimentally test, and ascertain the functionality of later-developed vectors containing a mutated ITR, which subsequently received its own patent protection (*see, e.g.*, McCarty (2008); McCarty (2003); McCarty (2001); U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457).

Due to the lack of direction and very limited guidance presented in the specification of the '717 patent, the Asserted Claims of the '717 patent require a high degree of trial and error in determining which combination of structures in the patented technology would be conducive to supporting increased base pairing and thus enhanced expression of a desired gene compared to a vector lacking sufficient base pairing. In other words, undue experimentation will be required to practice the full scope of the Asserted Claims.

ii. Factor 3: Presence or Absence of Working Examples

With regard to functionally-defined genus claims in unpredictable arts, the Federal Circuit has "refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim." *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As discussed above, *see supra*, there is a single purported working example of an rAAV vector which shows "enhanced expression" in the '717 patent, and that example is limited to use of a half-size AAV GFP vector that has nearly 100% base pairing and shows enhanced expression compared to an rAAV vector that lacks any base pairing.[9] Further, as discussed, this vector was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other cells (*see, e.g., id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any host cell. Moreover, it is likely the purported working example is inoperative, in whole or in part. This single purported working example does not amount to a demonstration with reasonable specificity of how to make and use other potential embodiments across the full scope of the Asserted Claims.

iii. Factors 4-6: Nature of the Invention, State of the Prior Art, and Relative Skill of Those in the Art

The nature of the claimed invention is a method utilizing an rAAV vector with a heterologous sequence with a coding region that forms intrastrand base pairs sufficient to enhance

[9] As discussed *supra*, the TNFR-Fc example (Example 13) appears to be prophetic and does not describe any details regarding whether the vector encoding TNFR-Fc is designed to give rise to intrastrand base pairing. Similarly, Example 5 describes an rAAV vector encoding human alkaline phosphatase and bacterial neomycin resistance genes used as controls, but this vector does not appear to possess intrastrand base pairing in the coding region and thus do not exemplify the claims. *Id.* at 32:9-19.

expression of the sequence as compared to an rAAV vector which lacks sufficient intrastrand base pairing to enhance said expression. As the ’717 patent admits, the state of the art was such that the field was still in its early stages at the time of filing (1999). *See, e.g.*, ’717 patent at 1:29-37 (“Recombinant vectors based on parvovirus, such as adeno-associated virus (AAV), show promise for gene therapy. However, obtaining efficient, sufficient levels of expression of a transgene in various cell types has presented problems. Some cell types are impermissive in the sense that initiation of transcription or translation of the transgene is inefficient, with expression accordingly very slow to initiate, if it initiates at all.”). Thus, before the invention could be practiced, it would be necessary to make and screen each candidate rAAV vector for sufficient intrastrand base pairing in its heterologous sequence to enhance expression of said sequence. And although the level of skill in the art was relatively high at the time of filing (1999), skill alone cannot stand in for a total absence of guidance in the specification.

iv. Factor 7: Predictability or Unpredictability of the Art

As the ’717 patent specification admits, this was a particularly unpredictable field at the time of filing (1999). *See, e.g.*, ’717 patent at 4:34-37 (“there can be difficulties in obtaining sufficient levels of expression of heterologous sequences from rAAV vectors and viruses containing such vectors”). This unpredictability would have been compounded by the breadth of the claims, which read on the use of all heterologous sequences (e.g., RNA) and all vector lengths. In particular, as discussed above, the lower size limit of the vectors described in the ’717 patent would have been wholly inoperable. Further, minor changes to characteristics of the rAAV vector, including size, rAAV serotype, etc. could potentially result in significant, unpredictable changes to the level of intrastrand base pairing and expression of the heterologous sequence. Without testing, a person of ordinary skill in the art could not have predicted whether a given rAAV vector

within the vast genus of rAAV vectors claimed would contain sufficient intrastrand base pairing to enhance expression compared to an equally undefined second vector, let alone meet any of the other claim limitations.

v. Factor 8: Breadth of the Claims

Independent claims 1 and 2 of the ’717 patent (and their dependent claims) are extremely broad and contain several limitations that are unbounded and/or defined only by broad functional requirements, as explained at length above. *See supra* Sections V.B.1 and V.B.2.a.i. Given the breadth of disclosure, a person of ordinary skill in the art would require significant experimentation to devise a construct that meets the functional limitations in the claims of the ’717 patent, i.e., that has sufficient intrastrand base pairing such that expression of a heterologous sequence is enhanced relative to a construct that lacks sufficient intrastrand base pairing to enhance expression.

As discussed above, the specification merely invites the person of ordinary skill in the art to perform his or her own experimentation to determine the amount of intrastrand base pairing that would work to “enhance[] expression” for any given coding region and rAAV serotype in order to meet the limitations of the Asserted Claims. As a result, an undue amount of experimentation would be required for a person of ordinary skill in the art to make and use the alleged invention of the Asserted Claims of the ’717 patent.

b. Dependent Claims 3-8, 11-17, and 20

As explained above with respect to the lack of written description, the dependent claims of the ’717 patent further recite features that provide no meaningful limitation as to claim scope, as the dependent claims still purport to encompass a nearly limitless universe of nearly all types of serotype of AAV, gene of interest, amount of intrastrand base paring (which is functionally defined as “enhanc[ing]” expression), and, under Plaintiffs’ proposed claim constructions, provide no meaningful limits regarding the number, location, and sequence of ITR(s). For at least the same

reasons set forth in Sections V.B.1 and V.B.2.a, the asserted dependent claims are invalid for lack of enablement.

3. Invalidity under 35 U.S.C. § 112, Second Paragraph for Indefiniteness

Under 35 U.S.C. § 112, ¶ 2, a patent "is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig. Instruments, Inc.*, 572 U.S. 898, 901 (2014). A patent must be "precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them. Otherwise there would be a zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims." *Id.* at 909-910 (internal quotations and citations omitted).

i. "forms intrastrand base pairs such that expression of the coding region of [a] heterologous sequence is enhanced relative to a second rAAV vector that lacks sufficient intrastrand base pairing to enhance said expression"

Claims 1 and 2 of the '717 patent and their dependent claims require, among other things, an rAAV vector comprising a single-stranded heterologous nucleotide sequence comprising a coding region which "forms intrastrand base pairs such that expression of the coding region of [a] heterologous sequence is enhanced relative to a second rAAV vector that lacks sufficient intrastrand base pairing to enhance said expression." "Enhanced" in this context is indefinite, as the specification fails to explain (1) how much intrastrand base pairing is required to result in "enhanced" expression, (2) at what point in time the expression should be measured, and (3) how much expression amounts to "enhanced" expression. The specification only provides generalized statements regarding the required "enhanced" expression, but enhanced expression purportedly resulting from intrastrand base pairing is not expressly defined in the patent specification and

purportedly encompasses any enhancement, measured by any means, at any point in time relative to any other rAAV that has a different and undefined amount of intrastrand base pairing.

With regard to intrastrand base pairing, the ’717 specification fails to elaborate on what position or quantity of intrastrand base pairing will achieve the “enhanced” expression, making it impossible to know how one is potentially infringing. For example, the patent explains that “a recombinant viral vector containing a sequence or region that forms intrastrand base-pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the *degree* of intrastrand base pairing. *Id.* at 10:59-64 (emphasis added). The patent further explains that “the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%. 95%, 98%, 99%.” *Id.* at 10:64-67. The patent also explains that “[t]he region(s) of intrastrand complementarity . . . in the recombinant viral vector 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.” *Id.* at 14:51-59 (emphasis added). The patent further teaches 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.* at 14:65-67 (emphasis added). These sweeping statements do not put the public on notice of what the claimed invention is—i.e., how much intrastrand base pairing would be needed in specific vectors to arrive at enhanced expression.

Next, with regard to the temporal aspect of measuring expression, the ’717 patent specification does not define what time points should be used to measure such a rate. The single

purported working example (Example 6) which measures differences in rates of expression only conducts this measurement at 48 and 72 hours and only provides the rate of expression for the GFP expression in the half-sized vector, not the control vector. A person of ordinary skill in the art would know that expression levels will vary over time. Thus, a person of ordinary skill in the art could potentially infringe at one point in time, but not another.

With regard to how much expression amounts to "enhanced" expression, the patent again provides little guidance. The '717 specification teaches that intrastrand base-pairing contributes to increased levels and/or increased rate of heterologous sequence expression, *id.* at 7:61-64, and defines "expression" as follows:

"Expression" includes transcription and/or translation. Methods of detecting transcription, such as Northern analysis, and translation, such as Western analysis or ELISA, are well known in the art. These methods also permit measuring differing levels of transcription and/or translation, whether that difference is between or among different vectors, different times, different host cells, etc. *Id.* at 13:23-29.

Based on this definition, a person of ordinary skill in the art would not know whether "enhanced expression" relates to the rate of expression (e.g., the speed), or the level of expression (e.g., the amount). Further, from this definition, a person of ordinary skill in the art would be unable to determine whether to detect transcription, translation, or both, and what method or methods by which said expression should be assessed. The different measurement techniques disclosed in the '717 specification possess different sensitivity levels which could yield different results when measuring expression from the same rAAV vector. The Federal Circuit has held patent claims invalid for indefiniteness where a claim term may be determined by multiple methods, the testing results of which "will necessarily fall within or outside the claim scope

depending on the . . . method chosen." *Honeywell Intern. v. ITC*, 341 F.3d 1332, 1341 (Fed. Cir. 2003).

Moreover, the purported comparator against which expression levels are measured, i.e., a second rAAV vector that "lacks sufficient intrastrand base pairing," is not clearly defined in the specification. The single purported working example in the specification discloses an rAAV vector with close to 100% intrastrand base pairing in the rAAV vector and whose expression is "enhanced" over an rAAV vector with no intrastrand base pairing. Ultimately, the claim limitation is circular, whereby an undefined sufficiency of base pairing and expression in a first rAAV is relative to an undefined insufficiency of base pairing and expression in a second rAAV (whose insufficiency is relative to the first rAAV).

ii. "along most or all of its length"

Claims 3-6 and 12-15 of the '717 patent require, among other things, an rAAV vector comprising a single-stranded heterologous nucleotide sequence comprising a coding region wherein either the heterologous sequence or the coding region "forms a double-stranded structure along most or all of its length." Requiring constructs that form a double-stranded structure along most or all of the length of the heterologous sequence or coding region is indefinite, as the specification fails to explain the circumstances under, and characteristics by which, "most or all" of the heterologous sequence or coding region is double-stranded in order to accomplish the claimed function of enhanced expression.

The patent states that "a recombinant viral vector containing a sequence or region that forms intrastrand base-pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the degree of intrastrand base pairing." '717 patent at 10:60-64. Despite that a person of ordinary skill in the art would understand "most" to mean "more than

half," the patent provides no other guidance regarding the circumstances or characteristics of the claimed double-stranded structure, instead stating broadly 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.* at 14:65-67 (emphasis added). The patent broadly provides that "[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." *Id.* at 10:33-37. Further, the patent broadly states that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:64-67. The patent specification and claims provide no guidance as to what circumstances or characteristics of the "most or all" double-stranded structure are necessary or sufficient to accomplish the claimed function of enhanced expression, e.g., where and how much intrastrand base pairing must occur (ranging from 50-100% of 5 to 500+ nucleotides anywhere in the coding region or any number of nucleotides in the heterologous sequence) and whether or what conditions must be satisfied to enhance expression (e.g., type of cell, type of AAV, type of nucleotide, intracellular conditions, extracellular conditions, etc.).

These overbroad claims reciting forming a double-stranded structure along most or all of the length of a nucleotide sequence or coding region do not put the public on notice of what the claimed invention is, thus making it impossible to know whether one is potentially infringing. *See, e.g.*, *Nautilus*, 572 U.S. at 901.

iii. "conditions that allow"/"conditions which allow"

Claims 1, 3-8, and 11 of the '717 patent require, among other things, a method for introducing a polynucleotide into a cell comprising contacting the cell with a rAAV particle comprising an rAAV vector under "conditions that allow" uptake of the rAAV vector. Contacting

a cell with a rAAV particle comprising an rAAV vector under "conditions that allow" uptake of the rAAV vector is indefinite, as the specification fails to explain what these "conditions" should be , other than conditions that do not prevent such events from occurring.

The patent merely states that "[t]hese cells result from contact of the vector polynucleotide with a host cell using methods well-known in the art for introducing nucleic acids into cells under conditions which allow uptake of nucleic acid and nonhomologous insertion of exogenous nucleic acid into a genome." '717 patent at 17:48-52. The patent specification and claims provide no guidance as to what these conditions are that would allow uptake of the rAAV vector. These overbroad claims reciting "conditions that allow" uptake of the rAAV vector do not put the public on notice of what the claimed invention is—i.e., what the parameters of these "conditions" are, thus making it impossible to know whether one is potentially infringing. *See, e.g., Nautilus*, 572 U.S. at 901.

Claims 2, 12-17, and 20 of the '717 patent require, among other things, a method for expressing a polynucleotide coding region in a cell comprising subjecting the cell to "conditions which allow" expression of the coding region. Subjecting the cell to "conditions which allow" expression of the coding region is indefinite, as the specification fails to explain what these "conditions" should be.

The patent merely states that "[t]hese methods comprise subjecting the cell containing a recombinant viral vector, preferably a parvovirus vector such as an rAAV, to conditions which allow expression, whereby a coding region of the heterologous sequence of the recombinant viral vector is expressed." '717 patent at 26:32-36. The patent specification and claims provide no guidance as to what these conditions are that would allow expression of the coding region. These overbroad claims reciting "conditions which allow" expression of the coding region do not put the

public on notice of what the claimed invention is—i.e., what the parameters of these "conditions" are, thus making it impossible to know whether one is potentially infringing. *See, e.g., Nautilus*, 572 U.S. at 901.

For at least these reasons, the Asserted Claims of the '717 patent are invalid under 35 U.S.C. § 112 as indefinite.

VI. Invalidity Contentions As To The '888 Patent

A. The '888 Patent Claims Are Invalid for Anticipation and/or Obviousness

Each Asserted Claim of the '888 patent is invalid for anticipation and/or obviousness. In addition to the information set forth below, a chart identifying where specifically in each item of prior art each limitation of each Asserted Claim of the '888 patent is found is attached as Appendix C, which is incorporated herein. Pinpoint citations to material in the prior art are exemplary of the disclosures and teachings of the prior art. Those citations should not be construed as limiting the disclosure of any prior art or as reflecting the only section of a prior art reference disclosing a particular limitation or teaching.

1. Independent Claim 1

The '888 patent admits that by August 9, 1999, the use of rAAV virus particles "containing rAAV vectors" was well known. *See, e.g.*, '888 patent at 4:1-4 ("Both the rAAV vectors and rAAV virus particles containing rAAV vectors can be used to express various heterologous gene products in host cells by transformation or transduction respectively."). The '888 patent further admits that it was well-known that co-infection with a helper virus engendered safety concerns and identified methods known in the art to remove or inactive the helper virus. *See e.g.*, *id.* at 4:18-21 ("infection of the host cell with a helper virus may be undesirable because of safety concerns related to other properties of helper viruses and helper virus functions"); *id.* at 25:6-20 ("Optionally, rAAV virus

preparations can be further processed to enrich for rAAV particles, deplete helper virus particles, or otherwise render them suitable for administration to a subject. See Atkinson et al. for exemplary techniques (WO 99/11764). Purification techniques can include isopynic gradient centrifugation, and chromatographic techniques. Reduction of infectious helper virus activity can include inactivation by heat treatment or by pH treatment as is known in the art. Other processes can include concentration, filtration, diafiltration, or mixing with a suitable buffer or pharmaceutical excipient.”).

The ’888 patent admits that by August 9, 1999, it was well known that rAAV vectors can be “encapsulated into AAV virus particles to form recombinant adeno-associated viruses (rAAV).” *Id.* at 3:39-40. The ’888 patent further admits that by August 9, 1999, the use of an rAAV vector comprising a single-stranded heterologous nucleotide sequence was well-known. *See, e.g., id.* at 3:20-25 (“The native AAV genome has been used as the basis of vector systems for the delivery and expression of heterologous genes in host cells such as mammalian cells, such as for gene therapy.”) (*citing* Muzyczka (1992) *Curr. Top. Microbiol. Immunol.* 158:97-129; Carter, B. J. (1992) *Curr. Op. Biotechnol.* 3:535-539; and Flotte et al. (1995) *Gene Therapy* 2:357-362). The ’888 patent further admits that “[r]ecombinant AAV (rAAV) vectors, based on the native AAV genome, are generally produced by deletion of rep and/or cap sequences and [their] replacement by a heterologous sequence. Thus, rAAV vectors generally comprise a single-stranded DNA molecule comprising a heterologous gene sequence or sequences flanked by at least one AAV ITR, and typically by two AAV ITRs, one at each end.” ’888 patent at 3:26-32.

The ’888 patent further admits that by August 9, 1999, it was well-known that “efficient, productive packaging in an AAV virus particle is limited to vectors having approximately the size of an AAV genome (i.e., approximately 4.7 kb) or smaller” and that by August 9, 1999, those

skilled in the art had already used smaller rAAV genomes. *Id.* at 3:40-43; 46-54 (*citing* Dong et al. (1996) *Hum. Gene Therapy* 7:2101-2112 for teaching the use of "rAAV genomes having sizes between 2 kb and 6 kb"); *see also id.* at 9:55-56 ("The maximum size vector that can be packaged to yield an infectious viral particle is approximately 5.2 kb."); *id.* at 15:41-44 ("In the case of an rAAV vector of the invention, its length may be less than about. . . .5.5."). Indeed, by August 9, 1999, the use of rAAV vectors of approximately half size was well-known and described in numerous prior art references. *See, e.g.*, Hörster (1999); Muzyczka (1992); Hermens (1997); Dong (1996).

Hörster (1999) describes the use of "fusion constructs between the indicators luciferase and gfp and the HIV-1-directed antisense sequence AR6 or ribozyme Rz12." Hörster (1999) at 1232. Hörster (1999) describes 12 fusion constructs comprising single stranded heterologous nucleotide sequences. *Id.* Hörster (1999) discloses approximately half size rAAV vector fragments comprising heterologous sequences encoding luciferase, gfp, AR6, and/or Rz12 flanked by ITRs in Figures 1 and 3. *Id.* at 1232-33. Hörster (1999) describes these constructs as "shown to be packageable to form infectious particles." *Id.* at 1235. Hörster (1999) further describes producing the infectious particles using a system that "provides all necessary helper functions for rAAV particle formation by plasmid-coded genes thereby avoiding the use of infectious adenovirus." *Id.* at 1233.

Muzyczka (1992) describes the use of rAAV vectors "containing the *dl*3-94/neo genome (50% of wild type size)" and "the neomycin phosphotransferase gene." Muzyczka (1992) at 111-12. The *dl*3-94/neo genome (50% of wild type size, *i.e.*, the approximately half size vector) "were found to consist predominantly of particles that had the density of AAV particles containing a wild type complement of DNA. When the DNA in these particles was examined it was found to consist

of three kinds of molecules. The predominant DNA molecule was an inverted dimer of the *dl*3-94/neo genome. Such molecules occur as a natural consequence of the AAV DNA replication mechanism and have been described in studies of spontaneously occurring deletions or AAV defective interfering (DI) genomes." *Id.* at 112-13 (citations omitted). Muzyczka (1992) also describes in Figure 6 that "[h]uman cells are transfected with the AAV recombinant plasmid and a complementing plasmid which is defective for packaging but supplies the wild type AAV gene products. The cells are also infected with adenovirus (*Ad*) to supply helper function. The virus stock produced contains both adenovirus and the AAV recombinant virus. Adenovirus is inactivated by heat or removed by density gradient centrifugation." *Id.* at 112.

Hermens (1997) describes the generation of an rAAV virus with a vector "containing an expression cassette for B-50/GAP-43." Hermens (1997) at 153. Hermens describes the B-50/GAP-43 open reading frame (ORF) as "cloned into pcDNAI/Amp5.0 (Invitrogen). This resulted in pcDNAB-50 containing a CMV-B-50-A+ expression cassette. Subsequently, from a plasmid designated psub201 (a recombinant plasmid from which an infectious AAV genome can be excised Samulski, et al., 1987) the AAV-coding sequences are replaced by the CMV-B-50-A+ expression cassette (2.1 kb) of pcDNAB-50. This resulted in plasmid psub201B-50." *Id.* at 153. Hermens (1997) describes that "[s]ince AAV is heat stable the heating step results in the elimination of heat labile infectious adenovirus," or alternatively, inactivating the helper virus (Ad) by "[f]ollowing centrifugation at 1500 g for 20 min at 4°C to remove the cell debris, the supernatant was heated at 56°C for 30 min." *Id.*

Dong (1996) describes rAAV vectors "from 2 kb to 6 kb in size" that carry "a chloramphenicol acetyltransferase (CAT) reporter gene." Dong (1996) at 2101. Dong (1996) describes that these vectors "were packaged into AAV virions" during a "miniscale production of

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recombinant AAV (rAAV)." *Id.* at 2103-04. Dong (1996) further describes that "the adenovirus were heat-inactivated at 65°C for 30 min." *Id.* at 2103. Dong (1996) also describes that "on the Southern blot of virion DNA, only [the] sample from the 1.9-kb vector contained DNA that appeared twice as large as single stranded DNA on an alkaline gel (Fig. 5, lane 2, DS). When the vector DNAs were isolated from infected cells in the absence of adenovirus-mediated double-strand conversion, the majority of the 1.9-kb vectors were in double-stranded form, and none was observed in any of the larger vectors." *Id.* at 2107-08.

The '888 patent admits that by August 9, 1999, it was well-known that the AAV life cycle involves the generation of "a self-complementary double-stranded molecule that is covalently closed at one end" called "the replicative form (RF)." '888 patent at 2:15-18; *see also* Carter (1984) at 212 ("These molecules consist of complementary strands which are covalently joined at one terminus by a hairpin structure formed by virtue of the palindromic terminal sequence 126 nucleotides in length."). The '888 patent further admits that by August 9, 1999, it was well-known that "formation of the RF is required for transcription of viral proteins (or, in the case of recombinant AAV, the transcription of heterologous sequences such as a transgene) to occur, since cellular RNA polymerizing systems require a double-stranded template." '888 patent at 2:43-48; *see also* Carter (1984) at 219 ("Also, as shown in Fig. 2, the RF structure is the configuration that would be expected during replication of AAV DNA."). The '888 patent also admits that when a recombinant viral vector has a sequence complexity that is approximately one half its length, "a vector is able to form a 'snapback' molecule which is double stranded along most or all of its length, thus analogous to the RF produced during AAV infection." '888 patent at 15:16-19; *see also id.* at 18:32-35 ("Upon replication, the half-size genome is copied into a complementary DNA strand that is covalently attached to its template at one end (see FIGS. 1 and 3), forming a structure

that will 'snap back' into a hairpin duplex."); *id.* at 33:51-57 ("Alkaline gel analysis, shown in Fig. 7A, indicates that preparations of virus particles having vector genomes that were made from a half-size plasmid contain DNA molecules that have a single-stranded length that is the same as a native AAV genome (second lane from left). This is what would be expected if 'snap-back'-type RF molecules have been packaged in in these virus particles."); Carter (1984) at 216, 222 (indicating that DNA 1.41b, "which appeared to be mainly hairpin molecules," had a "mean molecular size estimated from gel electrophoresis of about 50% of genome length"). The '888 patent further admits that vectors of the alleged invention:

> [C]an be produced by constructing a parvovirus vector, such as an rAAV vector, that has a size approximately one-half of a native genome and allowing such a vector to replicate in a host cell. . . . Upon replication, the half-size genome is copied into a complementary DNA strand that is covalently attached to its template at one end (see FIGS. 1 and 3), forming a structure that will "snap back" into a hairpin duplex. . . . These recombinant parvovirus vectors comprise an ITR sequence between the heterologous sequences (i.e., an ITR sequence flanked on both sides by heterologous sequences)."

'888 patent at 18:26-44; *see also* Carter (1984) at 212 "Some variant genomes have a conformation similar to that of certain intracellular replicating forms of parvovirus DNA. These molecules consist of complementary strands which are covalently joined at one terminus by a hairpin structure formed by virtue of the [ITR]. These molecules at a neutral pH spontaneously renature with zero-order kinetics to form duplex structures."). As the '888 patent depicts in Figs. 1 and 3, "the heterologous sequence [generated from such half-sized vectors] forms base pairs essentially along its entire length, thus analogous to an AAV replicative form." '888 patent at 5:10-12.

Literature dated after August 9, 1999, e.g., McCarty (2008), supports the admissions of the '888 patent by disclosing that such self-complimentary rAAV vectors "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 dimeric inverted repeat

will be no larger than the normal AAV packaging capacity (~4,700 nucleotides)." McCarty (2008) at 1649. McCarty (2008) further recognizes that "[a]lthough this further restricts the transgene carrying capacity of an already small viral vector, it offers a substantial premium in the efficiency, and speed of onset, of transgene expression because dsDNA conversion is independent of host-cell DNA synthesis and vector concentration." *Id.* (*citing* McCarty (2001), Gene Ther 8:1248-54).

Thus, each of Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996) teach the approximately half size vector comprising a region which forms intrastrand base pairs such that expression of a coding region of a heterologous sequence is enhanced. *See e.g.*, Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996). Moreover, the prior art discloses rAAV preparations, essentially free of helper virus, comprising an rAAV particle comprising an rAAV genome. *See e.g.*, Hörster (1999), Muzyczka (1992), Hermens (1997), Dong (1996), Berns (1996), Carter (1996), Kaplitt (1995), Bartlett (1995), Xiao (1998), Ferrari (1996), Ferrari (1997), Samulski (1987), WO9911764 (1997), Phillips (1997), Welch (1998), Su (1996), Zolotukhin (1996), WO9732018 (1996), Mamounas (1995), WO9717458 (1995), Fisher (1996), WO9947691 (1999), and WO9528493 (1994). A person of ordinary skill in the art would have been motivated to combine such teachings with a reasonable expectation of success to meet the claim limitations of claim 1.

Accordingly, the disclosure in Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996) of rAAV virus preparation, essentially free of helper virus, comprising rAAV vector particles containing rAAV vectors comprising a heterologous sequence and having a length that is approximately a half size vector, inherently anticipate and/or render obvious (alone or in the combinations identified in Appendix C) claim 1 of the '888 patent because, as the '888 patent admits, such vectors necessarily and inevitably contain "a heterologous nucleotide sequence

comprising a coding region and one or more inverted terminal repeat (ITR) sequences flanking said heterologous sequence, wherein the total amount of unique sequence present in the heterologous sequence is about one-half of the heterologous sequence and wherein the heterologous sequence forms intrastrand base pairs along most of 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."

2. Dependent Claims 2, 4, and 6

The dependent claims of the '888 patent are additionally invalid over the prior art, at least based on the references and combinations set forth in Appendix C. As set forth in Appendix C, the prior art discloses, expressly or inherently, each and every limitation of the dependent claims, including the claimed features of the rAAV vector (claims 2 and 4) and a composition comprising the rAAV virus preparation and a pharmaceutically acceptable excipient (claim 6). A person of ordinary skill in the art would have been motivated to pursue the combinations listed in Appendix C with a reasonable expectation of success in achieving the asserted dependent claims. For example, as the '888 patent admits, "[r]ecombinant vectors based on parvovirus, such as adeno-associated virus (AAV), show promise for gene therapy." '888 patent at 1:34-35. The '888 patent also admits that the dependent claim limitations related to producing an rAAV particle with the rAAV vector were known in the art. *See e.g., id.* at 3:39-40 ("rAAV vectors can be encapsidated into AAV virus particles to form recombinant adeno-associated viruses (rAAV)."). The '888 patent also admits that the dependent claim limitations directed to rep function, cap function, and helper functions were well known in the art. *See e.g., id.* at 2:57-62 ("Helper functions involved in the replication of the [replicative form] can be provided by co-infection of AAV-infected cells with adenoviruses, herpesviruses or poxviruses. Carter (1990) supra. Alternatively, cells may contain integrated genes, viral or otherwise, that supply helper function."). The prior art listed in

Appendix C is directed to, *e.g.*, preparations and compositions of rAAV virus comprising rAAV vectors capable of forming intrastrand base pairs that enhance expression. A person of ordinary skill in the art, as of August 19, 1999, would have been familiar with this prior art and would have been motivated to combine these teachings, and the others set forth in Appendix C, with a reasonable expectation of success, thereby rendering obvious dependent claims 2, 4, and 6.

B. The '888 Patent Claims Are Invalid under 35 U.S.C. § 112

In addition, or in the alternative, Novartis contends that the Asserted Claims of the '888 patent do not satisfy one or more requirements of 35 U.S.C. § 112. Novartis identifies the below grounds upon which the Asserted Claims of the '888 patent are invalid based on lack of written description under 35 U.S.C. § 112, first paragraph, lack of enablement under 35 U.S.C. § 112, first paragraph, and indefiniteness under 35 U.S.C. § 112, second paragraph.

1. Invalidity under 35 U.S.C. § 112, First Paragraph for Inadequate Written Description

As discussed *supra*, a patent's specification must contain a written description of the claimed invention. 35 U.S.C. § 112, ¶ 1. The description must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*) (citations omitted). In other words, the specification must reasonably convey that the inventor had possession of the claimed subject matter as of the filing date. *Id.*

To satisfy the written description requirement for a claimed genus, a specification must describe the claimed invention in such a way that a person of ordinary skill in the art would understand that the entire genus that is being claimed has been invented, and not just a single species of the genus. *Carnegie Mellon Univ. v. Hoffman-La Roche, Inc.*, 541 F.3d 1115, 1124 (Fed. Cir. 2008). In particular, when attempting to claim a functionally-defined genus, "a sufficient

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description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.* at 1350 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)). "A vague functional description and an invitation for further research does not constitute written disclosure . . . ." *Id.* at 1356. And "if the art is unpredictable, then disclosure of more species is necessary to adequately show possession of the entire genus." *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1125 (Fed. Cir. 2004). While it is "not fatal" that members of a genus are not disclosed in a patent, the specification should provide other means of identifying which members of the genus would interact with other variable elements. *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330 (Fed. Cir. 2021).

The Asserted Claims of the '888 patent are invalid under 35 U.S.C. § 112, ¶ 1, because the claimed rAAV preparations require a genus of rAAV genomes that is neither supported by a representative number of species nor by a disclosure of structural features common to the members of the claimed genus responsible for the claimed functions that would allow a person of ordinary skill in the art to visualize or recognize the other members of the genus. As explained in detail below, the specification of the '888 patent does not reasonably convey to a person of ordinary skill in the art that the inventor had possession of the vast—nearly limitless—genus of rAAV genomes used in the Asserted Claims. The claims use structural and functional language in an attempt to claim a vast genus of genomes that achieve a particular result. Yet, the rAAV genomes claimed are not limited, for example, by serotype of AAV, gene of interest, or amount of intrastrand base paring (which is functionally defined as "enhanc[ing]" expression). Further, Plaintiffs dispute Defendants proposed claim constructions, which are consistent with the disclosures in the intrinsic

evidence and provide that each ITR of the claimed rAAV vectors is native AAV ITR sequence. By contrast, under Plaintiffs' proposed claim constructions, the claimed rAAV vectors are not limited, for example, by the number, location, and sequence of ITR(s). Rather, the Asserted Claims purport to define the rAAV genomes by functional properties, such as their ability to enhance expression of a heterologous sequence relative to vectors that lack sufficient intrastrand base pairing to enhance said expression. A person of ordinary skill in the art would have understood the purported scope of the claimed genus is exceedingly broad, unknown and unknowable, and consequently would require an expansive and random search for all of the different options of vectors that may or may not work.[10] *See Brenner v. Manson*, 383 U.S. 519, 536 (1966) ("a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

A "representative number of species" means that the species which are adequately described are representative of the entire genus. *Carnegie Mellon*, 541 F.3d at 1124. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. *Id.* For inventions in unpredictable arts, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. *Id.* The genus of rAAV genomes claimed in the '888 patent is not supported by a representative number of species. Despite the vast scope of the claimed genus, the '888 patent contains only minimal guidance and examples regarding what rAAV genomes would possess this function of enhanced expression. Indeed, the '888 patent provides just one

[10] Further, because the term "enhanced" as used in the Asserted Claims is indefinite (*infra*, Section VI.B.3.), a person of ordinary skill in the art would not be able to determine the purported scope of the claimed genus of vectors with reasonable certainty. Likewise, the term "lacks sufficient intrastrand base pairing" as used in the Asserted Claims is indefinite (*id.*), further highlighting that the purported scope of the claimed genus cannot be determined with reasonable certainty.

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exemplary structure (a half-sized vector containing a particular heterologous gene wherein each ITR of the vector is native AAV ITR sequence) that purportedly accomplishes the claimed function of enhanced expression. It also fails to inform a person of ordinary skill in the art about the amount of overall intrastrand base pairing (other than "along most or all of its length") necessary to achieve the required enhanced expression. More specifically, the specification fails to provide any specific details as to the structural features relating to the base pairing requirements set forth in the Asserted Claims. Yet subsequent research has shown that the location and amount of base pairing influences the amount of expression.

In determining whether the specification provides adequate written description support, products that post-date the patent's priority date, including an accused infringing product, can be taken into consideration. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374-75 (Fed. Cir. 2017). In particular, evidence showing that a claimed genus does not disclose a representative number of species may include post-filing evidence of species that fall within the claimed genus but are not disclosed by the patent. *Id.* at 1374. Despite the minimal teachings in the specification of the '888 patent outlined above, the claims purport to cover all structures (and iterations thereof)—including later-developed rAAV preparations with vectors containing mutated ITRs, which merited their own patent protection (*see, e.g.*, McCarty (2001); McCarty (2003); McCarty (2008); U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457)—that accomplish the "enhanced expression" function.

The '888 patent also fails to disclose structural features common to members of the genus that are responsible for the claimed functions such that one of skill in the art could visualize or recognize the members of the claimed genus of rAAV vectors, as explained in detail below. "[F]unctionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where

it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus." *AbbVie Deutschland GmbH & Co. KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014); *see also Juno*, 10 F.4th at 1337 (disclosure of two working embodiments "does not provide information sufficient to establish that a skilled artisan would understand how to identify the species of scFvs capable of binding to the limitless number of targets as the claims require.").

For at least the reasons discussed herein, and outlined in more detail for specific claim limitations below, the Asserted Claims of the '888 patent are invalid under 35 U.S.C. § 112, ¶ 1 for failing to satisfy the written description requirement.

a. Independent Claim 1

i. "a heterologous nucleotide sequence comprising a coding region. . . wherein the heterologous sequence forms intrastrand base pairs along most or all of its length"

The purported scope of the claims of the '888 patent is broad with respect to the limitations reciting "a heterologous nucleotide sequence comprising a coding region. . . wherein the heterologous sequence forms intrastrand base pairs along most or all of its length," as recited in independent claim 1, relative to the limited examples and disclosure in the specification. More specifically, the specification fails to provide detailed information as to these structural features, including with respect to the intrastrand base pairing requirements set forth in the claims.

The claims of the '888 patent purport to encompass a vast array of rAAV formats. For example, the "heterologous nucleotide sequence" is expressly defined in the '888 patent specification to purportedly encompass any "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." *Id.* at 9:20-26. The coding region is expressly

defined in the ’888 patent specification as “a ‘coding region’ of a heterologous sequence” and “is a sequence of contiguous nucleotides which gives rise in a host cell to a transcription and/or translation product.” *Id.* at 10:11-14. The ’888 patent specification states that “[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides.” *Id.* at 10:26-30. With respect to the limitation “the heterologous sequence forms intrastrand base pairs along most or all of its length,” the patent specification broadly states “the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%.” *Id.* at 10:56-60. Yet, the specification fails to provide any information as to where (if anywhere) in this exceptionally broad range intrastrand base pairing would be considered to be along “most” of the length of the heterologous nucleotide sequence and would accomplish the claimed function of enhanced expression. Thus, the purported scope of the heterologous nucleotide sequences encompassed by independent claim 1 (and its dependent claims) is limitless.

In contrast to the broad purported scope of claim 1, the ’888 patent specification teaches only one purported working example of an rAAV vector comprising a nucleotide sequence comprising a coding region for green fluorescent protein (GFP). *See* Examples 1-3, 5-8, 10-12.[11] This is the sole exemplary heterologous sequence comprising a coding region in the specification.

[11] The ’888 patent also teaches an example (Example 13) of an rAAV vector encoding a fusion protein of tumor necrosis factor receptor (TNFR) and an immunoglobulin constant region (Fc) produced “according to the Examples above.” ’888 patent at 37:8-12 (Example 13). However, the TNFR-Fc example appears to be prophetic and does not describe whether or how the vector encoding TNFR-Fc is designed to give rise to intrastrand base pairing. Example 5 describes an rAAV vector encoding human alkaline phosphatase and bacterial neomycin resistance gene used as a control, but it does not appear to possess intrastrand base pairing in the coding region and thus does not exemplify the claims. *Id.* at 31:48-52.

Other than GFP, the specification does not provide any additional examples of other coding regions falling within the purported scope of the claims that possess the claimed functional elements (e.g., intrastrand base pairing in the coding region). Yet, the claims purport to cover an unlimited number of heterologous sequences of unlimited size and function (or no function at all) and coding regions of a variety of lengths from 5 to more than 500 nucleotides in length. *Id.* at 10:26-30. Given the substantial structural variation purportedly encompassed by the functionally-defined genus, the ’888 patent specification does not disclose a representative number of species that achieves the claimed result sufficient to support the claimed genus of all single-stranded heterologous nucleotide sequences comprising a region which forms intrastrand base pairs. Furthermore, there is no structural feature of the nucleotide sequence that would be common to members of the genus because the claims purport to cover any nucleotide sequence, and the specification does not describe any correlation between any nucleotide sequence structure and the functional requirements of the claimed genus.

Thus, claim 1 of the ’888 patent lacks written description support for “a heterologous nucleotide sequence comprising a coding region. . . wherein the heterologous sequence forms intrastrand base pairs along most or all of its length” because a person of ordinary skill in the art would not reasonably believe that the ’888 patent inventor had possession of the claimed genus of any heterologous nucleotide sequence comprising a coding region wherein the heterologous sequence forms intrastrand base pairs along most or all of its length.

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ii. "a heterologous nucleotide sequence comprising a coding region…wherein the heterologous sequence forms intrastrand base pairs…such that expression of the coding region is enhanced relative to an rAAV vector that lacks sufficient intrastrand base pairing to enhance expression"

The '888 patent uses functional language to describe a desired result for the rAAV genome purportedly encompassed by independent claim 1 and claims dependent thereon. Specifically, claim 1 recites "a heterologous nucleotide sequence comprising a coding region…wherein the heterologous sequence forms intrastrand base pairs…such that *expression* of the coding region *is enhanced relative* to an rAAV vector that *lacks sufficient intrastrand base pairing to enhance* expression." *Id.* at claim 1 (emphasis added). The '888 patent states that "[i]t is understood that, for purposes of this invention, a recombinant viral vector containing a sequence or region that forms intrastrand base pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the degree of intrastrand base pairing." *Id.* at 10:52-56. The specification further teaches that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:56-60. The '888 patent describes that "[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." *Id.* at 10:26-30. In some embodiments, "the total amount of sequence that forms intrastrand base pairs (which could be in one or more regions) is greater than about 125 nucleotides, greater than about 250 nucleotides, greater than about 500 nucleotides, and/or greater than about 1,000 nucleotides." *Id.* at 14:62-67. Under the circumstances where a coding region is 5 nucleotides and the extent of intrastrand base pairing is 51%, the amount of intrastrand base pairing could be as little as 2 or 3 nucleotides. As discussed above, the '888 patent exemplifies a

single rAAV vector that purportedly achieved intrastrand base pairing across the entire coding region. Applicant did not possess rAAVs having 51% intrastrand base pairing across a 5-nucleotide coding region, i.e., fewer than 3 nucleotides, and having enhanced expression. Nor did the applicant possess any length of a heterologous nucleotide sequence other than the length of GFP and any other percentage of base pairing other than 100%. Indeed, even today, AAV vectors that are too short or too long cannot package and express efficiently. For example, "stuffer" sequences are sometimes used to lengthen AAV vectors and enhance expression in certain systems.

The '888 patent attempts to claim every rAAV preparation with an rAAV genome that would achieve the desired result. The specification states that an "[a]n 'AAV inverted terminal repeat (ITR)' sequence . . . is an approximately 145-nucleotide sequence that is present at both termini of the *native* single-stranded AAV genome." '888 patent at 11:5-8 (emphasis added). The specification also explains that *native* ITR sequences, i.e., from a native AAV2 genome, were used in the purported working examples. *Id.* at 15:56-58. Non-native ITR sequences were never tested or even constructed, according to the patent specification.

To the extent the '888 patent claims are construed to encompass *non-native* ITR sequences, the '888 patent claims are invalid for lack of written description, because the claimed genus of vectors comprising any modified, mutated, or non-native ITR is unsupported by the disclosure of the patent specification, which includes only a single purported working example wherein each ITR of the vector is native AAV ITR sequence from AAV2. As noted above, in determining whether the specification provides adequate written description support, products that post-date the patent's priority date, including an accused infringing product, can be taken into consideration. *Amgen Inc. v. Sanofi*, 872 F.3d at 1374-75. Here, to the extent the '888 patent claims are construed

to encompass non-native ITR sequences, the claims improperly purport to cover all structures (and iterations thereof) (including later-developed structures like those described in McCarty (2001), McCarty (2003) and McCarty (2008) containing a mutated ITR that was not yet invented at the time of filing the ’888 patent, and which merited its own patent protection (U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457)) that accomplish the “enhanced expression” function.

Yet, the ’888 patent specification provides only one structure (a half-sized vector containing a particular heterologous gene wherein each ITR of the vector is native AAV ITR sequence) that purportedly accomplishes the claimed function of enhanced expression. The single purported working example compares expression from an rAAV vector encoding GFP which has “half-complexity” with expression of GFP from an rAAV vector that possesses no intrastrand base pairing. *See, e.g., id.* at 36:38-42. The specification explains that a “half-complexity” vector is one that forms a “snapback” molecule and is double-stranded along most or all of its length. *Id.* at 15:12-20; *see also id.* at 7:60-67 (“rAAV vectors which contained two copies of [GFP] in opposite orientation, and were accordingly able to form a double-stranded molecule due to intrastrand base pairing, displayed significantly higher expression levels (as indicated by percentage of cells expressing reporter gene) in 293 and HeLa cells compared to another vector which was not able to form intrastrand base pairing of the GFP gene.”).

Thus, the single purported working example in the specification discloses an rAAV vector with 100% intrastrand base pairing in the rAAV vector whose expression is “enhanced” over an rAAV vector with no intrastrand base pairing. The ’888 patent inventor acknowledged as much during prosecution of a patent application in the family when arguing to overcome a rejection under 35 U.S.C. § 112, ¶ 1 for lack of written description regarding the “enhanced expression” limitation. *See* GENZ_NOV_00002135 (“In fact, data in Example 8 indicated that the *entire*

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genome of such vectors [that have significantly enhanced expression of GFP] is base-paired") (emphasis added); *see also* GENZ_NOV_00002136 ("Example 8 shows an entire genome of a rAAV vector is base-paired").

This one purported working example does not amount to a disclosure of a representative number of species corresponding to the purported scope of the claimed functional genus of rAAV vectors with enhanced expression. The specification does not provide any examples of enhanced expression with amounts of intrastrand base pairing less than 100% in the coding region or examples of enhanced expression over comparator vectors that possess at least some intrastrand pairing. Given that the purported scope of claim 1 and its dependent claims cover substantial variation within the genus of permissible intrastrand base pairing for both the first rAAV genome and comparator rAAV vector in the claim, the specification does not disclose a representative number of species sufficient to support the claimed genus.

Nor was there any established correlation between vector base pairing structure and function (sufficient to enhance expression). This is abundantly clear from the lack of guidance provided by the '888 patent's incredibly broad (to the point of meaningless) disclosure regarding the level of intrastrand base pairing that can lead to enhanced expression. Indeed, as the '888 patent admits, this was a particularly unpredictable field. *See, e.g.*, '888 patent at 4:37-40 ("there can be difficulties in obtaining sufficient levels of expression of heterologous sequences from rAAV vectors and viruses containing such vectors"). Thus, significantly more disclosure was required for a person of ordinary skill in the art to conclude that the inventor possessed the full scope of the functionally defined genus recited in the claims.

For at least these reasons, claim 1 of the '888 patent (and its dependent claims) lacks written description support for "a heterologous nucleotide sequence comprising a coding region…wherein

the heterologous sequence forms intrastrand base pairs…such that expression of the coding region is enhanced relative to an rAAV vector that lacks sufficient intrastrand base pairing to enhance expression" because a person of ordinary skill in the art would not reasonably believe that the '888 patent inventor had possession of the claimed genus.

iii. "wherein the rAAV genome comprises a heterologous nucleotide sequence comprising…one or more inverted terminal repeat (ITR) sequences flanking said heterologous sequence"

The purported scope of the claims of the '888 patent is broad with respect to the limitations reciting a "wherein the rAAV genome comprises a heterologous nucleotide sequence comprising . . . one or more inverted terminal repeat (ITR) sequences flanking said heterologous sequence," as recited in independent claim 1, relative to the limited examples and disclosure provided in the specification. More specifically, claim 1 of the '888 patent (and its dependent claims) purportedly encompasses using an rAAV vector with only one ITR. The claims purport to encompass methods wherein the rAAV genome comprises "*one* or more inverted terminal repeat (ITR) sequence flanking said heterologous sequence." *Id.* at claim 1 (emphasis added).

In contrast, the purported working examples in the '888 patent specification describe use of a single half-size vector wherein each ITR of the vector (e.g., at both termini) is native AAV ITR sequence from AAV2. The '888 patent specification does not exemplify whether rAAV vectors of the invention with a single ITR can produce the "enhanced expression" result required by the claims. Indeed, post-filing date studies have shown that use of only a single ITR in the types of rAAV vectors claimed would be inoperable. Thus, claim 1 of the '888 patent (and its dependent claims) lacks written description support for "wherein the rAAV genome comprises a heterologous nucleotide sequence comprising…one or more inverted terminal repeat (ITR) sequences flanking said heterologous sequence" because a person of ordinary skill in the art would not reasonably

believe that the ’888 patent inventor had possession of, e.g., rAAV particles having the claimed *one* ITR sequence and which also possess the recited functional property of enhanced expression.

b. Dependent Claims 2, 4, and 6

The dependent claims of the ’888 patent merely recite additional features that provide no meaningful narrowing of independent claim 1, and the dependent claims therefore lack written description for the same reasons set forth above for claim 1, as well as for the additional reasons discussed below.

i. Dependent Claim 2

Claim 2 depends from claim 1 and further recites the heterologous sequence encodes a protein or an RNA of therapeutic interest. The patent specification does not define a “protein or an RNA of therapeutic interest,” and merely states broadly that “the terms ‘therapeutic gene’, ‘target polynucleotide’, ‘transgene’, ‘gene of interest’, ‘heterologous sequence’ and the like generally refer to a sequence or sequences to be transferred using a vector.” *Id.* at 12:38-41. Thus, claim 2 reads on an incredibly broad genus of structurally-defined proteins or RNAs that are instead defined entirely by their generic functional property of delivery using a vector. Moreover, claim 2 does not meaningfully limit any of the structural or functional components described above for the rAAV preparation itself, the genus of rAAV genomes of which is not limited by any serotype of AAV, gene of interest (broadly claimed as “a protein or an RNA of therapeutic interest”), type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as “along all or most of its length” and functionally defined as “enhanced expression”), or the number, location, or sequence of ITRs (under Plaintiffs’ proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a non-therapeutic detectable marker, which is not described as being of therapeutic interest. Thus, for at least the

reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the ’888 patent inventor had possession of the genus of claim 2.

ii. Dependent Claim 4

Claim 4 depends from claim 2 and further recites the rAAV virus preparation, wherein the heterologous sequence is a polynucleotide either (i) encoding a protein useful in gene therapy to relieve deficiencies caused by missing, defective, or sub-optimal levels of a structural protein or enzyme, (ii) transcribed into an anti-sense molecule, (iii) transcribed into a decoy that binds a transcription or translation factor, (iv) encodes a cellular modulator, (v) can make a recipient cell susceptible to a specific drug, (vi) for cancer therapy, or (vii) encodes an antigen or antibody. The patent specification does not define these broad categories of polynucleotides and merely states broadly that “Such polynucleotides include, but are not limited to: (i) polynucleotides encoding proteins useful in other forms of gene therapy to relieve deficiencies caused by missing, defective or sub-optimal levels of a structural protein or enzyme; (ii) polynucleotides that are transcribed into anti-sense molecules; (iii) polynucleotides that are transcribed into decoys that bind transcription or translation factors; (iv) polynucleotides that encode cellular modulators such as cytokines; (v) polynucleotides that can make recipient cells susceptible to specific drugs, such as the herpes virus thymidine kinase gene; (vi) polynucleotides for cancer therapy, such as ElA tumor suppressor genes or p53 tumor suppressor genes for the treatment of various cancers and (vii) polynucleotides that encode antigens or antibodies.” *Id.* at 12:48-61. Thus, claim 4 reads on an incredibly broad genus of structurally-undefined polynucleotides that are instead defined entirely by their generic functional properties outlined above. These categories of polynucleotides are not only incredibly broad and provide no practical limits on the heterologous sequence, but they are also not exemplified in the patent specification. Moreover, claim 4 does not meaningfully limit any of the structural or functional components described above for the rAAV virus preparation

itself, the rAAV genome genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length" and functionally defined as "enhanced expression"), or the number, location, or sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a non-therapeutic detectable marker. Thus, for at least the reasons explained herein and above for claims 1 and 2, a person of ordinary skill in the art would not reasonably have understood that the '888 patent inventor had possession of the genus of claim 4.

iii. Dependent Claim 6

Claim 6 depends from any one of claims 1-5 and further recites composition comprising the rAAV virus preparation and a pharmaceutically acceptable excipient. The patent specification broadly provides that a pharmaceutically acceptable excipient can be nearly any substance "includ[ing] but [] not limited to stabilizing agents, wetting and emulsifying agents, salts for varying osmolarity, encapsulating agents, and buffers" and can be supplied in nearly any manner, including "liquid solutions or suspension, as emulsions, or as solid forms suitable for dissolution or suspension in liquid prior to use" *Id.* at 16:54-63. Thus, claim 6 reads on an effectively limitless number of pharmaceutically acceptable excipients. Moreover, claim 6 does not meaningfully limit any of the structural or functional components described above for the rAAV virus preparation itself, the rAAV genome genus of which is not limited by any serotype of AAV, gene of interest, type or length of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along all or most of its length" and functionally defined as "enhanced expression"), or the number, location, and sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of

a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1, 2, and 4, a person of ordinary skill in the art would not reasonably have understood that the ’888 patent inventor had possession of the genus of claim 6.

2. Invalidity under 35 U.S.C. § 112, First Paragraph for Lack of Enablement

“To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.” *ALZA Corp. v. Andrx Pharms.*, LLC., 603 F.3d 935, 940 (Fed. Cir. 2010) (quoting *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997)). An essential question for an enablement analysis is “whether the scope of enablement of [a claim] is as broad as the scope of the claim.” *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212 (Fed. Cir. 1991). The applicant must disclose a range of embodiments that is adequate in relation to the breadth of the patent right being sought. *See, e.g.*, *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (finding scope of claims that encompassed any and all vaccines in any animal toward any RNA virus not enabled when only a single working example was provided).

The need to engage in “an iterative, trial-and-error process to practice the claimed invention,” where the specification provides “only a starting point, a direction for further research,” precludes a finding of enablement. *ALZA*, 603 F.3d at 941. Where the skilled artisan “would need to assay each of at least tens of thousands of candidates” and the specification offered “no guidance or predictions about particular substitutions” that would lead to other effective members, genus claims are not enabled based on undue experimentation. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385-86 (Fed. Cir. 2013). “[T]he enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those

requirements, especially where predictability and guidance fall short. In particular, it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim." *Amgen Inc. v. Sanofi Aventisub LLC*, 987 F.3d 1080, 1086 (Fed. Cir. 2021). Thus, "[w]hile functional claim limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language." *Id.* at 1087; *see also id.* ("[T]he use of broad functional claim limitations raises the bar for enablement . . . .")

As discussed *supra*, the claims of the '888 patent are broadly defined by structural and functional elements. Determining which combination of structures in the claimed rAAV preparations comprising rAAV genomes would result in enhanced expression of a desired gene (i.e., by supporting increased base pairing) would require an iterative, trial-and-error process that would amount to undue experimentation, due to the vast genus of rAAV genomes claimed. Indeed, for example, the inventor states that the intrastrand complementarity "may be any of a number of sizes," therefore including an unlimited spectrum of sizes, without providing any supporting detail or information regarding which sizes will accomplish the claimed function beyond those having 100% complementarity. *See* '888 patent at 14:51-67. Further, during prosecution of a patent application in this family, the inventor acknowledged that "[t]he specification teaches that intrastrand base pairing may be anywhere along the heterologous sequence, and may or may not be within a coding region of a heterologous sequence." GENZ_NOV_00002136. Again, this lack of specificity would require an iterative, trial-and-error process to determine which combination of structures in the claimed rAAV vectors would result in enhanced expression of a desired gene.

Undue experimentation is evaluated under the Wands factors, which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). An evaluation of the experimentation required under the *Wands* factors follows.

a. Independent Claim 1

i. Factors 1 and 2: Quantity of Experimentation Necessary and Amount of Direction or Guidance Presented

As discussed above, independent claim 1 of the ’888 patent (and its dependent claims) involves a vast genus of rAAV genomes that must meet certain functional limitations. Determining which combination of structures in a specific rAAV genome would result in enhanced expression (i.e., by supporting increased intrastrand base pairing) would require an excessive amount of experimentation across all heterologous sequences and lengths to yield sufficient intrastrand base pairing and purportedly enhanced expression. Further, post-filing date studies have shown that small changes to the structure of rAAV genomes could significantly impact the functionality of the rAAV virus preparations. The ’888 patent does not provide sufficient direction or guidance across the broad purported scope of unlimited heterologous sequences and vector lengths purportedly encompassed by the genus of rAAV genomes in independent claim 1 and its dependent claims.

Independent claim 1 of the ’888 patent (and its dependent claims) purportedly encompasses a vast array of rAAV formats. The claimed preparations contain *any* serotype of rAAV particle, and *any* serotype of rAAV vector (or rAAV genome), which are not required to be derived from the same serotype. In contrast, the only serotype of rAAV particles used in the purported working

Novartis Gene Therapies, Inc. et al. v. Genzyme Corporation
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example in the specification is rAAV serotype 2 particles. ’888 patent at 15:56-58. While the specification states that “it is fully expected that the same principles derived from analysis of AAV2 will be applicable to other AAV serotypes, since it is known that the various serotypes are quite closely related, both functionally and structurally, even at the genetic level,” (*id.* at 15:58-62), such a statement is merely expressing a hypothesis and invitation for further research by a person of ordinary skill in the art to use other AAV serotypes. Courts have found that claims were not enabled when the amount of experimentation “would take a substantial amount of time and effort,” and the “only ways for a person of ordinary skill to discover undisclosed claimed embodiments would be through either ‘trial and error, by making changes to the disclosed antibodies and then screening those antibodies for the desired binding and blocking properties,’ or else ‘by discovering the antibodies de novo’ according to a randomization-and-screening ‘roadmap.’” *Amgen*, 987 F.3d at 1088 (citing *Amgen Inc. v. Sanofi*, No. 14-1317, 2019 WL 4058927, *11–*12 (D. Del. Aug. 28, 2019).

The claims purport to encompass an rAAV preparation comprising *any* nucleotide sequence comprising a coding region. In contrast, the rAAV vector used in the purported working example only encodes green fluorescent protein. *Id.* at Fig. 5. Further, the claims purport to encompass a genus of rAAV genomes that only limits the amount of intrastrand base pairing vaguely to “along most or all of its length.” The rAAV vector is defined functionally as possessing enhanced expression relative to an rAAV vector that lacks an undefined amount of “sufficient” intrastrand base pairing to enhance expression. The patent states that the intrastrand complementary “may be any of a number of sizes,” therefore including an entirely unlimited spectrum of sizes, without providing any supporting detail or information regarding workable ranges. *See* ’888 patent at 14:51-67. With respect to the limitation “the heterologous sequence

forms intrastrand base pairs along most or all of its length," the patent specification broadly states "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:56-60. Yet, the specification fails to provide any information as to where (if anywhere) in this exceptionally broad range intrastrand base pairing would be considered to be along "most" of the length of the heterologous nucleotide sequence and would accomplish the claimed function of enhanced expression. No guidance is provided for any levels of base pairing less than 100% that can achieve the claimed enhanced expression.

Independent claim 1 of the '888 patent (and its dependent claims) further purportedly encompasses using an rAAV genome with only one ITR. The claims purport to encompass preparations wherein the rAAV genome "comprises a heterologous nucleotide sequence comprising…*one* or more inverted terminal repeat (ITR) sequences flanking said heterologous sequence." *Id.* at claim 1 (emphasis added). In contrast, the purported working examples in the '888 patent specification describe use of a single half-size vector wherein each ITR of the vector (e.g., at both termini) is native AAV ITR sequence from AAV2. The '888 patent specification does not exemplify whether rAAV genomes of the invention with, e.g., a single ITR can produce the "enhanced expression" result required by the claims. Indeed, post-filing date studies have shown that use of only a single ITR in the types of rAAV virus preparations claimed would be inoperable. Thus, the '888 patent does not provide sufficient direction or guidance to enable the use of, e.g., a single ITR.

Moreover, the '888 patent provides very little guidance as to how a person of ordinary skill in the art should determine whether enhanced expression is present. For example, the claims do not indicate when expression is to be assessed. In the Examples, an increased percentage of

fluorescent cells, as measured at two different time points (48 or 72 hours) post-infection, is shown for cells infected with the 100% intrastrand base paired rAAV vector compared to a second vector with no intrastrand base pairing. *Id.* at 32:7-33:17; 35:58-36:43. However, while some time presumably must pass for expression to reach a detectable level, it is possible that as time passes the expression may decrease. Conversely, it is possible that, as enough time passes, the control vector that "lacks sufficient intrastrand base pairing to enhance expression" may exhibit increased expression of a transgene so that it is not possible to determine a significant difference between expression levels of the vectors. The patent provides no guidance regarding how one skilled in the art would test for the claimed enhanced expression at either of these time points.

Moreover, it is evident from at least Figure 6F of the '888 patent, that the examples described in the specification used a lambda stuffer sequence in the control vector. The lambda stuffer was known to negatively impact expression. Thus, the examples described in the specification may have utilized a control that artificially suppressed expression due to the use of a lambda stuffer, thereby inflating the level of "enhanced expression" observed for the test vector. As a result, it is impossible for a person of ordinary skill in the art to determine, based on the examples provided in the specification, what characteristics of the claimed rAAV vectors (or rAAV genomes), e.g., amount of intrastrand base pairing, would be required to enhance expression over a vector that "lacks sufficient intrastrand base pairing."

The '888 patent disclosure further provides little to no guidance regarding determining intrastrand base pairing that is "sufficient" to enhance expression or what it means to "lack[] sufficient intrastrand base pairing" to enhance expression of the heterologous sequence. With regard to the length of the requisite level of intrastrand base pairing, the specification teaches that a region of intrastrand complementarity can be anywhere from as little as 5 to greater than 1000

nucleotides. *Id.* at 10:26:30. The specification also states that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about *any* of the following: 25%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:56-60 (emphasis added). Yet, the only purported working example discloses an rAAV vector with close to 100% intrastrand base pairing in the rAAV vector and whose expression is "enhanced" over an rAAV vector with no intrastrand base pairing. Moreover, it is likely the purported working example is inoperative, in whole or in part.

Further, to the extent the '888 patent claims are construed to encompass *non-native* ITR sequences, the '888 patent claims are invalid for lack of enablement, because experimentation across the full scope of rAAV vectors comprising any modified, mutated, or non-native ITR would require a substantial amount of time and effort, particularly in view of the limited disclosures in the patent specification (disclosing a single purported working example of an rAAV having intrastrand base pairing, *i.e.*, a half-size vector wherein each ITR of the vector is native AAV ITR sequence and comprising a heterologous nucleotide sequence containing a coding region for a detectable marker). Indeed, substantial time and effort was required to generate, experimentally test, and ascertain the functionality of later-developed vectors containing a mutated ITR, which subsequently received its own patent protection (*see, e.g.*, McCarty (2008); McCarty (2003); McCarty (2001); U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457).

Due to the lack of direction and very limited guidance presented in the specification of the '888 patent, the Asserted Claims of the '888 patent require a high degree of trial and error in determining which combination of structures in the patented technology would be conducive to supporting increased base pairing and thus enhanced expression of a desired gene compared to a

vector lacking sufficient base pairing. In other words, undue experimentation will be required to practice the full scope of the Asserted Claims.

ii. Factor 3: Presence or Absence of Working Examples

With regard to functionally-defined genus claims in unpredictable arts, the Federal Circuit has "refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim." *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As discussed above, *see supra*, there is a single purported working example of an rAAV vector which shows "enhanced expression" in the '888 patent, and that example is limited to use of a half-size AAV GFP vector that has nearly 100% base pairing and shows enhanced expression compared to an rAAV vector that lacks any base pairing.[12] Moreover, it is likely the purported working example is inoperative, in whole or in part. This single purported working example does not amount to a demonstration with reasonable specificity of how to make and use other potential embodiments across the full scope of the Asserted Claims.

iii. Factors 4-6: Nature of the Invention, State of the Prior Art, and Relative Skill of Those in the Art

The nature of the claimed invention is an rAAV viral preparation comprising an rAAV genome with a heterologous sequence with a coding region that forms intrastrand base pairs sufficient to enhance expression of the sequence as compared to an rAAV vector which lacks

[12] As discussed *supra*, the TNFR-Fc example (Example 13) appears to be prophetic and does not describe any details regarding whether the vector encoding TNFR-Fc is designed to give rise to intrastrand base pairing. Similarly, Example 5 describes an rAAV vector encoding human alkaline phosphatase and bacterial neomycin resistance genes used as controls, but this vector does not appear to possess intrastrand base pairing in the coding region and thus do not exemplify the claims. *Id.* at 31:48-52.

sufficient intrastrand base pairing to enhance said expression. As the ’888 patent admits, the state of the art was such that the field was still in its early stages at the time of filing (1999). *See, e.g.*, ’888 patent at 1:34-41 (“Recombinant vectors based on parvovirus, such as adeno-associated virus (AAV), show promise for gene therapy. However, obtaining efficient, sufficient levels of expression of a transgene in various cell types has presented problems. Some cell types are impermissive in the sense that initiation of transcription or translation of the transgene is inefficient, with expression accordingly very slow to initiate, if it initiates at all.”). Thus, before the invention could be practiced, it would be necessary to make and screen each candidate rAAV preparation comprising an rAAV genome for sufficient intrastrand base pairing in its heterologous sequence to enhance expression of said sequence. And although the level of skill in the art was relatively high at the time of filing (1999), skill alone cannot stand in for a total absence of guidance in the specification.

iv. Factor 7: Predictability or Unpredictability of the Art

As the ’888 patent specification admits, this was a particularly unpredictable field at the time of filing (1999). *See, e.g.*, ’888 patent at 4:37-40 (“there can be difficulties in obtaining sufficient levels of expression of heterologous sequences from rAAV vectors and viruses containing such vectors”). This unpredictability would have been compounded by the breadth of the claims, which read on all heterologous sequences (e.g., RNA) and all vector lengths. In particular, as discussed above, the lower size limit of the vectors described in the ’888 patent would have been wholly inoperable. Further, minor changes to characteristics of the rAAV vector, including size, rAAV serotype, etc. could potentially result in significant, unpredictable changes to the level of intrastrand base pairing and expression of the heterologous sequence. Without testing, a person of ordinary skill in the art could not have predicted whether a given rAAV vector

within the vast genus of rAAV vectors claimed would contain sufficient intrastrand base pairing to enhance expression compared to an equally undefined second vector, let alone meet any of the other claim limitations.

v. Factor 8: Breadth of the Claims

Independent claim 1 of the ’888 patent (and its dependent claims) is extremely broad and contains several limitations that are unbounded and/or defined only by broad functional requirements, as explained at length above. *See supra* Section VI.B.1 and VI.B.2.a.i. Given the breadth of disclosure, a person of ordinary skill in the art would require significant experimentation to devise a construct that meets the functional limitations in the claims of the ’888 patent, i.e., that has sufficient intrastrand base pairing along most or all of its length such that expression of a heterologous sequence is enhanced relative to a construct that lacks sufficient intrastrand base pairing to enhance expression.

As discussed above, the specification merely invites the person of ordinary skill in the art to perform his or her own experimentation to determine the amount of intrastrand base pairing that would work to “enhance[] expression” for any given coding region and rAAV serotype in order to meet the limitations of the Asserted Claims. As a result, an undue amount of experimentation would be required for a person of ordinary skill in the art to make and use the alleged invention of the Asserted Claims of the ’888 patent.

b. Dependent Claims 2, 4, and 6

As explained above with respect to the lack of written description, the dependent claims of the ’888 patent further recite features that provide no meaningful limitation as to claim scope, as the dependent claims still purport to encompass a nearly limitless universe of nearly all types of serotype of AAV, gene of interest, amount of intrastrand base paring (which is functionally defined as “enhanc[ing]” expression), and, under Plaintiffs’ proposed claim constructions, provide no

meaningful limits regarding the number, location, and sequence of ITR(s). For at least the same reasons set forth in Sections VI.B.1 and VI.B.2.a, the asserted dependent claims are invalid for lack of enablement.

3. Invalidity under 35 U.S.C. § 112, Second Paragraph for Indefiniteness

Under 35 U.S.C. § 112, ¶ 2, a patent "is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig. Instruments, Inc.*, 572 U.S. 898, 901 (2014). A patent must be "precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them. Otherwise there would be a zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims." *Id.* at 909-910 (internal quotations and citations omitted).

i. "along most or all of its length"

Claim 1 of the '888 patent and its dependent claims require, among other things, an rAAV genome comprising a heterologous sequence wherein the heterologous sequence forms intrastrand base pairs "along most or all of its length." Requiring constructs that form intrastrand base pairing along most or all of the length of the heterologous sequence is indefinite, as the specification fails to explain the circumstances under, and characteristics by which, such base-pairing along "most or all" of the length of the heterologous sequence occurs and accomplishes the claimed function of enhanced expression.

The patent states that "a recombinant viral vector containing a sequence or region that forms intrastrand base-pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the degree of intrastrand base pairing." '888 patent at 10:52-56. Despite that a person of ordinary skill in the art would understand "most" to mean "more than

half," the patent provides no other guidance regarding the circumstances or characteristics of the claimed intrastrand base pairing, instead stating broadly "[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.* at 14:51-53 (emphasis added). The patent broadly provides that "[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." *Id.* at 10:25-29. Further, the patent broadly states that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:56-60. The patent specification and claims provide no guidance as to what circumstances or characteristics of the intrastrand base pairing are necessary or sufficient to accomplish the claimed function of enhanced expression, e.g., how intrastrand base pairing in the heterologous sequence but outside the coding region would accomplish the claimed function; where and how much intrastrand base pairing must occur (ranging from 50-100% of any number of nucleotides anywhere in the heterologous sequence); and whether or what conditions must be satisfied to enhance expression (e.g., type of cell, type of AAV, type of nucleotide, intracellular conditions, extracellular conditions, etc.).

These overbroad claims reciting intrastrand base pairing along most or all of the length of a nucleotide sequence do not put the public on notice of what the claimed invention is, thus making it impossible to know whether one is potentially infringing. *See, e.g., Nautilus*, 572 U.S. at 901.

ii. "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 said expression"

Claim 1 of the ’888 patent and its dependent claims require, among other things, a heterologous nucleotide sequence that “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 said expression.” “Enhanced” in this context is indefinite, as the specification fails to explain (1) how much intrastrand base pairing is required to result in “enhanced” expression, (2) at what point in time the expression should be measured, and (3) how much expression amounts to “enhanced” expression. The specification only provides generalized statements regarding the required “enhanced” expression, but enhanced expression purportedly resulting from intrastrand base pairing is not expressly defined in the patent specification and purportedly encompasses any enhancement, measured by any means, at any point in time relative to any other rAAV that has a different and undefined amount of intrastrand base pairing

Despite the limitation “along most or all of its length,” with regard to intrastrand base pairing, the ’888 specification fails to elaborate on what position or quantity of intrastrand base pairing will achieve the “enhanced” expression, making it impossible to know how one is potentially infringing. For example, the patent explains that “a recombinant viral vector containing a sequence or region that forms intrastrand base-pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the *degree* of intrastrand base pairing. *Id.* at 10:52-56 (emphasis added). The patent further explains that “the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%. 95%, 98%, 99%.” *Id.* at 10:56-60. The patent also explains that “[t]he region(s) of intrastrand complementarity . . . in the recombinant viral vector 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." *Id.* at 14:38-46 (emphasis added). The patent further teaches 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.* at 14:51-53 (emphasis added). These sweeping statements do not put the public on notice of what the claimed invention is—i.e., how much intrastrand base pairing would be needed in specific rAAV genomes to arrive at enhanced expression.

Next, with regard to the temporal aspect of measuring expression, the '888 patent specification does not define what time points should be used to measure such a rate. The single purported working example (Example 6) which measures differences in rates of expression only conducts this measurement at 48 and 72 hours and only provides the rate of expression for the GFP expression in the half-sized vector, not the control vector. A person of ordinary skill in the art would know that expression levels will vary over time. Thus, a person of ordinary skill in the art could potentially infringe at one point in time, but not another.

With regard to how much expression amounts to "enhanced" expression, the patent again provides little guidance. The '888 specification teaches that intrastrand base-pairing contributes to increased levels and/or increased rate of heterologous sequence expression, *id.* at 7:57-60, and defines "expression" as follows:

"Expression" includes transcription and/or translation. Methods of detecting transcription, such as Northern analysis, and translation, such as Western analysis or ELISA, are well known in the art. These methods also permit measuring differing levels of transcription and/or translation,

whether that difference is between or among different vectors, different times, different host cells, etc. *Id.* at 13:11-17.

Based on this definition, a person of ordinary skill in the art would not know whether "enhanced expression" relates to the rate of expression (e.g., the speed), or the level of expression (e.g., the amount). Further, from this definition, a person of ordinary skill in the art would be unable to determine whether to detect transcription, translation, or both, and what method or methods by which said expression should be assessed. The different measurement techniques disclosed in the '888 specification possess different sensitivity levels which could yield different results when measuring expression from the same rAAV vector. The Federal Circuit has held patent claims invalid for indefiniteness where a claim term may be determined by multiple methods, the testing results of which "will necessarily fall within or outside the claim scope depending on the . . . method chosen." *Honeywell Intern. v. ITC*, 341 F.3d 1332, 1341 (Fed. Cir. 2003).

Moreover, the purported comparator against which expression levels are measured, i.e., an rAAV vector that "lacks sufficient intrastrand base pairing," is not clearly defined in the specification. The single purported working example in the specification discloses an rAAV vector with close to 100% intrastrand base pairing in the rAAV vector and whose expression is "enhanced" over an rAAV vector with no intrastrand base pairing. Ultimately, the claim limitation is circular, whereby an undefined sufficiency of base pairing and expression in a first heterologous sequence in an rAAV genome is relative to an undefined insufficiency of base pairing and expression in a comparator rAAV (whose insufficiency is relative to the heterologous sequence in the rAAV genome).

For at least these reasons, the Asserted Claims of the ’888 patent are invalid under 35 U.S.C. § 112 as indefinite.

VII. Invalidity Contentions As To The ’729 Patent

A. The ’729 Patent Claims Are Invalid for Anticipation and/or Obviousness

Each Asserted Claim of the ’729 patent is invalid for anticipation and/or obviousness. In addition to the information set forth below, a chart identifying where specifically in each item of prior art each limitation of each Asserted Claim of the ’729 patent is found is attached as Appendix D, which is incorporated herein. Pinpoint citations to material in the prior art are exemplary of the disclosures and teachings of the prior art. Those citations should not be construed as limiting the disclosure of any prior art or as reflecting the only section of a prior art reference disclosing a particular limitation or teaching.

1. Independent Claim 1

The ’729 patent admits that by August 9, 1999, the use of an rAAV vector comprising a single-stranded heterologous nucleotide sequence was well-known. *See, e.g.*, ’729 patent at 3:20-25 (“The native AAV genome has been used as the basis of vector systems for the delivery and expression of heterologous genes in host cells such as mammalian cells, such as for gene therapy.”) (*citing* Muzyczka (1992) *Curr. Top. Microbiol. Immunol.* 158:97-129; Carter, B. J. (1992) *Curr. Op. Biotechnol.* 3:535-539; and Flotte et al. (1995) *Gene Therapy* 2:357-362). The ’729 patent further admits that “[r]ecombinant AAV (rAAV) vectors, based on the native AAV genome, are generally produced by deletion of rep and/or cap sequences and [their] replacement by a heterologous sequence. Thus, rAAV vectors generally comprise a single-stranded DNA molecule comprising a heterologous gene sequence or sequences flanked by at least one AAV ITR, and typically by two AAV ITRs, one at each end.” *Id.* at 3:26-33.

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The ’729 patent further admits that by August 9, 1999, it was well-known that “efficient, productive packaging in an AAV virus particle is limited to vectors having approximately the size of an AAV genome (i.e., approximately 4.7 kb) or smaller” and that by August 9, 1999, those skilled in the art had already used smaller rAAV genomes. *Id.* at 3:40-43; 46-53 (*citing* Dong et al. (1996) Hum. Gene Therapy 7:2101-2112 for teaching the use of “rAAV genomes having sizes between 2 kb and 6 kb”); *see also id.* at 9:57-58 (“The maximum size vector that can be packaged to yield an infectious viral particle is approximately 5.2 kb.”); *id.* at 15:41-44 (“In the case of an rAAV vector of this invention, its length may be less than about. . . .5.5.”). Indeed, by August 9, 1999, the use of rAAV vectors of approximately half size was well-known and described in numerous prior art references. *See, e.g.*, Hörster (1999); Muzyczka (1992); Hermens (1997); Dong (1996).

Hörster (1999) describes the use of “fusion constructs between the indicators luciferase and gfp and the HIV-1-directed antisense sequence AR6 or ribozyme Rz12.” Hörster (1999) at 1232. Hörster (1999) describes 12 fusion constructs comprising single stranded heterologous nucleotide sequences. *Id.* Hörster (1999) discloses approximately half size rAAV vector fragments comprising heterologous sequences encoding luciferase, gfp, AR6, and/or Rz12 flanked by ITRs in Figures 1 and 3. *Id.* at 1232-33. Hörster (1999) also describes that “293T cells were seeded on 15 cm dishes and cotransfected with 18 µg of the vector construct and 18 µg of the helper plasmid pTGMA. . . .Three days after transfection the medium was collected and the cells harvested by scrapping. . . .The cell debris was removed by low speed centrifugation, CsCl was added to the supernatant to a final density of 1.38 g/ml, and the solution was underlayed with a cushion of 1.5 ml CsCl in PBS (1.5 g/ml).” *Id.* at 1236. Hörster (1999) also describes producing infectious rAAV particles using a system that “provides all necessary helper functions for rAAV particle formation

by plasmid-coded genes thereby avoiding the use of infectious adenovirus." *Id.* at 1233. Hörster (1999) describes a system "that provides all necessary helper functions for rAAV particle formation by plasmid-coded genes thereby avoiding the use of infectious adenovirus" and/or is "purified as described recently." *Id.* at 1233, 1236.

Muzyczka (1992) describes the use of rAAV vectors "containing the *dl*3-94/neo genome (50% of wild type size)" and "the neomycin phosphotransferase gene." Muzyczka (1992) at 111-12. The *dl*3-94/neo genome (50% of wild type size, *i.e.*, the approximately half size vector) "were found to consist predominantly of particles that had the density of AAV particles containing a wild type complement of DNA. When the DNA in these particles was examined it was found to consist of three kinds of molecules. The predominant DNA molecule was an inverted dimer of the *dl*3-94/neo genome. Such molecules occur as a natural consequence of the AAV DNA replication mechanism and have been described in studies of spontaneously occurring deletions or AAV defective interfering (DI) genomes." *Id.* at 112 (citations omitted). Muzyczka (1992) describes in Figure 6 that "[h]uman cells are transfected with the AAV recombinant plasmid and a complementing plasmid which is defective for packaging but supplies the wild type AAV gene products. The cells are also infected with adenovirus (*Ad*) to supply helper function. The virus stock produced contains both adenovirus and the AAV recombinant virus. Adenovirus is inactivated by heat or removed by density gradient centrifugation. *Id.* at 112. Muzyczka (1992) describes "growth of a recombinant stock requires the presence of both AAV and helper virus genes." *Id.* at 115. Muzyczka (1992) describes "a complementing plasmid in which there were no homologous sequences between the recombinant genome and the complementing plasmid. This plasmid consisted of the AAV coding sequences flanked by the adenovirus 5 terminal repeats." *Id.*

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at 116. Furthermore, Muzyczka (1992) describes that "[t]o inactivate the contaminating adenovirus, the recombinant stock was heated at 55-60°C for 2h." *Id.* at 111.

Hermens (1997) describes the generation of an rAAV virus with a vector "containing an expression cassette for B-50/GAP-43." Hermens (1997) at 153. Hermens describes the B-50/GAP-43 open reading frame (ORF) as "cloned into pcDNAI/Amp5.0 (Invitrogen). This resulted in pcDNAB-50 containing a CMV-B-50-A+ expression cassette. Subsequently, from a plasmid designated psub201 (a recombinant plasmid from which an infectious AAV genome can be excised Samulski, et al., 1987) the AAV-coding sequences are replaced by the CMV-B-50-A+ expression cassette (2.1 kb) of pcDNAB-50. This resulted in plasmid psub201B-50." *Id.* Hermens (1997) describes "AAVB-50 [] produced following $CaPO_4$ transfection of 5 µg of psub201B-50 with 25 µg of helper plasmid pAd8 (a plasmid containing the coding sequence of AAV2 flanked by Ad5 ITR's [] on ten Petri dishes (100 mm diameter) confluent 293T cells. After 6-8 hr the transfection medium was removed and the cells were infected for 1 hr with Ad*dl*309 with a MOI of 3. After the infection the cells were cultured in normal culture medium for another 48 hr before the virus was harvested as followed. . . . Before use an aliquot of the fractions was either heated at 56°C for 30 min. . . . Since AAV is heat stable the heating step results in the elimination of heat labile infectious adenovirus." *Id.* Hermens (1997) also describes "[f]ollowing centrifugation at 1500 g for 20 min at 4°C to remove the cell debris, the supernatant was heated at 56°C for 30 min. This step inactivates the helper virus (Ad)." *Id.* at 154.

Dong (1996) describes rAAV vectors "from 2 kb to 6 kb in size" that carry "a chloramphenicol acetyltransferase (CAT) reporter gene." Dong (1996) at 2101. Dong (1996) also describes that "on the Southern blot of virion DNA, only [the] sample from the 1.9-kb vector contained DNA that appeared twice as large as single stranded DNA on an alkaline gel (Fig. 5,

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lane 2, DS). When the vector DNAs were isolated from infected cells in the absence of adenovirus-mediated double-strand conversion, the majority of the 1.9-kb vectors were in double-stranded form, and none was observed in any of the larger vectors." *Id.* at 2107-08. Dong (1996) describes that "[t]he 'miniscale' production of recombinant AAV (rAAV) was accomplished according to the standard protocol with modifications. A helper plasmid, pAAV/Ad, which contains the rep-cap genes of AAV flanked by the adenovirus terminal repeats, was used for all experiments that involved AAV production, AAV vectors, pAVCNst-A to -L, were co-transfected with pAAV/Ad at a ratio of 1:5 into HeLa cells in six-well plates. . . .In experiments that involve isolating vector DNA from infected cells, the adenovirus were heat-inactivated at 65°C for 30 min." *Id.* at 2103.

The '729 patent admits that by August 9, 1999, it was well-known that the AAV life cycle involves the generation of "a self-complementary double-stranded molecule that is covalently closed at one end" called "the replicative form (RF)." '729 patent at 2:15-18; *see also* Carter (1984) at 212 ("These molecules consist of complementary strands which are covalently joined at one terminus by a hairpin structure formed by virtue of the palindromic terminal sequence 126 nucleotides in length."). The '729 patent further admits that by August 9, 1999, it was well-known that "formation of the RF is required for transcription of viral proteins (or, in the case of recombinant AAV, the transcription of heterologous sequences such as a transgene) to occur, since cellular RNA polymerizing systems require a double-stranded template." '729 patent at 2:43-48; *see also* Carter (1984) at 219 ("Also, as shown in Fig. 2, the RF structure is the configuration that would be expected during replication of AAV DNA."). The '729 patent also admits that when a recombinant viral vector has a sequence complexity that is approximately one half its length, "a vector is able to form a 'snapback' molecule which is double stranded along most or all of its length, thus analogous to the RF produced during AAV infection." '729 patent at 15:16-20; *see*

also id. at 18:30-35 ("Upon replication, the half-size genome is copied into a complementary DNA strand that is covalently attached to its template at one end (see FIGS. 1 and 3), forming a structure that will 'snap back' into a hairpin duplex."); *id.* at 33:54-60 ("Alkaline gel analysis, shown in Fig. 7A, indicates that preparations of virus particles having vector genomes that were made from a half-size plasmid contain DNA molecules that have a single-stranded length that is the same as a native AAV genome (second lane from left). This is what would be expected if 'snap-back'-type RF molecules have been packaged in these virus particles."); Carter (1984) at 216, 222 (indicating that DNA 1.41b, "which appeared to be mainly hairpin molecules," had a "mean molecular size estimated from gel electrophoresis of about 50% of genome length"). The '729 patent further admits that vectors of the alleged invention:

> [C]an be produced by constructing a parvovirus vector, such as an rAAV vector, that has a size approximately one-half of a native genome and allowing such a vector to replicate in a host cell. . . . Upon replication, the half-size genome is copied into a complementary DNA strand that is covalently attached to its template at one end (see FIGS. 1 and 3), forming a structure that will "snap back" into a hairpin duplex. . . . These recombinant parvovirus vectors comprise an ITR sequence between the heterologous sequences (i.e., an ITR sequence flanked on both sides by heterologous sequences)."

'729 patent at 18:26-44; *see also* Carter (1984) at 212 "Some variant genomes have a conformation similar to that of certain intracellular replicating forms of parvovirus DNA. These molecules consist of complementary strands which are covalently joined at one terminus by a hairpin structure formed by virtue of the [ITR]. These molecules at a neutral pH spontaneously renature with zero-order kinetics to form duplex structures."). As the '729 patent depicts in Figs. 1 and 3, "the heterologous sequence [generated from such half-sized vectors] forms base pairs essentially along its entire length, thus analogous to an AAV replicative form." '729 patent at 5:10-12.

Literature dated after August 9, 1999, e.g., McCarty (2008), supports the admissions of the '535 patent by disclosing that such self-complimentary rAAV vectors "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 dimeric inverted repeat will be no larger than the normal AAV packaging capacity (~4,700 nucleotides)." McCarty (2008) at 1649. McCarty (2008) further recognizes that "[a]lthough this further restricts the transgene carrying capacity of an already small viral vector, it offers a substantial premium in the efficiency, and speed of onset, of transgene expression because dsDNA conversion is independent of host-cell DNA synthesis and vector concentration." *Id.* at 1649 (*citing* McCarty (2001), Gene Ther 8:1248-54).

Thus, each of Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996) teach the approximately half size vector comprising a region which forms intrastrand base pairs such that expression of a coding region of a heterologous sequence is enhanced. *See e.g.*, Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996). Moreover, the prior art discloses methods for preparing rAAV comprising incubating a host cell under conditions that allow AAV replication and encapsidation, wherein such host cell comprises an rAAV vector, AAV rep function, AAV cap function, and helper virus function for AAV, and purifying rAAV particles produced from the host cell. *See e.g.*, Hörster (1999), Muzyczka (1992), Hermens (1997), Dong (1996), Berns (1996), Carter (1996), Kaplitt (1995), Bartlett (1995), Xiao (1998), Ferrari (1996), Ferrari (1997), Samulski (1987), WO9911764 (1997), Phillips (1997), Welch (1998), Su (1996), Zolotukhin (1996), WO9732018 (1996), Mamounas (1995), WO9717458 (1995), Fisher (1996), WO9947691 (1999), and WO9528493 (1994). A person of ordinary skill in the art would have been motivated to combine such teachings with a reasonable expectation of success to meet the claim limitations of claim 1.

Accordingly, the disclosure in Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996) of a method for preparing rAAV comprising (1) incubating a producer cell, with an rAAV vector that is less than about 2.5 kb, rep function, cap function, and helper virus function, under conditions allowing AAV replication and encapsidation and (2) purifying the rAAV particles, which comprise a genome that forms intrastrand base pairs causing enhanced, inherently anticipate and/or render obvious (alone or in the combinations identified in Appendix D) claim 1 of the ’729 patent because, as the ’729 patent admits, such vectors necessarily and inevitably contain “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.”

2. Dependent Claims 2-5 and 7-9

The dependent claims of the ’729 patent are additionally invalid over the prior art, at least based on the references and combinations set forth in Appendix D. As set forth in Appendix D, the prior art discloses, expressly or inherently, each and every limitation of the dependent claims, including the claimed method features (claims 2-5, 9) and a population of rAAV particles produced according to the methods (claims 7-8). A person of ordinary skill in the art would have been motivated to pursue the combinations listed in Appendix D with a reasonable expectation of success in achieving the asserted dependent claims. For example, as the ’729 patent admits, “[r]ecombinant vectors based on parvovirus, such as adeno-associated virus (AAV), show promise for gene therapy.” ’729 patent at 1:34-35. The ’729 patent also admits that the dependent claim limitations related to producing an rAAV particle with the rAAV vector were known in the art. *See e.g., id.* at 3:39-40 (“rAAV vectors can be encapsidated into AAV virus particles to form recombinant adeno-associated viruses (rAAV).”). The ’729 patent also admits that the dependent claim limitations directed to rep function, cap function, and helper functions were known in the

art. *See e.g.*, *id.* at 2:57-60 ("Helper functions involved in the replication of the [replicative form] can be provided by co-infection of AAV-infected cells with adenoviruses, herpesviruses or poxviruses. Carter (1990) supra. Alternatively, cells may contain integrated genes, viral or otherwise, that supply helper function."). The prior art listed in Appendix D is directed to, *e.g.*, methods of preparing rAAV including rAAV partciles containing rAAV vectors capable of forming intrastrand base pairs that enhance expression. A person of ordinary skill in the art, as of August 19, 1999, would have been familiar with this prior art and would have been motivated to combine these teachings, and the others set forth in Appendix D, with a reasonable expectation of success, thereby rendering obvious dependent claims 2-5 and 7-9.

B. The '729 Patent Claims Are Invalid under 35 U.S.C. § 112

In addition, or in the alternative, Novartis contends that the Asserted Claims of the '729 patent do not satisfy one or more requirements of 35 U.S.C. § 112. Novartis identifies the below grounds upon which the Asserted Claims of the '729 patent are invalid based on lack of written description under 35 U.S.C. § 112, first paragraph, lack of enablement under 35 U.S.C. § 112, first paragraph, and indefiniteness under 35 U.S.C. § 112, second paragraph.

1. Invalidity under 35 U.S.C. § 112, First Paragraph for Inadequate Written Description

As discussed *supra*, a patent's specification must contain a written description of the claimed invention. 35 U.S.C. § 112, ¶ 1. The description must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*) (citations omitted). In other words, the specification must reasonably convey that the inventor had possession of the claimed subject matter as of the filing date. *Id.*

To satisfy the written description requirement for a claimed genus, a specification must describe the claimed invention in such a way that a person of ordinary skill in the art would understand that the entire genus that is being claimed has been invented, and not just a single species of the genus. *Carnegie Mellon Univ. v. Hoffman-La Roche, Inc.*, 541 F.3d 1115, 1124 (Fed. Cir. 2008). In particular, when attempting to claim a functionally-defined genus, "a sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.* at 1350 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)). "A vague functional description and an invitation for further research does not constitute written disclosure . . . ." *Id.* at 1356. And "if the art is unpredictable, then disclosure of more species is necessary to adequately show possession of the entire genus." *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1125 (Fed. Cir. 2004). While it is "not fatal" that members of a genus are not disclosed in a patent, the specification should provide other means of identifying which members of the genus would interact with other variable elements. *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330 (Fed. Cir. 2021).

The Asserted Claims of the '729 patent are invalid under 35 U.S.C. § 112, ¶ 1, because the claimed method comprises using a genus of vectors that is neither supported by a representative number of species nor by a disclosure of structural features common to the members of the genus responsible for the claimed functions that would allow a person of ordinary skill in the art to visualize or recognize the other members of the genus. As explained in detail below, the specification of the '729 patent does not reasonably convey to a person of ordinary skill in the art that the inventor had possession of the vast—nearly limitless—genus of rAAV vectors used in the

methods of the Asserted Claims. The claims use structural and functional language in an attempt to claim methods that use a vast genus of vectors to achieve a particular result. Yet, the rAAV vectors used in the claimed methods are not limited, for example, by serotype of AAV, gene of interest, or amount of intrastrand base paring (which is functionally defined as "enhanc[ing]" expression). Further, Plaintiffs dispute Defendants proposed claim constructions, which are consistent with the disclosures in the intrinsic evidence and provide that each ITR of the claimed rAAV vectors is native AAV ITR sequence. By contrast, under Plaintiffs' proposed claim constructions, the claimed rAAV vectors are not limited, for example, by the number, location, and sequence of ITR(s). Rather, the Asserted Claims purport to define the rAAV vectors by functional properties, such as their ability to enhance expression of a coding region of a heterologous sequence relative to vectors that lack sufficient intrastrand base pairing to enhance said expression. A person of ordinary skill in the art would have understood the purported scope of the claimed methods using this genus is exceedingly broad, unknown and unknowable, and consequently would require an expansive and random search for all of the different options of vectors that may or may not work.[13] *See Brenner v. Manson*, 383 U.S. 519, 536 (1966) ("a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

A "representative number of species" means that the species which are adequately described are representative of the entire genus. *Carnegie Mellon*, 541 F.3d at 1124. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect

[13] Further, because the term "enhanced" as used in the Asserted Claims is indefinite (*infra*, Section VII.B.3.), a person of ordinary skill in the art would not be able to determine the purported scope of the claimed genus of vectors with reasonable certainty. Likewise, the term "lacks sufficient intrastrand base pairing" as used in the Asserted Claims is indefinite (*id.*), further highlighting that the purported scope of the claimed genus cannot be determined with reasonable certainty.

the variation within the genus. *Id.* For inventions in unpredictable arts, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. *Id.* The genus of vectors required by the methods claimed in the ’729 patent is not supported by a representative number of species. Despite the vast scope of the claimed genus, the ’729 patent contains only minimal guidance and examples regarding what rAAV vectors would possess this function of enhanced expression. Indeed, the ’729 patent provides just one exemplary structure (a half-sized vector containing a particular heterologous gene wherein each ITR of the vector is native AAV ITR sequence) that purportedly accomplishes the claimed function of enhanced expression. It also fails to inform a person of ordinary skill in the art about the amount of overall intrastrand base pairing necessary to achieve the required enhanced expression. More specifically, the specification fails to provide any specific details as to the structural features relating to the base pairing requirements set forth in the Asserted Claims. Yet subsequent research has shown that the location and amount of base pairing influences the amount of expression.

In determining whether the specification provides adequate written description support, products that post-date the patent’s priority date, including an accused infringing product, can be taken into consideration. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374-75 (Fed. Cir. 2017). In particular, evidence showing that a claimed genus does not disclose a representative number of species may include post-filing evidence of species that fall within the claimed genus but are not disclosed by the patent. *Id.* at 1374. Despite the minimal teachings in the specification of the ’729 patent outlined above, the claims purport to cover all structures (and iterations thereof)—including later-developed vectors containing mutated ITRs, which merited their own patent protection (*see, e.g.*, McCarty (2001); McCarty (2003); McCarty (2008); U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457)—that accomplish the “enhanced expression” function.

The ’729 patent also fails to disclose structural features common to members of the genus that are responsible for the claimed functions such that one of skill in the art could visualize or recognize the members of the claimed genus of rAAV vectors, as explained in detail below. “[F]unctionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus.” *AbbVie Deutschland GmbH & Co. KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014); *see also Juno*, 10 F.4th at 1337 (disclosure of two working embodiments “does not provide information sufficient to establish that a skilled artisan would understand how to identify the species of scFvs capable of binding to the limitless number of targets as the claims require.”).

For at least the reasons discussed herein, and outlined in more detail for specific claim limitations below, the Asserted Claims of the ’729 patent are invalid under 35 U.S.C. § 112, ¶ 1 for failing to satisfy the written description requirement.

a. Independent Claim 1

i. “rAAV particles compris[ing] a rAAV genome which forms intrastrand base pairs along its length”

The purported scope of the claims of the ’729 patent is broad with respect to the limitations reciting “rAAV particles compris[ing] a rAAV genome which forms intrastrand base pairs along its length,” as recited in independent claim 1, relative to the limited examples and disclosure in the specification. More specifically, the specification fails to provide any specific details as to the structural features relating to the base pairing requirements set forth in the claims.

Despite the vast scope of the claimed genus, the ’729 patent contains only minimal guidance and examples regarding what rAAV particles may be able to form intrastrand base

pairing along an undefined length of the rAAV genome. The patent specification broadly states "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:56-60. The specification fails to provide any information as to where (if anywhere) in this exceptionally broad range intrastrand base pairing would be considered to be along the length of the rAAV genome. The specification also fails to provide any information regarding the conditions or time points to assess whether an rAAV particle forms intrastrand base pairs along the length of the rAAV genome.

In contrast to the broad purported scope of claim 1, the '729 patent provides just one exemplary structure (one half-sized vector containing one particular heterologous gene) that purportedly forms intrastrand base pairing across nearly the full length of the heterologous gene. Other than GFP and nearly full length base pairing, the specification does not provide any additional examples of other coding regions falling within the purported scope of the claims that possess the claimed functional elements (e.g., intrastrand base pairing in the rAAV genome). Given the substantial structural variation purportedly encompassed by the functionally-defined genus, the '729 patent specification does not disclose a representative number of species that achieves the claimed result sufficient to support the claimed genus of all rAAV genomes which form intrastrand base pairs along their length. Furthermore, there is no structural feature of the rAAV genome that would be common to members of the genus because the claims purport to cover any rAAV genome, and the specification does not describe any correlation between any rAAV genome structure and the functional requirements of the claimed genus.

Thus, claim 1 of the '729 patent (and its dependent claims) lacks written description support for "rAAV particles compris[ing] a rAAV genome which forms intrastrand base pairs

along its length" because a person of ordinary skill in the art would not reasonably believe that the '729 patent inventor had possession of the claimed genus of any rAAV genome which forms intrastrand base pairs along its length.

ii. "a rAAV vector comprising a heterologous nucleotide sequence…wherein…expression of a coding region of the heterologous nucleotide is enhanced relative to a rAAV vector that lacks sufficient intrastrand base pairing to enhance said expression"

The '729 patent uses functional language to describe a desired result for the vectors used in the method purportedly encompassed by independent claim 1 and claims dependent thereon. Specifically, claim 1 recites "a rAAV vector comprising a heterologous nucleotide sequence . . . wherein . . . *expression* of a coding region of the heterologous nucleotide *is enhanced relative* to a rAAV vector that *lacks sufficient intrastrand base pairing to enhance said expression*." *Id.* at claim 1 (emphasis added). The '729 patent states that "[i]t is understood that, for purposes of this invention, a recombinant viral vector containing a sequence or region that forms intrastrand base pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the degree of intrastrand base pairing." *Id.* at 10:52-56. The specification further teaches that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:56-60. The '729 patent describes that "[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." *Id.* at 10:26-30. In some embodiments, "the total amount of sequence that forms intrastrand base pairs (which could be in one or more regions) is greater than about 125 nucleotides, greater than about 250 nucleotides, greater than about 500 nucleotides, and/or greater than about 1,000 nucleotides."

Id. at 14:62-67. Under the circumstances where a coding region is 5 nucleotides and the extent of intrastrand base pairing is 25%, the amount of intrastrand base pairing could be as little as 1 or 2 nucleotides. As discussed above, the ’729 patent exemplifies a single rAAV vector that purportedly achieved intrastrand base pairing across the entire coding region. Applicant did not possess rAAVs having 25% intrastrand base pairing across a 5-nucleotide coding region, i.e., fewer than 2 nucleotides, and having enhanced expression. Nor did the applicant possess any coding regions having lengths other than the length of GFP and any other percentage of base pairing other than 100%. Indeed, even today, AAV vectors that are too short or too long cannot package and express efficiently. For example, “stuffer” sequences are sometimes used to lengthen AAV vectors and enhance expression in certain systems.

The ’729 patent attempts to claim methods using every rAAV vector that would achieve the desired result. The specification states that an “[a]n ‘AAV inverted terminal repeat (ITR)’ sequence . . . is an approximately 145-nucleotide sequence that is present at both termini of the *native* single-stranded AAV genome.” ’729 patent at 11:13-16 (emphasis added). The specification also explains that *native* ITR sequences, i.e., from a native AAV2 genome, were used in the purported working examples. *Id.* at 16:5-7. Non-native ITR sequences were never tested or even constructed, according to the patent specification.

To the extent the ’729 patent claims are construed to encompass *non-native* ITR sequences, the ’729 patent claims are invalid for lack of written description, because the claimed genus of vectors comprising any modified, mutated, or non-native ITR is unsupported by the disclosure of the patent specification, which includes only a single purported working example wherein each ITR of the vector is native AAV ITR sequence from AAV2. As noted above, in determining whether the specification provides adequate written description support, products that post-date

the patent's priority date, including an accused infringing product, can be taken into consideration. *Amgen Inc. v. Sanofi*, 872 F.3d at 1374-75. Here, to the extent the '729 patent claims are construed to encompass non-native ITR sequences, the claims improperly purport to cover all structures (and iterations thereof) (including later-developed structures like those described in McCarty (2001), McCarty (2003) and McCarty (2008) containing a mutated ITR that was not yet invented at the time of filing the '729 patent, and which merited its own patent protection (U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457)) that accomplish the "enhanced expression" function.

Yet, the '729 patent specification provides only one structure (a half-sized vector containing a particular heterologous gene and wherein each ITR of the vector is native AAV ITR sequence) that purportedly accomplishes the claimed function of enhanced expression. The single purported working example compares expression from an rAAV vector encoding GFP which has "half-complexity" with expression of GFP from an rAAV vector that possesses no intrastrand base pairing. *See, e.g.*, *id.* at 36:51-55. The specification explains that a "half-complexity" vector is one that forms a "snapback" molecule and is double-stranded along most or all of its length. *Id.* at 15:12-20; *see also id.* at 7:60-67 ("rAAV vectors which contained two copies of [GFP] in opposite orientation, and were accordingly able to form a double-stranded molecule due to intrastrand base pairing, displayed significantly higher expression levels (as indicated by percentage of cells expressing reporter gene) in 293 and HeLa cells compared to another vector which was not able to form intrastrand base pairing of the GFP gene.").

Thus, the single purported working example in the specification discloses an rAAV vector with 100% intrastrand base pairing in the rAAV vector whose expression is "enhanced" over an rAAV vector with no intrastrand base pairing. The '729 patent inventor acknowledged as much during prosecution of a patent application in the family when arguing to overcome a rejection

under 35 U.S.C. § 112, ¶ 1 for lack of written description regarding the "enhanced expression" limitation. *See* GENZ_NOV_00002135 ("In fact, data in Example 8 indicated that the *entire* genome of such vectors [that have significantly enhanced expression of GFP] is base-paired") (emphasis added); *see also* GENZ_NOV_00002136 ("Example 8 shows an entire genome of a rAAV vector is base-paired").

This one purported working example does not amount to a disclosure of a representative number of species corresponding to the purported scope of the claimed functional genus of rAAV vectors with enhanced expression. The specification does not provide any examples of enhanced expression with amounts of intrastrand base pairing less than 100% in the coding region or examples of enhanced expression over comparator vectors that possess at least some intrastrand pairing. Given that the purported scope of claim 1 and its dependent claims cover substantial variation within the genus of permissible intrastrand base pairing for both the first and second rAAV vectors in the claim, the specification does not disclose a representative number of species sufficient to support the claimed genus.

Nor was there any established correlation between vector base pairing structure and function (sufficient to enhance expression). This is abundantly clear from the lack of guidance provided by the '729 patent's incredibly broad (to the point of meaningless) disclosure regarding the level of intrastrand base pairing that can lead to enhanced expression. Indeed, as the '729 patent admits, this was a particularly unpredictable field. *See, e.g.*, '729 patent at 4:37-40 ("there can be difficulties in obtaining sufficient levels of expression of heterologous sequences from rAAV vectors and viruses containing such vectors"). Thus, significantly more disclosure was required for a person of ordinary skill in the art to conclude that the inventor possessed the full scope of the functionally defined genus recited in the claims.

For at least these reasons, claim 1 of the ’729 patent (and their dependent claims) lack written description support for “a rAAV vector comprising a heterologous nucleotide sequence…wherein…*expression* of a coding region of the heterologous nucleotide is *enhanced relative to* a rAAV vector that *lacks sufficient intrastrand base pairing to enhance* said expression” because a person of ordinary skill in the art would not reasonably believe that the ’729 patent inventor had possession of the vast genus required by the claimed methods.

iii. “a host cell”

The purported scope of the claims of the ’729 patent is broad with respect to the limitations reciting a “host cell,” as recited in independent claim 1, relative to the limited examples and disclosure in the specification. More specifically, the specification fails to provide any definition of the term “cell,” but instead describes “[t]ypes of cells into which the polynucleotides of the invention can be introduced” as including, but not limited to “eucaryotic cells, procaryotic cells and Archaea. Eucaryotic cells include animal cells, plant cells, yeast cells and, in a preferred embodiment, mammalian cells, more preferably, human cells, mammalian, including human, cells include cell lines as well as primary cells, such as primary foreskin fibroblasts.” ’729 patent at 26:29-35. The ’729 patent specification defines “host cell” as a cell “which has been or can be a recipient for a vector(s) of this invention and the progeny thereof. The progeny may not be necessarily be [sic] completely identical (in morphology or in genomic of total DNA complement) to the original parent cell due to-natural, accidental, or deliberate mutation.” *Id.* at 12:31-37.

The claims of the ’729 patent thus purport to encompass a broad genus of any cell type, including at least the genus of cells described in the specification, which includes Archaea, and prokaryotic and eukaryotic cells. ’729 patent at 26:29-35. Thus, the purported scope of the cells encompassed by independent claim 1 (and its dependent claims) is limitless.

In contrast to the broad purported scope of claim 1, the ’729 patent specification teaches only two purported working examples of cell types (both mammalian, not prokaryotic or Archaea) transduced with an rAAV vector: 293 cells, which are a human embryonic kidney cell line, and HeLa cells. *See id.* at 7:60-67; Examples 3, 5-10; Tables 1-3, 5. These are the sole exemplary cell types discussed in the specification. Other than these two mammalian cell types, the specification does not provide any examples of prokaryotic cells or Archaea that fall within the purported scope of the claims, or what conditions would allow uptake of the rAAV vector into such cell types or whether enhanced expression from of the coding region in an rAAV vector can be achieved in such cell types. Given the substantial variation purportedly encompassed by the genus, the ’729 patent specification does not disclose a representative number of species that achieves the claimed result sufficient to support the claimed genus of all cell types. Furthermore, there is no structural feature of the cells that would be common to members of the genus because the claims purport to cover any cell type, and the specification does not describe any correlation between any structure and the functional requirements of the claimed genus of cells.

Thus, claim 1 of the ’729 patent (and its dependent claims) lacks written description support for “a host cell” because a person of ordinary skill in the art would not reasonably believe that the ’729 patent inventor had possession of the claimed genus of any cell type.

iv. “a rAAV vector comprising a heterologous nucleotide sequence and one or more AAV inverted terminal repeat (ITR) sequences flanking said heterologous sequence”

The purported scope of the claims of the ’729 patent is broad with respect to the limitations reciting a “a rAAV vector comprising a heterologous nucleotide sequence and one or more AAV inverted terminal repeat (ITR) sequences flanking said heterologous sequence,” as recited in independent claim 1, relative to the limited examples and disclosure provided in the specification.

More specifically, claim 1 of the ’729 patent (and its dependent claims) purportedly encompasses using an rAAV vector with only one ITR. The claims purport to encompass methods wherein the rAAV vector comprises “*one* or more AAV inverted terminal repeat (ITR) sequences flanking said heterologous sequence.” *Id.* at claim 1 (emphasis added).

In contrast, the purported working examples in the ’729 patent specification describe use of a single half-size vector wherein each ITR of the vector (e.g., at both termini) is native AAV ITR sequence from AAV2. The ’729 patent specification does not exemplify whether rAAV vectors of the invention with a single ITR can produce the “enhanced expression” result required by the claims. Indeed, post-filing date studies have shown that use of only a single ITR in the types of rAAV vectors claimed would be inoperable. Thus, claim 1 of the ’729 patent (and its dependent claims) lacks written description support for “a rAAV vector comprising a heterologous nucleotide sequence and one or more inverted terminal repeat (ITR) sequences flanking said heterologous sequence” because a person of ordinary skill in the art would not reasonably believe that the ’729 patent inventor had possession of, e.g., rAAV vectors having the claimed *one* ITR sequence and which also possess the recited functional property of enhanced expression.

b. Dependent Claims 2-5 and 7-9

The dependent claims of the ’729 patent merely recite additional features that provide no meaningful narrowing of independent claim 1, and the dependent claims therefore lack written description for the same reasons set forth above for claim 1, as well as for the additional reasons discussed below.

i. Dependent Claim 2

Claim 2 depends from claim 1 and further recites wherein rep and cap functions are provided by a rep-cap cassette that is stably integrated in the host cell genome. Claim 2 does not meaningfully limit any of the structural or functional components described above for the rAAV

itself, the rAAV vector genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along its length"), or any number, location, and sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the '729 patent inventor had possession of the genus of claim 2.

ii. Dependent Claim 3

Claim 3 depends from claim 1 and further recites wherein rep and cap functions are provided by a plasmid. Claim 3 does not meaningfully limit any of the structural or functional components described above for the rAAV itself, the rAAV vector genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along its length"), or any number, location, and sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the '729 patent inventor had possession of the genus of claim 3.

iii. Dependent Claim 4

Claim 4 depends from claim 1 and further recites wherein the rAAV vector is provided in a plasmid. Claim 4 does not meaningfully limit any of the structural or functional components described above for the rAAV itself, the rAAV vector genus of which is not limited by any serotype

of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along its length"), or the number, location, and sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the '729 patent inventor had possession of the genus of claim 4.

iv. Dependent Claim 5

Claim 5 depends from claim 1 and further recites wherein the rAAV vector is stably integrated into the host cell genome. Claim 5 does not meaningfully limit any of the structural or functional components described above for the rAAV itself, the rAAV vector genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as "along its length"), or the number, location, and sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the '729 patent inventor had possession of the genus of claim 5.

v. Dependent Claim 7

Claim 7 depends from claim 1 and further recites a population of rAAV particles produced according to the method of claim 1. Claim 7 does not meaningfully limit any of the structural or functional components described above for the rAAV itself, the rAAV vector genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of

intrastrand base paring (which is vaguely described as “along its length”), or the number, location, and sequence of ITRs (under Plaintiffs’ proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the ’729 patent inventor had possession of the genus of claim 7.

vi. Dependent Claim 8

Claim 8 depends from claim 1 and further recites a population of rAAV vectors produced according to the method of claim 1. Claim 8 does not meaningfully limit any of the structural or functional components described above for the rAAV itself, the rAAV vector genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand base paring (which is vaguely described as “along its length”), or the number, location, and sequence of ITRs (under Plaintiffs’ proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the ’729 patent inventor had possession of the genus of claim 8.

vii. Dependent Claim 9

Claim 9 depends from claim 1 and further recites wherein the rAAV particles are purified to deplete the helper virus. Claim 9 does not meaningfully limit any of the structural or functional components described above for the rAAV itself, the rAAV vector genus of which is not limited by any serotype of AAV, gene of interest, type of heterologous sequence, amount of intrastrand

base paring (which is vaguely described as "along its length"), or the number, location, and sequence of ITRs (under Plaintiffs' proposed claim constructions), despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the '729 patent inventor had possession of the genus of claim 9.

2. Invalidity under 35 U.S.C. § 112, First Paragraph for Lack of Enablement

"To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *ALZA Corp. v. Andrx Pharms.*, LLC., 603 F.3d 935, 940 (Fed. Cir. 2010) (quoting *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997)). An essential question for an enablement analysis is "whether the scope of enablement of [a claim] is as broad as the scope of the claim." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212 (Fed. Cir. 1991). The applicant must disclose a range of embodiments that is adequate in relation to the breadth of the patent right being sought. *See, e.g.*, *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (finding scope of claims that encompassed any and all vaccines in any animal toward any RNA virus not enabled when only a single working example was provided).

The need to engage in "an iterative, trial-and-error process to practice the claimed invention," where the specification provides "only a starting point, a direction for further research," precludes a finding of enablement. *ALZA*, 603 F.3d at 941. Where the skilled artisan "would need to assay each of at least tens of thousands of candidates" and the specification offered "no guidance or predictions about particular substitutions" that would lead to other effective

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members, genus claims are not enabled based on undue experimentation. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385-86 (Fed. Cir. 2013). "[T]he enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those requirements, especially where predictability and guidance fall short. In particular, it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim." *Amgen Inc. v. Sanofi Aventisub LLC*, 987 F.3d 1080, 1086 (Fed. Cir. 2021). Thus, "[w]hile functional claim limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language." *Id.* at 1087; *see also id.* ("[T]he use of broad functional claim limitations raises the bar for enablement . . . .")

As discussed *supra*, the rAAV vectors used in the claims of the '729 patent are broadly defined by structural and functional elements. Determining which combination of structures in the claimed methods using rAAV vectors would result in enhanced expression of a desired gene (i.e., by supporting increased base pairing) would require an iterative, trial-and-error process that would amount to undue experimentation, due to the vast genus of rAAV vectors purportedly encompassed by the methods claimed. Indeed, for example, the inventor states that the intrastrand complementarity "may be any of a number of sizes," therefore including an unlimited spectrum of sizes, without providing any supporting detail or information regarding which sizes will accomplish the claimed function beyond those having 100% complementarity. *See* '729 patent at 14:51-67. Further, during prosecution of a patent application in this family, the inventor acknowledged that "[t]he specification teaches that intrastrand base pairing may be anywhere along the heterologous sequence, and may or may not be within a coding region of a heterologous

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sequence." GENZ_NOV_00002136. Again, this lack of specificity would require an iterative, trial-and-error process to determine which combination of structures in the claimed rAAV vectors would result in enhanced expression of a desired gene.

Undue experimentation is evaluated under the Wands factors, which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). An evaluation of the experimentation required under the *Wands* factors follows.

a. Independent Claim 1

i. Factors 1 and 2: Quantity of Experimentation Necessary and Amount of Direction or Guidance Presented

As discussed above, independent claim 1 of the '729 patent (and its dependent claims) comprises incubating any cell type to purify rAAV particles. In contrast, the purported working examples in the '729 patent specification describe using two immortalized human cell lines (HEK 293 cells and HeLa cells). *See, e.g.*, Examples 7 and 11 (using HeLa cell lines), Example 6 (using human 293 cells, a HEK cell line). Based on results with just two cell types (one of which the specification teaches is considered inefficient at expressing rAAV vectors, i.e., HeLa cells), the specification extrapolates broadly that "[c]ell types that were traditionally considered impermissive in the sense of inefficient expression (whether due to time course and/or levels of expression) of parvovirus vectors are now practical, useable, hosts." *Id.* at 8:7-10. Further, as discussed above, the '729 patent specification describes "[t]ypes of cells into which the polynucleotides of the invention can be introduced" as including, but not limited to "eucaryotic cells, procaryotic cells and Archaea." '729 patent at 26:29-31. However, post-filing date studies

have shown that expression of the types of rAAV vectors claimed in a prokaryotic cell would be inoperable. Thus, the ’729 patent does not provide sufficient direction or guidance across the limitless scope of cell types in independent claim 1 and its dependent claims.

Independent claim 1 of the ’729 patent (and its dependent claims) further purports to encompass using an rAAV vector with only one ITR. The claims purport to encompass methods wherein the rAAV vector comprises “*one* or more inverted terminal repeat (ITR) sequences flanking said heterologous sequence.” *Id.* at claim 1 (emphasis added). In contrast, the purported working examples in the ’729 patent specification describe use of a single half-size vector wherein each ITR of the vector (e.g., at both termini) is native AAV ITR sequence from AAV2. The ’729 patent specification does not exemplify whether rAAV vectors of the invention with, e.g., a single ITR can produce the “enhanced expression” result required by the claims. Indeed, post-filing date studies have shown that use of only a single ITR in the types of rAAV vectors claimed would be inoperable. Thus, the ’729 patent does not provide sufficient direction or guidance to enable the use of, e.g., a single ITR.

Independent claim 1 (and its dependent claims) further purportedly encompasses methods requiring a vast genus of rAAV vectors that must meet certain functional limitations. Determining which combination of structures in a specific vector would result in enhanced expression (i.e., by supporting increased intrastrand base pairing) would require an excessive amount of experimentation across all heterologous sequences and lengths to yield sufficient intrastrand base pairing and purportedly enhanced expression. Further, post-filing date studies have shown that small changes to the structure of rAAV vectors could significantly impact the functionality of the vectors. The ’729 patent does not provide sufficient direction or guidance across the broad

purported scope of unlimited heterologous sequences and vector lengths purportedly encompassed by the genus of rAAV vectors in independent claim 1 and its dependent claims.

Independent claim 1 of the ’729 patent (and its dependent claims) purportedly encompasses methods using a vast array of rAAV formats. The claimed methods involve using vectors from *any* serotype of rAAV particle, and *any* serotype of rAAV vector, which are not required to be derived from the same serotype. In contrast, the only serotype of rAAV particles used in the purported working example in the specification is rAAV serotype 2 particles. ’729 patent at 15:56-58. While the specification states that “it is fully expected that the same principles derived from analysis of AAV2 will be applicable to other AAV serotypes, since it is known that the various serotypes are quite closely related, both functionally and structurally, even at the genetic level,” (*id.* at 15:58-62), such a statement is merely expressing a hypothesis and invitation for further research by a person of ordinary skill in the art to use other AAV serotypes. Courts have found that claims were not enabled when the amount of experimentation “would take a substantial amount of time and effort,” and the “only ways for a person of ordinary skill to discover undisclosed claimed embodiments would be through either ‘trial and error, by making changes to the disclosed antibodies and then screening those antibodies for the desired binding and blocking properties,’ or else ‘by discovering the antibodies de novo’ according to a randomization-and-screening ‘roadmap.’” *Amgen*, 987 F.3d at 1088 (citing *Amgen Inc. v. Sanofi*, No. 14-1317, 2019 WL 4058927, *11–*12 (D. Del. Aug. 28, 2019).

The ’729 patent claims purport to encompass methods using an rAAV vector comprising *any* nucleotide sequence comprising a coding region. In contrast, the rAAV vector used in the purported working example only encodes green fluorescent protein. *Id.* at Fig. 5. Further, the claims purport to encompass methods using a genus of rAAV vectors that set no limits on the

amount of intrastrand base pairing in the coding region. Rather, the rAAV vector is defined functionally as possessing enhanced expression relative to a second rAAV vector that lacks an undefined amount of "sufficient" intrastrand base pairing to enhance expression. The patent states that the intrastrand complementarity "may be any of a number of sizes," therefore including an entirely unlimited spectrum of sizes, without providing any supporting detail or information regarding workable ranges. *See* '729 patent, 14:51-67. The only embodiment exemplified in the patent is described as a vector that is base paired "along most or all of its length." *Id.* at 15:12-19. No guidance is provided for any levels of base pairing less than 100% that can achieve the claimed enhanced expression.

Moreover, the '729 patent provides very little guidance as to how a person of ordinary skill in the art should determine whether enhanced expression is present. For example, the claims do not indicate when expression is to be assessed. In the Examples, an increased percentage of fluorescent cells, as measured at two different time points (48 or 72 hours) post-infection, is shown for cells infected with the 100% intrastrand base paired rAAV vector compared to a second vector with no intrastrand base pairing. *Id.* at 32:3-33:16; 36:3-55. However, while some time presumably must pass for expression to reach a detectable level, it is possible that as time passes the expression may decrease. Conversely, it is possible that, as enough time passes, the control vector that "lacks sufficient intrastrand base pairing to enhance expression" may exhibit increased expression of a transgene so that it is not possible to determine a significant difference between expression levels of the vectors. The patent provides no guidance regarding how one skilled in the art would test for the claimed enhanced expression at either of these time points.

Moreover, it is evident from at least Figure 6F of the '729 patent, that the examples described in the specification used a lambda stuffer sequence in the control vector. The lambda

stuffer was known to negatively impact expression. Thus, the examples described in the specification may have utilized a control that artificially suppressed expression due to the use of a lambda stuffer, thereby inflating the level of "enhanced expression" observed for the test vector. As a result, it is impossible for a person of ordinary skill in the art to determine, based on the examples provided in the specification, what characteristics of the rAAV vectors in the claimed methods, e.g., amount of intrastrand base pairing, would be required to enhance expression over a vector that "lacks sufficient intrastrand base pairing."

The '729 patent disclosure further provides little to no guidance regarding determining intrastrand base pairing that is "sufficient" to enhance expression or what it means to "lack[] sufficient intrastrand base pairing" to enhance expression of the heterologous sequence. With regard to the length of the requisite level of intrastrand base pairing, the specification teaches that a region of intrastrand complementarity can be anywhere from as little as 5 to greater than 1000 nucleotides. *Id.* at 10:26-30. The specification also states that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about *any* of the following: 25%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:56-60 (emphasis added). Yet, the only purported working example discloses an rAAV vector with close to 100% intrastrand base pairing in the rAAV vector and whose expression is "enhanced" over an rAAV vector with no intrastrand base pairing. Moreover, it is likely the purported working example is inoperative, in whole or in part.

Further, to the extent the '729 patent claims are construed to encompass *non-native* ITR sequences, the '729 patent claims are invalid for lack of enablement, because experimentation across the full scope of rAAV vectors comprising any modified, mutated, or non-native ITR would require a substantial amount of time and effort, particularly in view of the limited disclosures in

the patent specification (disclosing a single purported working example of an rAAV having intrastrand base pairing, *i.e.*, a half-size vector wherein each ITR of the vector (e.g., at both termini) is native AAV ITR sequence from AAV2 and comprising a heterologous nucleotide sequence containing a coding region for a detectable marker). Indeed, substantial time and effort was required to generate, experimentally test, and ascertain the functionality of later-developed vectors containing a mutated ITR, which subsequently received its own patent protection (*see, e.g.*, McCarty (2008); McCarty (2003); McCarty (2001); U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457).

Due to the lack of direction and very limited guidance presented in the specification of the ’729 patent, the Asserted Claims of the ’729 patent require a high degree of trial and error in determining which combination of structures in the patented technology would be conducive to supporting increased base pairing and thus enhanced expression of a desired gene compared to a vector lacking sufficient base pairing. In other words, undue experimentation will be required to practice the full scope of the Asserted Claims.

ii. Factor 3: Presence or Absence of Working Examples

With regard to functionally-defined genus claims in unpredictable arts, the Federal Circuit has “refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim.” *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As discussed above, *see supra*, there is a single purported working example of an rAAV vector which shows “enhanced expression” in the ’729 patent, and that example is limited to use of a half-size AAV GFP vector that has nearly 100% base pairing and shows enhanced expression compared to an rAAV vector

that lacks any base pairing.[14] Further, as discussed, this vector was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other cells (*see, e.g., id.* at Example 1, 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any host cell. Moreover, it is likely the purported working example is inoperative, in whole or in part. This single purported working example does not amount to a demonstration with reasonable specificity of how to make and use other potential embodiments across the full scope of the Asserted Claims.

iii. Factors 4-6: Nature of the Invention, State of the Prior Art, and Relative Skill of Those in the Art

The nature of the claimed invention is a method for preparing an rAAV by incubating a host cell comprising an rAAV vector comprising a heterologous sequence and purifying rAAV particles produced from the host cell, wherein the rAAV particles comprise an rAAV genome which forms intrastrand base pairs along its length, such that expression of a coding region of the heterologous sequence is enhanced as compared to an rAAV vector which lacks sufficient intrastrand base pairing to enhance said expression. As the ’729 patent admits, the state of the art was such that the field was still in its early stages at the time of filing (1999). *See, e.g.*, ’729 patent at 1:34-41 (“Recombinant vectors based on parvovirus, such as adeno-associated virus (AAV), show promise for gene therapy. However, obtaining efficient, sufficient levels of expression of a transgene in various cell types has presented problems. Some cell types are impermissive in the sense that initiation of transcription or translation of the transgene is inefficient, with expression

[14] As discussed *supra*, the TNFR-Fc example (Example 13) appears to be prophetic and does not describe any details regarding whether the vector encoding TNFR-Fc is designed to give rise to intrastrand base pairing. Similarly, Example 5 describes an rAAV vector encoding human alkaline phosphatase and bacterial neomycin resistance genes used as controls, but this vector does not appear to possess intrastrand base pairing in the coding region and thus do not exemplify the claims. *Id.* at 31:30-32:23.

accordingly very slow to initiate, if it initiates at all."). Thus, before the invention could be practiced, it would be necessary to make and screen each candidate rAAV vector for sufficient intrastrand base pairing in its heterologous sequence to enhance expression of said sequence. And although the level of skill in the art was relatively high at the time of filing (1999), skill alone cannot stand in for a total absence of guidance in the specification.

iv. Factor 7: Predictability or Unpredictability of the Art

As the '729 patent specification admits, this was a particularly unpredictable field at the time of filing (1999). *See, e.g.*, '729 patent at 4:37-40 ("there can be difficulties in obtaining sufficient levels of expression of heterologous sequences from rAAV vectors and viruses containing such vectors"). This unpredictability would have been compounded by the breadth of the claims, which read on the use of all heterologous sequences and all vector lengths. In particular, as discussed above, the lower size limit of the vectors described in the '729 patent would have been wholly inoperable. Further, minor changes to characteristics of the rAAV vector, including size, rAAV serotype, etc. could potentially result in significant, unpredictable changes to the level of intrastrand base pairing and expression of the heterologous sequence. Without testing, a person of ordinary skill in the art could not have predicted whether a given rAAV vector within the vast genus of rAAV vectors claimed would contain sufficient intrastrand base pairing to enhance expression compared to an equally undefined second vector, let alone meet any of the other claim limitations.

v. Factor 8: Breadth of the Claims

Independent claim 1 of the '729 patent (and its dependent claims) is extremely broad and contains several limitations that are unbounded and/or defined only by broad functional requirements, as explained at length above. *See supra* Section VII.B.1 and VII.B.2.a.i. Given the

breadth of disclosure, a person of ordinary skill in the art would require significant experimentation to devise a construct that meets the functional limitations in the claims of the ’729 patent, i.e., that has sufficient intrastrand base pairing such that expression of a heterologous sequence is enhanced relative to a construct that lacks sufficient intrastrand base pairing to enhance expression.

As discussed above, the specification merely invites the person of ordinary skill in the art to perform his or her own experimentation to determine the amount of intrastrand base pairing that would work to “enhance expression” for any given coding region and rAAV serotype in order to meet the limitations of the Asserted Claims. As a result, an undue amount of experimentation would be required for a person of ordinary skill in the art to make and use the alleged invention of the Asserted Claims of the ’729 patent.

b. Dependent Claims 2-5 and 7-9

As explained above with respect to the lack of written description, the dependent claims of the ’729 patent further recite features that provide no meaningful limitation as to claim scope, as the dependent claims still purport to encompass a nearly limitless universe of nearly all types of serotype of AAV, gene of interest, amount of intrastrand base paring (which is functionally defined as “enhanc[ing]” expression), and provide no meaningful limits regarding the number, location, and sequence of ITR(s). For at least the same reasons set forth in Sections VII.B.1 and VII.B.2.a, the asserted dependent claims are invalid for lack of enablement.

3. Invalidity under 35 U.S.C. § 112, Second Paragraph for Indefiniteness

Under 35 U.S.C. § 112, ¶ 2, a patent “is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” *Nautilus, Inc. v. Biosig. Instruments, Inc.*, 572 U.S. 898, 901 (2014). A patent must be “precise enough to afford

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clear notice of what is claimed, thereby apprising the public of what is still open to them. Otherwise there would be a zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims." *Id.* at 909-910 (internal quotations and citations omitted).

i. "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"

Claim 1 of the '729 patent and its dependent claims require, among other things, an rAAV vector comprising a heterologous nucleotide sequence wherein "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." "Enhanced" in this context is indefinite, as the specification fails to explain (1) how much intrastrand base pairing is required to result in "enhanced" expression, (2) at what point in time the expression should be measured, and (3) how much expression amounts to "enhanced" expression. The specification only provides generalized statements regarding the required "enhanced" expression, but enhanced expression purportedly resulting from intrastrand base pairing is not expressly defined in the patent specification and purportedly encompasses any enhancement, measured by any means, at any point in time relative to any other rAAV that has a different and undefined amount of intrastrand base pairing.

With regard to intrastrand base pairing, the '729 specification fails to elaborate on what position or quantity of intrastrand base pairing will achieve the "enhanced" expression, making it impossible to know how one is potentially infringing. For example, the patent explains that "a recombinant viral vector containing a sequence or region that forms intrastrand base-pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the *degree* of intrastrand base pairing. *Id.* at 10:52-56 (emphasis added). The patent further explains that "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least

about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%. 95%, 98%, 99%." *Id.* at 10:56-60. The patent also explains that "[t]he region(s) of intrastrand complementarity . . . in the recombinant viral vector 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." *Id.* at 14:38-46 (emphasis added). The patent further teaches 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.* at 14:51-53 (emphasis added). These sweeping statements do not put the public on notice of what the claimed invention is—i.e., how much intrastrand base pairing would be needed in specific vectors to arrive at enhanced expression.

Next, with regard to the temporal aspect of measuring expression, the '729 patent specification does not define what time points should be used to measure such a rate. The single purported working example (Example 6) which measures differences in rates of expression only conducts this measurement at 48 and 72 hours and only provides the rate of expression for the GFP expression in the half-sized vector, not the control vector. A person of ordinary skill in the art would know that expression levels will vary over time. Thus, a person of ordinary skill in the art could potentially infringe at one point in time, but not another.

With regard to how much expression amounts to "enhanced" expression, the patent again provides little guidance. The '729 specification teaches that intrastrand base-pairing contributes to increased levels and/or increased rate of heterologous sequence expression, *id.* at 7:61-64, and defines "expression" as follows:

"Expression" includes transcription and/or translation. Methods of detecting transcription, such as Northern analysis, and translation, such as Western analysis or ELISA, are well known in the art. These methods also permit measuring differing levels of transcription and/or translation, whether that difference is between or among different vectors, different times, different host cells, etc. *Id.* at 13:11-17.

Based on this definition, a person of ordinary skill in the art would not know whether "enhanced expression" relates to the rate of expression, e.g., the speed, or the level of expression, e.g., the amount. Further, from this definition, a person of ordinary skill in the art would be unable to determine whether to detect transcription, translation, or both, and what method or methods by which said expression should be assessed. The different measurement techniques disclosed in the '729 specification possess different sensitivity levels which could yield different results when measuring expression from the same rAAV vector. The Federal Circuit has held patent claims invalid for indefiniteness where a claim term may be determined by multiple methods, the testing results of which "will necessarily fall within or outside the claim scope depending on the . . . method chosen." *Honeywell Intern. v. ITC*, 341 F.3d 1332, 1341 (Fed. Cir. 2003).

Moreover, the purported comparator against which expression levels are measured, i.e., a second rAAV vector that "lacks sufficient intrastrand base pairing," is not clearly defined in the specification. The single purported working example in the specification discloses an rAAV vector with close to 100% intrastrand base pairing in the rAAV vector and whose expression is "enhanced" over an rAAV vector with no intrastrand base pairing. Ultimately, the claim limitation is circular, whereby an undefined sufficiency of base pairing and expression in a first rAAV is relative to an undefined insufficiency of base pairing and expression in a second rAAV (whose insufficiency is relative to the first rAAV).

For at least these reasons, the Asserted Claims of the ’729 patent are invalid under 35 U.S.C. § 112 as indefinite.

ii. “along its length”

Claim 1 of the ’729 patent and its dependent claims require, among other things, an rAAV genome which forms intrastrand base pairs “along its length.” Requiring constructs that form intrastrand base pairing along the length of the rAAV genome is indefinite, as the specification fails to explain how much intrastrand base pairing is required to constitute pairing “along” its length, and further fails to explain the circumstances under, and characteristics by which, such base-pairing along the length of the rAAV genome occurs and accomplishes the claimed function of enhanced expression.

The patent states that “a recombinant viral vector containing a sequence or region that forms intrastrand base-pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the degree of intrastrand base pairing.” ’729 patent at 10:52-56. The patent also states 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.* at 14:51-53 (emphasis added). Further, the patent broadly states that “the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%.” *Id.* at 10:56-60. This exceptionally broad range of values provides no information as to whether any of these values represent intrastrand base pairing (or what amount of intrastrand base pairing occurs) along the length of the rAAV genome, or any information as to what circumstances or characteristics of such base-pairing are necessary or sufficient to accomplished the claimed function of enhanced expression, e.g., how intrastrand base pairing in the rAAV genome but outside the heterologous sequence and outside the coding region would accomplish the claimed

function; where and how much intrastrand base pairing must occur (ranging from 25-100% of any number of nucleotides anywhere in the rAAV genome); and whether or what conditions must be satisfied to enhance expression (e.g., type of cell, type of AAV, type of nucleotide, intracellular conditions, extracellular conditions, etc.). The patent specification and claims provide no guidance as to what amount of intrastrand base pairing, e.g., an unspecified percentage over an unspecified length of nucleotides, or an unspecified number over an unspecified length of nucleotides, or something else entirely, might be defined as intrastrand base pairing along the length of a heterologous sequence.

These overbroad claims reciting intrastrand base pairing along the length of an rAAV genome do not put the public on notice of what the claimed invention is—i.e., how much intrastrand base pairing constitutes "along the length," thus making it impossible to know whether one is potentially infringing. *See, e.g.*, *Nautilus*, 572 U.S. at 901.

iii. "conditions that allow"

Claims 1-5 and 7-9 of the '729 patent require, among other things, a method for preparing a rAAV wherein the method comprises incubating a host cell under "conditions that allow" AAV replication and encapsidation. Incubating a host cell under "conditions that allow" AAV replication and encapsidation as part of a method of preparing an rAAV vector is indefinite, as the specification fails to explain what these "conditions" should be, other than conditions that do not prevent such events from occurring.

The patent provides three exemplary approaches to packaging AAV, including that "[o]ne exemplary technique of this third approach is outlined in [WO 95/13365 (Targeted Genetics Corporation and Johns Hopkins University) . . . In a preferred embodiment, an AAV packaging plasmid comprising the rep gene operably linked to a heterologous promoter is introduced into the cell, and then the cell is incubated under conditions that allow replication and packaging of the

rAAV vector sequence into particles." '729 patent at 22:17-30. The patent specification and claims provide no guidance as to what these conditions are that would allow replication and packaging of the rAAV vector sequence into particles. These overbroad claims reciting "conditions that allow" AAV replication and encapsidation do not put the public on notice of what the claimed invention is—i.e., what the parameters of these "conditions" are, thus making it impossible to know whether one is potentially infringing. *See, e.g., Nautilus*, 572 U.S. at 901.

For at least these reasons, the Asserted Claims of the '729 patent are invalid under 35 U.S.C. § 112 as indefinite.

VIII. Invalidity Contentions As To The '054 Patent

A. The '054 Patent Claims Are Invalid for Anticipation and/or Obviousness

Each Asserted Claim of the '054 patent is invalid for anticipation and/or obviousness. In addition to the information set forth below, a chart identifying where specifically in each item of prior art each limitation of each Asserted Claim of the '054 patent is found is attached as Appendix E, which is incorporated herein. Pinpoint citations to material in the prior art are exemplary of the disclosures and teachings of the prior art. Those citations should not be construed as limiting the disclosure of any prior art or as reflecting the only section of a prior art reference disclosing a particular limitation or teaching.

1. Independent Claims 1 and 19

The '054 patent admits that by August 9, 1999, the use of an rAAV vector comprising a single-stranded heterologous nucleotide sequence was well-known. *See, e.g.*, '054 patent at 3:24-27 ("The native AAV genome has been used as the basis of vector systems for the delivery and expression of heterologous genes in host cells such as mammalian cells, such as for gene therapy.") (*citing* Muzyczka (1992) *Curr. Top. Microbiol. Immunol.* 158:97-129; Carter, B. J. (1992) *Curr.*

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Op. Biotechnol. 3:535-539; and Flotte et al. (1995) *Gene Therapy* 2:357-362). The ’054 patent further admits that “[r]ecombinant AAV (rAAV) vectors, based on the native AAV genome, are generally produced by deletion of rep and/or cap sequences and [their] replacement by a heterologous sequence. Thus, rAAV vectors generally comprise a single-stranded DNA molecule comprising a heterologous gene sequence or sequences flanked by at least one AAV ITR, and typically by two AAV ITRs, one at each end.” *Id.* at 3:30-36.

The ’054 patent further admits that by August 9, 1999, it was well-known that “efficient, productive packaging in an AAV virus particle is limited to vectors having approximately the size of an AAV genome (i.e., approximately 4.7 kb) or smaller” and that by August 9, 1999, those skilled in the art had already used smaller rAAV genomes. *Id.* at 3:43-46; 49-56 (*citing* Dong et al. (1996) Hum. Gene Therapy 7:2101-2112 for teaching the use of “rAAV genomes having sizes between 2 kb and 6 kb”); *see also id.* at 9:66-67 (“The maximum size vector that can be packaged to yield an infectious viral particle is approximately 5.2 kb.”); *id.* at 15:47-50 (“In the case of an rAAV vector of this invention, its length may be less than about. . . .5.5.”). Indeed, by August 9, 1999, the use of rAAV vectors of approximately half size was well-known and described in numerous prior art references. *See, e.g.*, Hörster (1999); Muzyczka (1992); Hermens (1997); Dong (1996).

The ’054 patent further admits that it was well-known that co-infection with a helper virus engendered safety concerns and identified methods known in the art to remove or inactive the helper virus. *See e.g.*, *id.* at 4:22-25 (“infection of the host cell with a helper virus may be undesirable because of safety concerns related to other properties of helper viruses and helper functions”); *id.* at 25:16-26 (“Optionally, rAAV virus preparations can be further processed to enrich for rAAV particles, deplete helper virus particles, or otherwise render them suitable for

administration to a subject. See Atkinson et al. for exemplary techniques (WO 99/11764). Purification techniques can include isopynic gradient centrifugation, and chromatographic techniques. Reduction of infectious helper virus activity can include inactivation by heat treatment or by pH treatment as is known in the art. Other processes can include concentration, filtration, diafiltration, or mixing with a suitable buffer or pharmaceutical excipient.”).

Hörster (1999) describes the use of “fusion constructs between the indicators luciferase and gfp and the HIV-1-directed antisense sequence AR6 or ribozyme Rz12.” Hörster (1999) at 1232. Hörster (1999) describes 12 fusion constructs comprising single stranded heterologous nucleotide sequences. *Id.* Hörster (1999) discloses approximately half size rAAV vector fragments comprising heterologous sequences encoding luciferase, gfp, AR6, and/or Rz12 flanked by ITRs in Figures 1 and 3. *Id.* at 1232-33. Hörster (1999) also describes producing infectious rAAV particles using a system that “provides all necessary helper functions for rAAV particle formation by plasmid-coded genes thereby avoiding the use of infectious adenovirus. The concentrations of infectious partciples (IP) after one CsCl gradient purification followed by dialysis was typically equal to or greater than 5 X 10^8 IP/ml.” *Id.* at 1233. Hörster (1999) describes using “wtAAV, AAV-gfp and AAV-gfp-AR6-particles of varying infective doses of up to a MOI of 125 to transduce HeLaP4/CCR5 cells.” *Id.* at 1234. Hörster (1999) also describes that “[t]ransduced cells showed *gfp* expression according to the MOI used.” *Id.* at 1234.

Muzyczka (1992) describes the use of rAAV vectors “containing the *dl*3-94/neo genome (50% of wild type size)” and “the neomycin phosphotransferase gene.” Muzyczka (1992) at 111-12. The *dl*3-94/neo genome (50% of wild type size, *i.e.*, the approximately half size vector) “were found to consist predominantly of particles that had the density of AAV particles containing a wild type complement of DNA. When the DNA in these particles was examined it was found to consist

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of three kinds of molecules. The predominant DNA molecule was an inverted dimer of the *dl*3-94/neo genome. Such molecules occur as a natural consequence of the AAV DNA replication mechanism and have been described in studies of spontaneously occurring deletions or AAV defective interfering (DI) genomes." *Id.* at 112 (citations omitted). Muzyczka (1992) describes in Figure 6 "[g]rowth of an AAV recombinant virus stock. Human cells are transfected with the AAV recombinant plasmid and a complementing plasmid which is defective for packaging but supplies the wild type AAV gene products. The cells are also infected with adenovirus (Ad) to supply helper function. The virus stock produced contains both adenovirus and the AAV recombinant virus. Adenovirus is inactivated by heat or removed by density gradient centrifugation." *Id.* Myzyczka (1992) also describes that the rAAV vectors "proved to be capable of efficiently transducing foreign DNA into human cells." *Id.* at 110.

Hermens (1997) describes the generation of an rAAV virus with a vector "containing an expression cassette for B-50/GAP-43." Hermens (1997) at 153. Hermens describes the B-50/GAP-43 open reading frame (ORF) as "cloned into pcDNAI/Amp5.0 (Invitrogen). This resulted in pcDNAB-50 containing a CMV-B-50-A+ expression cassette. Subsequently, from a plasmid designated psub201 (a recombinant plasmid from which an infectious AAV genome can be excised Samulski, et al., 1987) the AAV-coding sequences are replaced by the CMV-B-50-A+ expression cassette (2.1 kb) of pcDNAB-50. This resulted in plasmid psub201B-50." *Id.* Hermens (1997) describes "the application of an alternative viral vector, based on adeno-associated virus, has been shown to direct long-term expression of a foreign gene in the brain without noticeable toxicity." *Id.* at 149. Hermens (1997) describes that "[s]ince AAV is heat stable the heating step results in the elimination of heat labile infectious adenovirus," or alternatively, inactivating the helper virus

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(Ad) by "[f]ollowing centrifugation at 1500 g for 20 min at 4°C to remove the cell debris, the supernatant was heated at 56°C for 30 min." *Id.* at 153.

Dong (1996) describes rAAV vectors "from 2 kb to 6 kb in size" that carry "a chloramphenicol acetyltransferase (CAT) reporter gene." Dong (1996) at 2101. Dong (1996) also describes that "on the Southern blot of virion DNA, only [the] sample from the 1.9-kb vector contained DNA that appeared twice as large as single stranded DNA on an alkaline gel (Fig. 5, lane 2, DS). When the vector DNAs were isolated from infected cells in the absence of adenovirus-mediated double-strand conversion, the majority of the 1.9-kb vectors were in double-stranded form, and none was observed in any of the larger vectors." *Id.* at 2107-08. Dong (1996) describes that "AAV particles carrying vectors ranging from 1,918 to 51,113 nucleotides in size transferred CAT genes into HeLa cells. This demonstrated that vectors up to 5.1 kb in size were packaged into AAV virions, and consequently transduced into target cells." *Id.* at 2104. Dong (1996) also describes how "adenoviruses were heat-inactivated at 65°C for 30 min." *Id.* at 2103.

The '054 patent admits that by August 9, 1999, it was well-known that the AAV life cycle involves the generation of "a self-complementary double-stranded molecule that is covalently closed at one end" called "the replicative form (RF)." '054 patent at 2:19-22; *see also* Carter (1984) at 212 ("These molecules consist of complementary strands which are covalently joined at one terminus by a hairpin structure formed by virtue of the palindromic terminal sequence 126 nucleotides in length."). The '054 patent further admits that by August 9, 1999, it was well-known that "formation of the RF is required for transcription of viral proteins (or, in the case of recombinant AAV, the transcription of heterologous sequences such as a transgene) to occur, since cellular RNA polymerizing systems require a double-stranded template." '054 patent at 2:47-52; *see also* Carter (1984) at 219 ("Also, as shown in Fig. 2, the RF structure is the configuration that

would be expected during replication of AAV DNA."). The '054 patent also admits that when a recombinant viral vector has a sequence complexity that is approximately one half its length, "a vector is able to form a 'snapback' molecule which is double-stranded along most or all of its length, thus analogous to the RF produced during AAV infection." '054 patent at 15:22-25; *see also id.* at 18:38-41 ("Upon replication, the half-size genome is copied into a complementary DNA strand that is covalently attached to its template at one end (see FIGS. 1 and 3), forming a structure that will 'snap back' into a hairpin duplex."); *id.* at 33:60-66 ("Alkaline gel analysis, shown in Fig. 7A, indicates that preparations of virus particles having vector genomes that were made from a half-size plasmid contain DNA molecules that have a single-stranded length that is the same as a native AAV genome (second lane from left). This is what would be expected if 'snap-back'-type RF molecules have been packaged in these virus particles."); Carter (1984) at 216, 222 (indicating that DNA 1.41b, "which appeared to be mainly hairpin molecules," had a "mean molecular size estimated from gel electrophoresis of about 50% of genome length"). The '054 patent further admits that vectors of the alleged invention:

> [C]an be produced by constructing a parvovirus vector, such as an rAAV vector, that has a size approximately one-half of a native genome and allowing such a vector to replicate in a host cell. . . . Upon replication, the half-size genome is copied into a complementary DNA strand that is covalently attached to its template at one end (see FIGS. 1 and 3), forming a structure that will "snap back" into a hairpin duplex."

'054 patent at 18:32-41; *see also* Carter (1984) at 212 "Some variant genomes have a conformation similar to that of certain intracellular replicating forms of parvovirus DNA. These molecules consist of complementary strands which are covalently joined at one terminus by a hairpin structure formed by virtue of the [ITR]. These molecules at a neutral pH spontaneously renature with zero-order kinetics to form duplex structures."). As the '054 patent depicts in Figs. 1 and 3, "the heterologous sequence [generated from such half-sized vectors] forms base pairs essentially

along its entire length, thus analogous to an AAV replicative form." '054 patent at 5:15-17. The '054 patent admits that "[t]hese recombinant parvovirus vectors comprise an ITR sequence between the heterologous sequences (i.e., an ITR sequence flanked on both sides by heterologous sequences)." *Id.* at 18:47-50. Therefore, these approximately half size vectors necessarily and inevitably comprise ITR-heterologous sequence-ITR-heterologous sequence-ITR.

Literature dated after August 9, 1999, e.g., McCarty (2008), supports the admissions of the '054 patent by disclosing that such self-complimentary rAAV vectors "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 dimeric inverted repeat will be no larger than the normal AAV packaging capacity (~4,700 nucleotides)." McCarty (2008) at 1649. McCarty (2008) further recognizes that "[a]lthough this further restricts the transgene carrying capacity of an already small viral vector, it offers a substantial premium in the efficiency, and speed of onset, of transgene expression because dsDNA conversion is independent of host-cell DNA synthesis and vector concentration." *Id.* (*citing* McCarty (2001), Gene Ther 8:1248-54). McCarty (2008) further supports the admissions of the '054 patent by disclosing that such self-complimentary vectors "[e]ach displaced daughter strand comprises a ssDNA inverted repeat with a complete ITR at each end and a mutated ITR in the middle (Figure 1, step 9d)" and that "[p]roduction and purification of scAAV vector from mutated ITR constructs is the same as conventional ssAAV." *Id.*; *see also* McCarty (2001) at 1249 ("The self-complementary (scAAV) GFP dimer and mEpo dimer vectors fold into a complete duplex DNA with one extra copy of the terminal repeat while the GFPneo, LacZ, and mEpoλ [which had sizes greater than that of an approximately half sized vector] require cell-mediated DNA synthesis of the complementary strand.").

Thus, each of Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996) teach the approximately half size vector comprising a region which forms intrastrand base pairs such that expression of a coding region of a heterologous sequence is enhanced. *See e.g.*, Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996). Moreover, the prior art discloses compositions comprising purified rAAV particles comprising an AAV capsid and a single-stranded rAAV vector genome, as well as methods of expressing a polynucleotide coding sequence in a cell, wherein the coding sequence is introduced into the cell by contacting the cell with a composition comprising a purified rAAV particle comprising an AAV capsid and single-stranded rAAV vector genome, in the absence of an AAV helper virus, under conditions that allow expression of the coding sequence. *See e.g.*, Hörster (1999), Muzyczka (1992), Hermens (1997), Dong (1996), Berns (1996), Carter (1996), Kaplitt (1995), Bartlett (1995), Xiao (1998), Ferrari (1996), Ferrari (1997), Samulski (1987), WO9911764 (1997), Phillips (1997), Welch (1998), Su (1996), Zolotukhin (1996), WO9732018 (1996), Mamounas (1995), WO9717458 (1995), Fisher (1996), WO9947691, and WO9528493 (1994). A person of ordinary skill in the art would have been motivated to combine such teachings with a reasonable expectation of success to meet the claim limitations of claims 1 and 19.

Accordingly, the disclosure in Hörster (1999), Muzyczka (1992), Hermens (1997), and Dong (1996) of (1) a composition comprising a purified rAAV particle with an AAV capsid and an rAAV genome wherein the genome has in the 5’ to 3’ direction an ITR-heterologous sequence-ITR-heterologous sequence-ITR and (2) a method for introducing a polynucleotide into a cell comprising contacting the cell, essentially in the absence of an AAV helper virus, with a composition comprising a purified rAAV particle with a single stranded genome that has in the 5’ to 3’ direction an ITR-heterologous sequence-ITR-heterologous sequence-ITR having a length that

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is approximately a half size vector, inherently anticipate and/or render obvious (alone or in the combinations identified in Appendix E) claims 1 and 19 of the ’054 patent because, as the ’054 patent admits, such methods using such vectors necessarily and inevitably contain a “first heterologous nucleotide sequence [that] can form intrastrand base pairs with the second nucleotide sequence along most or all of its length.”

2. Dependent Claims 2-7, 9, 11-13, 15, 17-18, 20-27, 30-32, 34, and 36

The dependent claims of the ’054 patent are additionally invalid over the prior art, at least based on the references and combinations set forth in Appendix E. As set forth in Appendix E, the prior art discloses, expressly or inherently, each and every limitation of the dependent claims, including the claimed features of the rAAV vector (claims 3-7, 9, 11-13, 15, 23-27, 30-32, and 34), the claimed features of the composition (claims 2, 17, 22, and 36), the claimed features of the method (claim 18), including wherein the cell is a mammalian or human cell (claims 20-21). A person of ordinary skill in the art would have been motivated to pursue the combinations listed in Appendix E with a reasonable expectation of success in achieving the asserted dependent claims. For example, as the ’054 patent admits, “[r]ecombinant vectors based on parvovirus, such as adeno-associated virus (AAV), show promise for gene therapy.” ’054 patent at 1:38-39. The ’054 patent also admits that the dependent claim limitations related to introducing a polynucleotide into a mammalian host cell under conditions that allow uptake of the rAAV vector were known in the art. *See e.g., id.* at 3:24-29 (“The native AAV genome has been used as the basis for vector systems for the delivery and expression of heterologous genes in host cells such as mammalian cells, such as for gene therapy.”). The ’054 patent also admits that a vector of between 4.5 kb and 5.2 kb can be packaged in a particle. *See e.g., id.* at 3:49-56 (“In one study of the effect of genome length on packaging efficiency, rAAV genomes having sizes between 2 kb and 6 kb were compared. Dong

et al. (1996) *Hum. Gene Therapy* 7:2101-2112. It was observed that vectors having sizes between approximately 2 and approximately 6 kb were packaged into virus particles with similar efficiency."). The prior art listed in Appendix E is directed to, *e.g.*, compositions of purified rAAV particles containing rAAV vector capable of forming intrastrand base pairs that enhance expression and methods of using such compositions and vectors to express a polynucleotide coding sequence in a cell. A person of ordinary skill in the art, as of August 19, 1999, would have been familiar with this prior art and would have been motivated to combine these teachings, and the others set forth in Appendix E, with a reasonable expectation of success, thereby rendering obvious dependent claims 2-7, 9, 11-13, 15, 17-18, 20-27, 30-32, 34, and 36.

B. The '054 Patent Claims Are Invalid under 35 U.S.C. § 112

In addition, or in the alternative, Novartis contends that the Asserted Claims of the '054 patent do not satisfy one or more requirements of 35 U.S.C. § 112. Novartis identifies the below grounds upon which the Asserted Claims of the '054 patent are invalid based on lack of written description under 35 U.S.C. § 112, first paragraph, lack of enablement under 35 U.S.C. § 112, first paragraph, and indefiniteness under 35 U.S.C. § 112, second paragraph.

1. Invalidity under 35 U.S.C. § 112, First Paragraph for Inadequate Written Description

As discussed *supra*, a patent's specification must contain a written description of the claimed invention. 35 U.S.C. § 112, ¶ 1. The description must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d at 1351 (*en banc*) (citations omitted). In other words, the specification must reasonably convey that the inventor had possession of the claimed subject matter as of the filing date. *Id.*

To satisfy the written description requirement for a claimed genus, a specification must describe the claimed invention in such a way that a person of ordinary skill in the art would understand that the genus that is being claimed has been invented, and not just a species of the genus. *Carnegie Mellon Univ. v. Hoffman-La Roche, Inc.*, 541 F.3d at 1124. In particular, when attempting to claim a functionally-defined genus, "a sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.* at 1350 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d at 1568-69). "A vague functional description and an invitation for further research does not constitute written disclosure . . . ." *Id.* at 1356. And "if the art is unpredictable, then disclosure of more species is necessary to adequately show possession of the entire genus." *Bilstad v. Wakalopulos*, 386 F.3d at 1125. While it is "not fatal" that members of a genus are not disclosed in a patent, the specification should provide other means of identifying which members of the genus would interact with other variable elements. *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th at 1330.

The Asserted Claims of the '054 patent are invalid under 35 U.S.C. § 112, ¶ 1, because the claimed genus of vectors is neither supported by a representative number of species nor by a disclosure of structural features common to the members of the claimed genus responsible for the claimed functions that would allow a person of ordinary skill in the art to visualize or recognize the other members of the genus. As explained in detail below, the specification of the '054 patent does not reasonably convey to a person of ordinary skill in the art that the inventor had possession of the vast—nearly limitless—genus of rAAV vectors used in the Asserted Claims. The claims use structural and functional language in an attempt to claim a vast genus of vectors, yet the rAAV

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vectors claimed are not limited, for example, by heterologous nucleotide or coding sequence of interest, location of an internal ITR, any serotype of AAV, or any defined amount of intrastrand base paring (which "can form" along "most" of the length of a nucleotide).

A person of ordinary skill in the art would have understood the purported scope of the claimed genus is exceedingly broad, unknown and unknowable, and consequently would require an expansive and random search for all of the different options of vectors that may or may not work. *See Brenner v. Manson*, 383 U.S. at 536 ("a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

A "representative number of species" means that the species which are adequately described are representative of the entire genus. *Carnegie Mellon*, 541 F.3d at 1124. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. *Id.* For inventions in unpredictable arts, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. *Id.* The genus of vectors claimed in the '054 patent is not supported by a representative number of species. Despite the vast scope of the claimed genus, the '054 patent contains only minimal guidance and examples regarding what rAAV vectors may be able to form intrastrand base pairing along an undefined length of the nucleotide sequence. Indeed, the '054 patent provides just one exemplary structure (one half-sized vector containing one particular heterologous gene and wherein each ITR of the vector is native AAV ITR sequence) that purportedly forms intrastrand base pairing. The patent also fails to inform a person of ordinary skill in the art about how to assess whether intrastrand base pairing "can form," the location of or any other information about the "internal AAV ITR," or any specific details as to the structural features relating to the intrastrand base pairing requirements set forth in the claims.

The ’054 patent also fails to disclose structural features common to members of the genus that are responsible for the claimed functions such that one of skill in the art could visualize or recognize the members of the claimed genus of rAAV vectors, as explained in detail below. “[F]unctionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus.” *AbbVie Deutschland GmbH & Co. KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014); *see also Juno*, 10 F.4th at 1337 (disclosure of two working embodiments “does not provide information sufficient to establish that a skilled artisan would understand how to identify the species of scFvs capable of binding to the limitless number of targets as the claims require.”).

For at least the reasons discussed herein, and outlined in more detail for specific claim limitations below, the Asserted Claims of the ’054 patent are invalid under 35 U.S.C. § 112, ¶ 1 for failing to satisfy the written description requirement.

a. Independent Claims 1 and 19

i. “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”

The purported scope of the claims of the ’054 patent is broad with respect to the limitations “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” and “the first heterologous nucleotide sequence can form intrastrand base pairs with the

second nucleotide sequence along most or all of its length," as recited in independent claims 1 and 19, relative to the limited examples and disclosure in the specification. The specification fails to provide detailed information as to these structural features, including with respect to the intrastrand base pairing requirements set forth in the claims.

The claims of the '054 patent purport to encompass a vast array of rAAV formats. For example, the heterologous nucleotide sequence is expressly defined in the patent specification to purportedly encompass any "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." '054 patent at 9:31-37. Independent claim 1 of the '054 patent does not limit the heterologous nucleotide sequence to one that contains a coding region. Indeed, independent claim 1 of the '054 patent provides no limitation as to the size of the heterologous nucleotide sequence or what the heterologous nucleotide sequence can be. Although independent claim 19 of the '054 patent recites that "the first or the second heterologous nucleotide comprises the coding sequence," the patent broadly defines "a 'coding region' of a heterologous sequence" as any "sequence of contiguous nucleotides which gives rise in a host cell to a transcription and/or translation product." *Id.* at 10:21-24. The '054 patent also broadly provides that a "coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." *Id.* at 10:35-39. Thus, the purported scope of the heterologous nucleotide sequences (claim 1 and its dependent claims) and coding sequences (claim 19 and its dependent claims) purportedly encompassed by the claims is limitless.

With respect to the limitation "internal ITR," the phrase is mentioned only four times in the entire '054 patent specification, and each provides a circular explanation: (1) "the rAAV

contains an additional, internal (i.e., a non-terminal ITR)" (*id.* at 5:19-22), (2) "an rAAV vector, further comprises an internal ITR (i.e., an ITR that is flanked on both sides by heterologous sequences) (*id.* at 15:27-31); (3) "[t]his internal ITR preferably divides the heterologous sequence" (*id.* at 15:31-33); and (4) "intrastrand base pairing occurs between region(s) on either side of the internal ITR" (*id.*). The patent specification provides no limitation as to what the internal ITR is or where the internal ITR should be located in the rAAV vector, so long as it is between two heterologous nucleotide sequences of unlimited size and indeterminate structure.

With respect to the limitation "the first heterologous nucleotide sequence can form intrastrand base pairs with the second nucleotide sequence along most or all of its length," the patent claims do not require the formation of intrastrand base pairs but merely the possibility that intrastrand base pairs "can form." Further, the patent specification broadly states "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:65-11:2. The specification also fails to provide any information regarding the conditions or time points to assess whether an rAAV vector "can form" intrastrand base pairs, let alone along most or all of the length of the heterologous nucleotide sequence. Further, the applicant admitted during prosecution of this patent family that "[t]he specification teaches that intrastrand base pairing may be anywhere along the heterologous sequence, and may or may not be within a coding region of a heterologous sequence." GENZ_NOV_00002136.

In contrast to the broad purported scope of the claims, the '054 patent teaches only one purported working example of an rAAV vector purportedly having intrastrand base pairing, *i.e.*, a half-size vector comprising a heterologous nucleotide sequence containing a coding region for a

detectable marker, green fluorescent protein (GFP). *See* ’054 patent at Examples 1-3, 5-8, 10-12.[15] Other than GFP, the specification does not provide any additional examples of any other heterologous nucleotide sequences or coding sequences falling within the purported scope of the claims that possess the claimed functional elements (e.g., intrastrand base pairing “can form” between the heterologous nucleotide sequences). Yet, the claims purport to cover an unlimited number of heterologous nucleotide sequences of unlimited size and function (or no function at all) or coding regions of a variety of lengths from 5 to more than 500 nucleotides in length. *Id.* at 10:35-39. The ’054 patent does not demonstrate possession, for example, of an rAAV comprising a coding sequence that is 5 nucleotides in length and that “can form” an indeterminate level of intrastrand base pairing. Indeed, even today, AAV vectors that are too short or too long cannot package and express efficiently. For example, “stuffer” sequences are still used today to lengthen AAV vectors for optimal expression. Given the substantial structural variation purportedly encompassed by the claimed genus, the ’054 patent specification does not disclose a representative number of species that achieves the claimed result sufficient to support the claimed genus of all single-stranded heterologous nucleotide sequences comprising a region which “can form” intrastrand base pairs. Furthermore, there is no structural feature of the nucleotide sequence that would be common to members of the genus because the claims purport to cover any nucleotide

[15] The ’054 patent also teaches an example (Example 13) of an rAAV vector encoding a fusion protein of tumor necrosis factor receptor (TNFR) and an immunoglobulin constant region (Fc) produced “according to the Examples above.” ’054 patent at 37:5-15 (Example 13). However, the TNFR-Fc example appears to be prophetic and does not describe whether or how the vector encoding TNFR-Fc is designed to give rise to intrastrand base pairing. Example 5 describes a control rAAV vector encoding human alkaline phosphatase and bacterial neomycin resistance gene, but it does not appear to possess intrastrand base pairing in the heterologous nucleotide sequences and thus does not exemplify the claims. *Id.* at 31-51-32:4.

sequence, and the specification does not describe any correlation between any nucleotide sequence structure and the functional requirements of the claimed genus.

With respect to the 5' AAV ITR sequence and the 3' AAV ITR sequence present at both termini of the rAAV vector, the patent specification states that an "[a]n 'AAV inverted terminal repeat (ITR)' sequence . . . is an approximately 145-nucleotide sequence that is present at both termini of the *native* single-stranded AAV genome." *Id.* at 11:14-17 (emphasis added). The patent specification explains that *native* ITR sequences, i.e., from a native AAV2 genome, were used in the purported working examples. *Id.* at 15:62-64. Non-native ITR sequences were never tested or even constructed, according to the patent specification.

To the extent the '054 patent claims are construed to encompass *non-native* ITR sequences, the '054 patent claims are invalid for lack of written description, because the claimed genus of vectors comprising any modified, mutated, or non-native ITR is unsupported by the disclosure of the patent specification, which includes only a single purported working example wherein each ITR of the vector is native AAV ITR sequence from AAV2. In determining whether the specification provides adequate written description support, products that post-date the patent's priority date, including an accused infringing product, can be taken into consideration. *Amgen Inc. v. Sanofi*, 872 F.3d at 1374-75. Here, to the extent the '054 patent claims are construed to encompass non-native ITR sequences, the claims improperly attempt to cover a genus of structures and iterations thereof—including later-developed vectors containing a mutated ITR (*see, e.g.*, McCarty (2008)—despite the fact that such structures were not disclosed by the patent. *Id.* at 1374.

For at least these reasons, independent claims 1 and 19 of the '054 patent (and their dependent claims) lack written description support for "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," because a person of ordinary skill in the art would not reasonably believe that the '054 patent inventor had possession of the claimed genus of any heterologous nucleotide sequence comprising a region which forms intrastrand base pairs along an unspecified length of the heterologous nucleotide sequence.

ii. "a method of expressing a polynucleotide coding sequence in a cell, comprising subjecting the cell to conditions which allow expression of the coding sequence, wherein the coding sequence is introduced into the cell by contacting the cell essentially in the absence of an AAV helper virus with a composition comprising a purified recombinant adeno-associated virus (rAAV) particle"

The purported scope of the claims of the '054 patent is broad with respect to the limitations reciting a "a method of expressing a polynucleotide coding sequence in a cell, comprising subjecting the cell to conditions which allow expression of the coding sequence, wherein the coding sequence is introduced into the cell by contacting the cell essentially in the absence of an AAV helper virus with a composition comprising a purified recombinant adeno-associated virus (rAAV) particle," as recited in independent claim 19, relative to the limited examples and disclosure provided in the specification. More specifically, the specification fails to provide any definition of the term "cell," but instead describes "[t]ypes of cells into which the polynucleotides of the invention can be introduced" as including, but not limited to "eucaryotic cells, procaryotic cells and Archaea. Eucaryotic cells include animal cells, plant cells, yeast cells and, in a preferred embodiment, mammalian cells, more preferably, human cells, mammalian, including human, cells include cell lines as well as primary cells, such as primary foreskin fibroblasts." '054 patent at 26:39-45.

The claims of the ’054 patent thus purport to encompass a broad genus of any cell type, including at least the genus of cells described in the specification, which includes Archaea, prokaryotic, and eukaryotic cells. *Id.* at 26:39-45. Thus, the purported scope of the cells encompassed by independent claim 19 (and its dependent claims) is limitless.

In contrast to the broad purported scope of claim 19, the ’054 patent specification teaches only two purported working examples of cell types transduced with an rAAV vector: 293 cells, which are a human embryonic kidney cell line and HeLa cells (both mammalian, not prokaryotic or Archaea). *See id.* at 7:66-8:6; Examples 3, 5-7, 9-10; Tables 1-3, 5. These are the sole exemplary cell types discussed in the specification. Other than these two mammalian cell types, the specification does not provide any examples of prokaryotic cells or Archaea that fall within the purported scope of the claims, or what conditions would allow uptake of the rAAV vector into such cell types or whether enhanced expression from of the coding region in an rAAV vector can be achieved in such cell types. Given the substantial variation purportedly encompassed by the genus, the ’054 patent specification does not disclose a representative number of species that achieves the claimed result sufficient to support the claimed genus of all cell types. Furthermore, there is no structural feature of the cells that would be common to members of the genus because the claims purport to cover any cell type, and the specification does not describe any correlation between any structure and the functional requirements of the claimed genus of cells.

b. Dependent Claims 2-7, 9, 11-13, 15, 17-18, 20-27, 30-32, 34, and 36

The dependent claims of the ’054 patent merely recite additional features that provide no meaningful narrowing of the claimed feature of “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" recited in independent claims 1 and 19. Thus, the dependent claims lack written description for the same reasons set forth above for claims 1 and 19, as well as for the additional reasons discussed below.

i. Dependent Claims 2 and 22

Claim 2 depends from claim 1 and further recites that the composition comprising the rAAV particle, which comprises the rAAV vector genome, "is essentially free of helper virus." Claim 22 depends from claim 19 and also recites that "the composition is essentially free of helper virus." Claims 2 and 22 do not further limit any of the structural or functional components described above for the rAAV vector itself, the genus of which is not limited by any type of heterologous sequence, any length of heterologous sequence, any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1 and 19, a person of ordinary skill in the art would not reasonably have understood that the '054 patent inventor had possession of the genus of claim 2 or claim 22.

ii. Dependent Claims 3 and 23

Claim 3 depends from claim 1 and further recites that the size of the rAAV vector genome is "about 4.5 kilobase to about 5.2 kilobase." Claim 23 depends from claim 19 and also recites that vector genome "has a size of about 4.5 kilobase to about 5.2 kilobase." Claims 3 and 23 do not meaningfully limit any of the structural or functional components described above for the rAAV vector, the genus of which is not limited by any type of heterologous sequence, nearly any length of heterologous sequence, any positioning of an internal ITR, and an unspecified amount of

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intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1 and 19, a person of ordinary skill in the art would not reasonably have understood that the ’054 patent inventor had possession of the genus of claim 3 or 23.

iii. Dependent Claims 4 and 24

Claim 4 depends from claim 1 and further recites that the internal ITR is “approximately in the center of the vector genome.” Claim 24 depends from claim 19 and also recites that the internal ITR is “approximately in the center of the vector genome.” As explained above, the specification provides no guidance as to what the internal ITR is, much less where an approximate center of the vector genome might be. The patent specification provides no information on whether or how the positioning between the two heterologous nucleotide sequences relates to the positioning in the approximate center of the vector genome. In addition, claims 4 and 24 do not meaningfully limit any of the other structural or functional components described above for the rAAV vector, the genus of which is not limited by any type of heterologous sequence, any length of heterologous sequence, and an unspecified amount of intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1 and 19, a person of ordinary skill in the art would not reasonably have understood that the ’054 patent inventor had possession of the genus of claim 4 or 24.

iv. Dependent Claims 5 and 25

Claim 5 depends from claim 1 and further recites that the “two heterologous nucleotide sequences are inverted complements of each other.” Claim 25 depends from claim 19 and also

recites that the "two heterologous nucleotide sequences are inverted complements of each other." Claims 5 and 19 do not meaningfully limit the structural or functional components described above for the rAAV vector, the genus of which still broadly purportedly encompasses any type of heterologous sequence, nearly any length of heterologous sequence, and any positioning of an internal ITR, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1 and 19, a person of ordinary skill in the art would not reasonably have understood that the '054 patent inventor had possession of the genus of claim 5 or 25.

v. Dependent Claim 6

Claim 6 depends from claim 1 and further recites that "the first or the second heterologous nucleotide sequence comprises a coding sequence." As explained above, the patent specification broadly states the coding region can encode a nearly limitless number of molecules and "can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." '054 patent at 10:35-39. Claim 6 thus provides no meaningful limitation for the structural or functional components described above for the rAAV vector, the genus of which is not limited by any type of heterologous sequence comprising a coding sequence, nearly any length of heterologous sequence comprising a coding sequence (from 5 to more than 500 nucleotides), any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the '054 patent inventor had possession of the genus of claim 6.

vi. Dependent Claims 7 and 26

Claim 7 depends from claim 6 and further recites that the coding sequence is any one of six molecules, none of which was constructed or tested in the patent specification. Claim 26 depends from claim 19 and also recites these six molecules, none of which was constructed or tested in the patent specification. In particular, claims 7 and 26 require the coding sequence to be "(i) a polynucleotide encoding a protein useful in gene therapy to relieve deficiencies caused by missing, defective or sub-optimal levels of a structural protein or enzyme; (ii) a polynucleotide that is transcribed into an anti-sense molecule; (iii) a polynucleotide that is transcribed into a decoy that binds a transcription or translation factor, (iv) a polynucleotide that encodes a cellular modulator; (v) a polynucleotide that can make a recipient cell susceptible to a specific drug; (vi) a polynucleotide for cancer therapy; or (vii) a polynucleotide that encodes an antigen or antibody." As explained above, the patent specification describes the construction and testing of a single purported working example of a half-size rAAV vector having a coding region for a detectable marker (GFP), not any of the molecules recited in claims 7 and 26. Further, claims 7 and 26 do not meaningfully limit the structural or functional components described above for the rAAV vector, the genus of which is not limited by nearly any length of heterologous sequence comprising a coding sequence (from 5 to more than 500 nucleotides), any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing. Thus, for at least the reasons explained herein and above for claims, 1, 6, and 19, a person of ordinary skill in the art would not reasonably have understood that the '054 patent inventor had possession of the genus of claim 7 or 26.

vii. Dependent Claims 9 and 27

Claim 9 depends from claim 6 and further recites that the coding sequence is a molecule that was not constructed or tested in the patent specification. Claim 27 depends from claim 19 and also recites the molecule that was not constructed or tested in the patent specification. In particular,

claims 9 and 27 require the coding sequence to encode "a protein or an RNA of therapeutic interest." As explained above, the patent specification describes the construction and testing of a single purported working example of a half-size rAAV vector having a coding region for a detectable marker, which is not described as being of therapeutic interest. Further, claims 9 and 27 do not meaningfully limit the structural or functional components described above for the rAAV vector, the genus of which broadly purports to encompass nearly any length of heterologous sequence comprising a coding sequence (from 5 to more than 500 nucleotides), any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing. Thus, for at least the reasons explained herein and above for claims 1, 6, and 19, a person of ordinary skill in the art would not reasonably have understood that the '054 patent inventor had possession of the genus of claim 9 or 27.

viii. Dependent Claims 11 and 30

Claim 11 depends from claim 6 and further recites that the coding sequence "is operably linked to a promoter sequence." Claim 30 depends from claim 19 and also recites that the coding sequence "is operably linked to a promoter sequence." Claims 11 and 19 do not meaningfully limit the structural or functional components described above for the rAAV vector, the genus of which broadly purports to encompass any type of heterologous sequence comprising a coding sequence, nearly any length of heterologous sequence comprising a coding sequence (from 5 to more than 500 nucleotides), any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. This single vector may have contained a CMV promoter sequence but is insufficient to support the broad genus purportedly encompassing, inter alia, any promoter sequence. Thus, for at least the reasons explained herein and above for claims 1, 6, and

19, a person of ordinary skill in the art would not reasonably have understood that the ’054 patent inventor had possession of the genus of claim 11 or 30.

ix. Dependent Claims 12 and 31

Claim 12 depends from claim 11 and further recites that the promoter sequence is “(i) an SV40 late promoter, (ii) a baculovirus polyhedron enhancer/promoter element, (iii) a Herpes Simplex Virus thymidine kinase (HSY tk), (iv) an immediate 40 early promoter from cytomegalovirus (CMV), (v) a retroviral promoter including LTR elements, or (vi) a heavy metal ion inducible promoters and a promoter from T7 phage.” Claim 31 depends from claim 30 and recites the same promoter sequences. Claims 12 and 31 do not meaningfully limit the structural or functional components described above for the rAAV vector, the genus of which broadly purports to encompass any type of heterologous sequence comprising a coding sequence, nearly any length of heterologous sequence comprising a coding sequence (from 5 to more than 500 nucleotides), any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. This single vector may have contained a CMV promoter sequence (*see, e.g., id.* at 28:66-29:2 (Example 1 describing “[a]n AAV vector (AAV-cmv-intron-EGFP)”). As such, at least five of the six promoters recited in claim 6 were neither constructed nor tested. Thus, for at least the reasons explained herein and above for claims 1, 6, 11, and 19, a person of ordinary skill in the art would not reasonably have understood that the ’054 patent inventor had possession of the genus of claim 12 or 31.

x. Dependent Claims 13 and 32

Claim 13 depends from claim 11 and further recites that the coding sequence is “further operably linked to an enhancer sequence.” Claim 32 depends from claim 30 and also recites that

the coding sequence is "further operably linked to an enhancer sequence." The patent specification and claims 13 and 32 fail to provide any further detail as to what the enhancer sequence might be. Thus, the purported scope of the enhancers encompassed by claims 13 and 32 is vast and may encompass any type of enhancer and nearly any length of enhancer. In addition, claims 13 and 32 do not meaningfully limit the structural or functional components described above for the rAAV vector, the genus of which broadly purports to encompass any type of heterologous sequence comprising a coding sequence, nearly any length of heterologous sequence comprising a coding sequence (from 5 to more than 500 nucleotides), any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. It is unclear if this vector contains an enhancer, but even assuming that it does, this single vector is insufficient to support the broad genus purportedly encompassing, *inter alia*, any enhancer sequence. Thus, for at least the reasons explained herein and above for claims 1, 6, 11, and 19, a person of ordinary skill in the art would not reasonably have understood that the '054 patent inventor had possession of the genus of claim 13 or 32.

xi. Dependent Claims 15 and 34

Claim 15 depends from claim 6 and further recites that the coding sequence is "operably linked to a polyadenylation signal." Claim 34 depends from claim 19 and also recites that the coding sequence is "operably linked to a polyadenylation signal." The patent specification and claims 15 and 34 fail to provide any further detail as to what the polyadenylation signal sequence might be, and thus, the purported scope may encompass nearly any length and any sequence of polyadenylation signal. In addition, claims 15 and 34 do not meaningfully limit the structural or functional components described above for the rAAV vector, the genus of which broadly purports

to encompass any type of heterologous sequence comprising a coding sequence, nearly any length of heterologous sequence comprising a coding sequence (from 5 to more than 500 nucleotides), any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. It is unclear if this vector contains a polyadenylation signal, but even assuming that it does, this single vector is insufficient to support the broad genus purportedly encompassing, inter alia, any polyadenylation signal. Thus, for at least the reasons explained herein and above for claim 1, 6, and 19, a person of ordinary skill in the art would not reasonably have understood that the ’054 patent inventor had possession of the genus of claim 13 or 34.

xii. Dependent Claims 17 and 36

Claim 17 depends from claim 1 and further comprises “a pharmaceutically acceptable excipient.” Claim 36 depends from claim 19 and also comprises “a pharmaceutically acceptable excipient.” The patent specification broadly provides that a pharmaceutically acceptable excipient can be nearly any substance “includ[ing] but [] not limited to stabilizing agents, wetting and emulsifying agents, salts for varying osmolarity, encapsulating agents, and buffers” and can be supplied in nearly any manner, including “liquid solutions or suspension, as emulsions, or as solid forms suitable for dissolution or suspension in liquid prior to use.” *Id.* at 16:59-17:1. Thus, claims 17 and 36 read on an effectively limitless number of pharmaceutically acceptable excipients. Moreover, claims 17 and 36 do not further limit any of the structural or functional components described above for the rAAV vector itself, the genus of which broadly purports to encompass any type of heterologous sequence, any length of heterologous sequence, any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a

heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, for at least the reasons explained herein and above for claims 1 and 19, a person of ordinary skill in the art would not reasonably have understood that the ’054 patent inventor had possession of the genus of claim 17 or 36.

xiii. Dependent Claim 18

Claim 18 depends from claim 1 and recites a “method of introducing an rAAV genome into a cell, comprising contacting the cell essentially in the absence of an AAV helper virus with the composition of claim 1 under conditions that allow uptake of the rAAV vector, whereby the rAAV vector is introduced into the cell.” Neither claim 18 nor the specification provides any further detail as to what the cell is, how the function of “allow[ing] uptake of the rAAV vector” would be achieved, or how much uptake is needed. The specification provides no limitation as to cell type, whether eukaryotic, prokaryotic, mammalian, or non-mammalian. *Id.* at 25:64-67. Further, claim 18 does not further limit any of the structural or functional components described above for the rAAV vector itself, the genus of which broadly purports to encompass any type of heterologous sequence, any length of heterologous sequence, any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, claim 18 purports to encompass an unknown and unknowable number of cells and methods of introducing an rAAV genome into such cells, including cell types and whether such cells and methods are in an *in vitro*, *in vivo*, laboratory testing, or clinical administration setting. This vector was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions (*see, e.g., id.* at Example 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, inter alia, any cell, any method

of contacting the cell, any method or amount of uptake, and any method or amount of introducing the rAAV into the cell. Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the ’054 patent inventor had possession of the genus of claim 18.

xiv. Dependent Claim 20

Claim 20 depends from claim 19 and further recites that “the cell is a mammalian cell.” Claim 20 does not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which broadly purports to encompass any type of heterologous sequence comprising a coding sequence, nearly any length of heterologous sequence comprising a coding sequence (from 5 to more than 500 nucleotides), any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, claim 20 purports to encompass an unknown and unknowable number of mammalian cells and methods of expressing a polynucleotide coding sequence in such cells, including mammalian cell types and whether such mammalian cells and methods are in an *in vitro*, *in vivo*, laboratory testing, or clinical administration setting. This vector was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other mammalian cells (*see, e.g., id.* at Example 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, *inter alia*, any mammalian cell. Thus, for at least the reasons explained herein and above for claim 19, a person of ordinary skill in the art would not reasonably have understood that the ’054 patent inventor had possession of the genus of claim 20.

xv. Dependent Claim 21

Claim 21 depends from claim 19 and further recites that "the cell is a human cell." Claim 21 does not meaningfully limit any of the structural or functional components described above for the rAAV vector itself, the genus of which broadly purports to encompass any type of heterologous sequence comprising a coding sequence, nearly any length of heterologous sequence comprising a coding sequence (from 5 to more than 500 nucleotides), any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing, despite the limited disclosure in the patent specification of a single purported working example of a half-size rAAV vector having a heterologous nucleotide sequence containing a coding region for a detectable marker. Thus, claim 21 purports to encompass an unknown and unknowable number of human cells and methods of expressing a polynucleotide coding sequence in such cells, including human cell types and whether such human cells and methods are in an *in vitro*, *in vivo*, laboratory testing, or clinical administration setting. This vector was tested in only two immortalized human cell lines, i.e., an embryonic kidney 293 cell and a HeLa cell, under particular conditions, and in no other human cells or cell lines (*see, e.g., id.* at Example 3, 6, and 7), which provides insufficient support for the broad genus purportedly encompassing, inter alia, any human cell. Thus, for at least the reasons explained herein and above for claim 19, a person of ordinary skill in the art would not reasonably have understood that the '054 patent inventor had possession of the genus of claim 21.

2. Invalidity under 35 U.S.C. § 112, First Paragraph for Lack of Enablement

"To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *ALZA Corp. v. Andrx Pharms.*, LLC., 603 F.3d 935, 940 (Fed. Cir. 2010) (quoting *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997)). An essential question for an enablement

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analysis is "whether the scope of enablement of [a claim] is as broad as the scope of the claim." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212 (Fed. Cir. 1991). The applicant must disclose a range of embodiments that is adequate in relation to the breadth of the patent right being sought. *See, e.g.*, *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (finding scope of claims that encompassed any and all vaccines in any animal toward any RNA virus not enabled when only a single working example was provided).

The need to engage in "an iterative, trial-and-error process to practice the claimed invention," where the specification provides "only a starting point, a direction for further research," precludes a finding of enablement. *ALZA*, 603 F.3d at 941. Where the skilled artisan "would need to assay each of at least tens of thousands of candidates" and the specification offered "no guidance or predictions about particular substitutions" that would lead to other effective members, genus claims are not enabled based on undue experimentation. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385-86 (Fed. Cir. 2013). "[T]he enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those requirements, especially where predictability and guidance fall short. In particular, it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim." *Amgen Inc. v. Sanofi Aventisub LLC*, 987 F.3d 1080, 1086 (Fed. Cir. 2021). Thus, "[w]hile functional claim limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language." *Id.* at 1087; *see also id.* ("[T]he use of broad functional claim limitations raises the bar for enablement . . . .")

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As discussed *supra*, the claims of the ’054 patent are broadly defined by structural and functional elements. Determining which combination of structures in the claimed rAAV vectors would result in a construct that “can form” intrastrand base pairs along “most or all” of the length of a heterologous nucleotide sequence (which purportedly encompasses any type of heterologous sequence, any length of heterologous sequence, any positioning of an internal ITR, and an unspecified amount of intrastrand base pairing) would require an iterative, trial-and-error process that would amount to undue experimentation, due to the vast genus of rAAV vectors claimed. Indeed, the inventor provides 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.* at 14:57-59. The purported scope of claim 1 of the ’054 patent encompasses any type of heterologous nucleotide sequence, any length of heterologous nucleotide sequence, and an unspecified amount of intrastrand base pairing. The purported scope of claim 19 of the ’054 patent similarly encompasses any type of heterologous nucleotide sequence comprising a coding sequence, nearly any length of heterologous nucleotide sequence comprising a coding sequence, and an unspecified amount of intrastrand base pairing. Although claim 19 requires that “the first or the second heterologous nucleotide comprises the coding sequence,” the patent broadly provides that “[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides.” *Id.* at 10:35-39. Further, the applicant admitted during prosecution that “[t]he specification teaches that intrastrand base pairing may be anywhere along the heterologous sequence, and may or may not be within a coding region of a heterologous sequence.” GENZ_NOV_00002136. The patent further states “the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%.

65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:65-11:2. Practicing the full scope of the claim across the nearly limitless universe of types and lengths of heterologous nucleotide or coding sequences would require an iterative, trial-and-error process to determine which combination of structures in the claimed rAAV vectors would result in a construct that "can form" intrastrand base pairing along most or all of the heterologous nucleotide sequence.

Undue experimentation is evaluated under the Wands factors, which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). An evaluation of the experimentation required under the *Wands* factors follows.

a. Independent Claims 1 and 19

i. Factors 1 and 2: Quantity of Experimentation Necessary and Amount of Direction or Guidance Presented

As explained above, the Asserted Claims of the '054 patent use broad structural and functional language to purport to encompass a vast genus of rAAV vectors without limitation as to the type of heterologous nucleotide sequence, the length of heterologous nucleotide sequence, the positioning of an internal ITR, the serotype of AAV, the cell, or the undefined amount of intrastrand base paring (which "can form" along "most" of the length of a nucleotide). The '054 patent does not provide sufficient direction or guidance across this exceedingly broad purported scope of claimed subject matter. Determining whether and how these structures in an rAAV vector "can form" an undefined amount of intrastrand base pairing under undefined conditions would require an excessive amount of experimentation.

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Courts have found that claims were not enabled when the amount of experimentation "would take a substantial amount of time and effort," and the "only ways for a person of ordinary skill to discover undisclosed claimed embodiments would be through either 'trial and error, by making changes to the disclosed antibodies and then screening those antibodies for the desired binding and blocking properties,' or else 'by discovering the antibodies de novo' according to a randomization-and-screening 'roadmap.'" *Amgen*, 987 F.3d at 1088 (citing *Amgen Inc. v. Sanofi*, No. 14-1317, 2019 WL 4058927, *11–*12 (D. Del. Aug. 28, 2019).

As explained above, the '054 patent claims purport to encompass a broad universe of rAAV formats. The recited heterologous nucleotide sequence purportedly encompasses any "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." '054 patent at 9:31-37. Independent claim 1 does not require the heterologous nucleotide sequence to comprise a coding sequence and is unlimited as to the what the heterologous nucleotide sequence is and what size the heterologous nucleotide sequence can be. The patent broadly defines a coding region, which is recited in independent claim 19, as any "sequence of contiguous nucleotides which gives rise in a host cell to a transcription and/or translation product." *Id.* at 10:21-24. The '054 patent also broadly provides that a "coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." *Id.* at 10:35-39. The '054 patent claims recite the mere possibility that intrastrand base pairs "can form" along "most" or all of the length of the heterologous nucleotide sequence, but the specification provides no information regarding the conditions or time points to assess whether an rAAV vector "can form" intrastrand base pairs. Instead, the patent specification broadly states "the extent of intrastrand base

pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:65-11:2. The specification fails to provide any information as to the conditions or time points to assess whether an rAAV vector "can form" intrastrand base pairs, let alone along most or all of the length of the heterologous nucleotide sequence. In addition, the patent specification provides no limitation as to where the internal ITR should be located in the rAAV vector, so long as it is between two heterologous nucleotide sequences of unlimited size and indeterminate structure. *See, e.g., id.* at 5:19-22, 15:27-31, and 15:31-33.

Further, to the extent the '054 patent claims are construed to encompass *non-native* ITR sequences, the '054 patent claims are invalid for lack of enablement, because experimentation across the full scope of rAAV vectors comprising any modified, mutated, or non-native ITR would require a substantial amount of time and effort, particularly in view of the limited disclosures in the patent specification (disclosing a single purported working example of an rAAV having intrastrand base pairing, *i.e.*, a half-size vector wherein each ITR of the vector is native AAV ITR sequence and comprising a heterologous nucleotide sequence containing a coding region for a detectable marker). Indeed, substantial time and effort was required to generate, experimentally test, and ascertain the functionality of later-developed vectors containing a mutated ITR, which subsequently received its own patent protection (*see, e.g.*, McCarty (2008); McCarty (2003); McCarty (2001); U.S. Patent Nos. 7,465,583; 7,790,154; 8,361,457).

Yet the specification provides very little guidance as to how a person of ordinary skill in the art should determine whether and how these structures should be combined to yield this undefined amount of intrastrand base pairing under undefined conditions. Indeed, the '054 patent reports constructing only one rAAV having intrastrand base pairing, *i.e.*, a half-size vector

comprising a heterologous nucleotide sequence containing a coding region for a detectable marker, green fluorescent protein (GFP). *See* ’054 patent at Examples 1-3, 5-7, 10-12. The specification does not describe how to make any other heterologous nucleotide sequence (e.g., one that does not code anything), any other coding sequence (including any of those recited in the dependent claims), or any other lengths of heterologous nucleotide or coding sequences (e.g., a 5-nucleotide sequence, which is expressly defined as purportedly encompassed by the claims) in the recited rAAV, let alone whether or how these “can form” intrastrand base pairing along most or all of their lengths.

Thus, undue experimentation would be required to practice the full scope of the ’054 patent claims purportedly encompassing all types of heterologous nucleotide sequences, all lengths of heterologous nucleotide sequences, all positions of internal ITRs, and intrastrand base pairing that “can form,” under unspecified conditions, along most or all of the length of the nucleotide. Due to the lack of direction and very limited guidance presented in the specification of the ’054 patent, the Asserted Claims of the ’054 patent require a high degree of trial and error and are invalid for lack of enablement.

ii. Factor 3: Presence or Absence of Working Examples

With regard to claims directed to a functionally defined genus in unpredictable arts, the Federal Circuit has “refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one of a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim.” *PPG Indus., Inc. v. Guardian Indus. Corp*., 75 F.3d at 1564. As discussed above, the ’054 patent teaches only one purported working example of an rAAV vector purportedly having intrastrand base pairing, *i.e.*, a half-size vector comprising a heterologous nucleotide

sequence containing a coding region for a detectable marker, green fluorescent protein (GFP). *See* ’054 patent and Examples 1-3, 5-7, 10-12. Moreover, it is likely the purported working example is inoperative, in whole or in part. This single purported working example does not amount to a demonstration with reasonable specificity of how to make and use other potential embodiments across the full scope of the Asserted Claims, including all types of heterologous nucleotide sequences, all lengths of heterologous nucleotide sequences, all positions of internal ITRs, and an unspecified amount of intrastrand base pairing that “can form,” under unspecified conditions, along most or all of the length of the nucleotide. The insufficiency of working examples renders the claims of the ’054 patent invalid for lack of enablement.

iii. Factors 4-6: Nature of the Invention, State of the Prior Art, and Relative Skill of Those in the Art

The nature of the claimed invention is an rAAV vector comprising a 5’ AAV 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” of its length. As the ’054 patent admits, the state of the art was such that the field was still in its early stages at the time of filing (1999). *See, e.g., id.* at 1:38-45 (“Recombinant vectors based on parvovirus, such as adeno-associated virus (AAV), show promise for gene therapy. However, obtaining efficient, sufficient levels of expression of a transgene in various cell types has presented problems. Some cell types are impermissive in the sense that initiation of transcription or translation of the transgene is inefficient, with expression accordingly very slow to initiate, if it initiates at all.”). Thus, before the invention could have been practiced, it would have been necessary to make and screen each of the vast number of possible rAAV vectors, across numerous types of heterologous nucleotide sequences, numerous lengths of heterologous nucleotide

sequences, numerous positions of internal ITRs, and (for claim 19) numerous cell types, including determining whether intrastrand base pairing "can form," under unspecified conditions, along most or all of the length of the nucleotide. And although the level of skill in the art was relatively high at the time of filing, skill alone cannot stand in for a total absence of guidance in the specification.

iv. Factor 7: Predictability or Unpredictability of the Art

As the '054 patent admits, the field was particularly unpredictable at the time of filing (1999). *See, e.g.*, *id.* at 4:42-45 ("there can be difficulties in obtaining sufficient levels of expression of heterologous sequences from rAAV vectors and viruses containing such vectors"); 22:61-23:3 ("potential difficulties associated with the expression of the AAV rep gene in mammalian cell line (since the Rep proteins can not only limit their own expression but can also affect cellular metabolism) and producing rAAV virus preparations that are substantially free of contaminating virus and/or viral or cellular protein"). This unpredictability would have been compounded by the breadth of the claims, which purport to encompass all types of heterologous nucleotide sequences, all lengths of heterologous nucleotide sequences, all positions of internal ITRs, all cell types (claim 19), and intrastrand base pairing that "can form," under unspecified conditions, along most or all of the length of the nucleotide. For example, as discussed above, rAAV having heterologous nucleotide or coding sequences at the lower lengths purportedly encompassed by the claims (e.g., those have coding regions that are 5 nucleotides in length) would likely have been too short to be operable. Without testing across the full scope of the structures purportedly encompassed by the claims, a person of ordinary skill in the art could not have predicted whether a given rAAV vector within the broad genus might be able to form intrastrand base pairing along most or all of the length of the nucleotide.

v. Factor 8: Breadth of the Claims

The Asserted Claims of the ’054 patent are exceedingly broad with respect to both structure and function, as explained at length above. The specification provides no meaningful boundaries for these structural and functional claim limitations and instead broadens each to purportedly encompass all types of heterologous nucleotide sequences, all lengths of heterologous nucleotide sequences, all positions of internal ITRs, all types of cells, and intrastrand base pairing that “can form,” under unspecified conditions, along most or all of the length of the nucleotide. At best, the specification invites a person of ordinary skill in the art to perform his or her own experimentation to begin an endless testing process across the vast genus of rAAVs purportedly encompassed by the claims, including to determine whether any “can form” an indeterminate amount of intrastrand base pairing in order to meet the limitations of the claims. Thus, an undue amount of experimentation would have been required for a person of ordinary skill in the art to make and use the full scope of the alleged invention of the Asserted Claims of the ’054 patent, and the claims are invalid for lack of enablement.

b. Dependent Claims 2-7, 9, 11-13, 15, 17-18, 20-27, 30-32, 34, and 36

As explained above with respect to the lack of written description, the dependent claims of the ’054 patent further recite features that provide no meaningful limitation as to claim scope, as the dependent claims still purport to encompass a nearly limitless universe of nearly all types of heterologous nucleotide or coding sequences, nearly all lengths of heterologous nucleotide or coding sequences, nearly all positions of internal ITRs, nearly all types of cells, and intrastrand base pairing that “can form,” under unspecified conditions, along most or all of the length of the nucleotide. For at least the same reasons set forth in Sections VIII.B.1 and VIII.B.2.a, the asserted dependent claims are invalid for lack of enablement.

3. Invalidity under 35 U.S.C. § 112, Second Paragraph for Indefiniteness

Under 35 U.S.C. § 112, ¶ 2, a patent "is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig. Instruments, Inc.*, 572 U.S. at 901. A patent must be "precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them. Otherwise, there would be a zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims." *Id.* at 909-910 (internal quotations and citations omitted).

i. "along most or all of its length"

Claim 1 of the '054 patent and its dependent claims require, among other things, a single-stranded rAAV vector comprising a first heterologous nucleotide sequence and a second heterologous nucleotide sequence, wherein the first heterologous nucleotide sequence can form intrastrand base pairs with the second nucleotide sequence "along most or all of its length." Claim 19 of the '054 patent and its dependent claims similarly require that the first heterologous nucleotide sequence can form intrastrand base pairs with the second nucleotide sequence "along most or all of its length" and further provide that "the first or the second heterologous nucleotide comprises the coding sequence." These claims requiring constructs that "can form" intrastrand base pairing along most or all of the length of the nucleotide sequence are indefinite, as the specification fails to explain the circumstances under, and characteristics by which, such base-pairing along most or all of the length of the nucleotide sequence can occur. Further, these claims require merely that intrastrand base pairing *can form*, and the specification provides no information as to the circumstances, e.g., timing or conditions, under which the possible formation of intrastrand base pairing should be assessed.

The patent states that "a recombinant viral vector containing a sequence or region that forms intrastrand base-pairs exhibits enhanced expression when compared to an otherwise similar (or identical) vector except for the degree of intrastrand base pairing." '054 patent at 10:61-65. Despite that a person of ordinary skill in the art would understand "most" to mean "more than half," the patent provides no other guidance regarding the circumstances or characteristics of the claimed intrastrand base pairing, instead stating broadly "[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.* at 14:57-59 (emphasis added). Claim 1 of the '054 patent provides no information whatsoever as to what the heterologous nucleotide sequences are. Although claim 19 of the '054 patent states that "the first or the second heterologous nucleotide comprises the coding sequence," the patent broadly provides that "[a] coding region can be at least about any of the following: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 85, 100, 110, 120, 130, 145, 150, 160, 175, 200, 250, 300, 350, 400, 450, 500 or more contiguous nucleotides." *Id.* at 10:35-39. The patent further states "the extent of intrastrand base pairing need not be 100% of the sequence but may be at least about any of the following: 25%, 40%, 50%, 60%. 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, 99%." *Id.* at 10:65-11:2. With respect to claim 19 (and its dependent claims), the fact that one of the heterologous sequences may comprise a coding sequence of anywhere from 5 to more than 500 nucleotides still fails to provide any information as to whether intrastrand base pairing inside or outside of the coding region is sufficient to fall within the claim scope.

Furthermore, the '054 patent claims do not require the formation of intrastrand base pairs, but rather the mere possibility that intrastrand base pairs "can form." The specification does not define what conditions (e.g., reagents, amounts, temperatures, etc.) or what time points should be

used to assess whether an rAAV vector "can form" intrastrand base pairs, let alone along most or all of the length of its heterologous nucleotide sequences. If an rAAV vector does not form intrastrand base pairs under specific conditions (any parameter of which could be modified), it is impossible to know whether the same rAAV vector "can form" intrastrand base pairs under altogether different conditions.

These overbroad claims reciting intrastrand base pairing along most or all of the length of a nucleotide sequence do not put the public on notice of what the claimed invention is, thus making it impossible to know whether one is potentially infringing. *See, e.g., Nautilus*, 572 U.S. at 901.

ii. "conditions that allow"

Claims 18-27, 30-32, 34, and 36 of the '054 patent require, among other things, a method of introducing an rAAV genome into a cell comprising contacting the cell with the composition of claim 1 under "conditions that allow" uptake of the rAAV vector. Contacting a cell with a composition of claim 1 under "conditions that allow" uptake of the rAAV vector is indefinite, as the specification fails to explain what these "conditions" should be, other than conditions that do not prevent such events from occurring.

The patent merely states that "[t]hese cells result from contact of the vector polynucleotide with a host cell using methods well-known in the art for introducing nucleic acids into cells under conditions which allow uptake of nucleic acid and nonhomologous insertion of exogenous nucleic acid into a genome." '054 patent at 17:38-43. The patent specification and claims provide no guidance as to what these conditions are that would allow uptake of the rAAV vector. These overbroad claims reciting "conditions that allow" uptake of the rAAV vector do not put the public on notice of what the claimed invention is—i.e., what the parameters of these "conditions" are, thus making it impossible to know whether one is potentially infringing. *See, e.g., Nautilus*, 572 U.S. at 901.

For at least these reasons, the Asserted Claims of the ’054 patent are invalid under 35 U.S.C. § 112 as indefinite.

4. Invalidity under 35 U.S.C. § 112, Fourth Paragraph

Under 35 U.S.C. § 112, ¶ 4, a claim in dependent form “shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed.” 35 U.S.C. § 112, ¶ 4 (emphasis added).

a. Dependent Claim 27 Is an Improper Dependent Claim

Claim 27 is invalid for being an improper dependent claim because it does not further limit the claim from which it depends. Claim 27 depends from independent claim 19, as explained above, and recites “[t]he composition of claim 19, wherein the coding sequence encodes a protein or an RNA of therapeutic interest.” However, the preamble of independent claim 19 does not recite a composition and instead recites “[a] method of expressing a polynucleotide coding sequence in a cell.” Because claim 27 does not further limit the purported scope of the method recited in claim 19, it is invalid under 35 U.S.C. § 112, ¶ 4.

IX. Invalidity Contentions As To The ’542 Patent

A. The ’542 Patent Claims Are Invalid for Obviousness

Each Asserted Claim of the ’542 patent is invalid for obviousness. In addition to the information set forth below, a chart identifying where specifically in each item of prior art each limitation of each Asserted Claim of the ’542 patent is found is attached as Appendix F, which is incorporated herein. Pinpoint citations to material in the prior art are exemplary of the disclosures and teachings of the prior art. Those citations should not be construed as limiting the disclosure of any prior art or as reflecting the only section of a prior art reference disclosing a particular limitation or teaching.

1. Independent Claim 1

The ’542 patent purports to solve the problem of concentration induced viral vector aggregation. As the ’542 patent admits, the phenomenon of concentration induced AAV vector aggregation was well-known by June 1, 2004. ’542 patent at 1:41-64. The ’542 patent also admits that such aggregation was known to be undesirable, as it compromises stability, effectiveness, and testing protocols, and increases the potential for an immunogenic reaction upon administration to a subject. *Id.* at 2:9-47. The ’542 patent purports to be the first disclosure to link ionic strength and AAV stability, observing that “vector particles remain soluble when elevated ionic strength solutions (μ>200 mM) are used during purification and for final vector formulation.” ’542 patent at 10:29-31. But, as discussed below, ionic strength was a well-known factor in viral stability, as of June 1, 2004, and high ionic strengths had been used to prevent particle aggregation. Additionally, the inclusion of multivalent ions in viral compositions to improve stability had also been disclosed. A person of ordinary skill in the art, armed with the teachings in the prior art regarding the effects of salts and buffers on particle stability, would have found it obvious to arrive at those features of the compositions claimed in the ’542 patent.

i. Liu (2003) alone or in combination with Clark (2002), Huang (2000), Lochrie (2003), Wright (2003), Mingozzi (2002), Croyle (2001), Potter (2002), Gatlin (1999), and/or Sommer (2003), the admissions in the ’542 patent, and the knowledge of a person of ordinary skill in the art

Claim 1 of the ’542 patent is obvious over Liu (2003) alone, or over Liu (2003) in combination with Clark (2002), Huang (2000), Lochrie (2003), Wright (2003), Mingozzi (2002), Croyle (2001), Potter (2002), Gatlin (1999), and/or Sommer (2003), the admissions in the ’542 patent, and the knowledge of a person of ordinary skill in the art. Liu (2003) discloses compositions comprising purified, recombinant adenoviral particles. Liu (2003) at [00365]-[00375]. Liu

(2003)'s Example 17 discloses storage of an adenoviral composition comprising 25mM Tris at pH 7.5, 300mM NaCl, 5mM $MgCl_2$, 0.0025% polysorbate 80, 5% trehalose, and having a virus concentration of 1.62 x 10^{10} particles/ml and an ionic strength of ~315 mM with "no signs of settling or precipitation" and "no significant decrease in particle number." [00365]-[00371]. Thus, Liu (2003) teaches a composition for storing AAV comprising purified adenovirus particles having a pH between 7.5 and 8.0, multivalent ions in the form of magnesium, and an ionic strength of ~315 mM.[16] Liu (2003) also discloses the purification of an adenoviral composition in Example 18 comprising a virus concentration of 1.36 x 10^{10} particles/ml. *Id.* at [00372]-[00375].

Liu (2003) discloses that its particle composition can be subjected to ultrafiltration to increase the concentration of the particles with respect to the total composition, including by removal of water. *Id.* at [00157]-[00158]. Liu (2003) discloses that its purified particle compositions can comprise about $1x10^{15}$ particles or more. *Id.* at [00271]; *see also id.* at [0006]. Although the '542 patent claims viral titers in terms of viral genomes or "vg," a person of ordinary skill in the art would have recognized that the factors contributing to concentration-induced virus aggregation are independent of whether or not a particle contains a viral genome. Thus, virus compositions comprising particle/ml concentrations exceeding $1x10^{13}$ up to $6.4x10^{13}$ will have similar aggregation properties as the claimed compositions comprising genome/ml concentrations within that range. *See also* '542 patent at 1:46-48 ("In commonly used buffered-saline solutions, significant aggregation occurs at concentrations of 10^{13} particles/mL."); 1:60-64 ("The effective vector concentration limit may be even lower for vectors purified using column chromatography techniques because excess empty capsids are co-purified and contribute to particle

[16] As described in the '542 patent (and used herein), ionic strength is calculated according to the equation $\mu=\frac{1}{2}\Sigma c_i z_i^2$.'542 patent at 12:57-59.

concentration."); *see also id.* 1:46-48, 4:65-67, 7:13-17 (discussing aggregation in the context of concentrations measured in particles/ml). Indeed, in Wright (2003), the inventors "[a]ssum[ed] that full vector particles and empty capsids aggregate by a similar mechanism." Wright (2003) at 175.

Liu (2003) expressly discloses that its methods and formulations can be applied to AAV as well as adenovirus, identifying AAV as a "particularly preferred" type of particle. *See* Liu (2003) at [0008], [0009], [0011], [0020] ("Particularly preferred types of viral vector particles include adeno-associated viral vector particles and adenoviral vector particles."). Liu (2003) also discloses that methods of preparing and purifying AAV are known in the art. *Id.* at [0009], [0020] (citing Laughlin (1983), which describes production of recombinant AAV-2 particles).

Liu (2003) also discloses that Tris buffers, for example, 25mM Tris, 10mM NaCl, 5 mM MgCl2, 0.0025% polysorbate 80, at pH 7.5-8 are "capable of maintaining a pH at a range of temperatures used in the production and storage of the viral vector composition that is compatible with retaining the activity of viral gene transfer vectors (particularly adenoviral gene transfer vectors)." *Id.* at [00138]. Liu (2003) discloses elution from the SEC column with 250-600mM divalent salt. *See id.* at claim 192. Divalent salts are also contemplated for use to load and elute the SEC column, including with a composition comprising about 250-600 mM of a divalent salt, for example magnesium chloride. *Id.* at [00223].

The clarification steps, Benzonase digestion, and diafiltration steps described in Liu (2003) result in a "purified" recombinant adenoviral particle composition by removing debris, reducing the level of non-viral enveloped polynucleotides, and resulting in the removal of, or reduction in concentration of, at least one undesired biomolecule in the composition. *See, e.g.*, *id.* at [0005], [00170], [00162]; *see also* '542 patent at 10:54-11:50 (describing clarification, Benzonase

digestion and ultrafiltration/diafiltration steps in disclosed purification methods). Furthermore, Liu (2003) discloses that additional column purification steps can be performed on the filtered composition before formulation in the temporary storage buffer. *Id.* at [0005] ("The completely filtered composition can be further purified by one or more chromatography steps . . ."). Such additional column purification steps also result in a "purified" recombinant adenoviral particle composition. *See, e.g., id.* at [00172], [00201]-[00204], [00289]; *see also* '542 patent at 11:27-11:39 (describing the use of column chromatography to purify AAV2 particles).

A person of ordinary skill in the art would have been motivated to modify the compositions described in Liu (2003) to arrive the at claim 1 composition. The '542 patent admits that the challenges and motivations regarding AAV aggregation are similar to those encountered when formulating other viruses, including adenovirus, and when developing protein therapeutics. '542 patent at 2:58-65 ("As is well established for protein therapeutics, an important aspect of vector stability is solubility during preparation and storage, and vector aggregation is a problem that needs to be fully addressed.") (internal citations omitted); 5:67-6:4 ("the composition and methods of the present invention may also be useful with other AAV serotypes/variants, or other viral vectors such as adenoviruses, lentiviruses and retroviruses"). Thus, the '542 patent admits that prior art teachings directed to stability of other viruses, including adenoviruses, and protein stability are relevant to developing rAAV formulations, motivating a person of ordinary skill in the art to rely on such teachings when addressing aggregation in rAAV compositions.

As discussed above, Liu (2003) expressly discloses a composition of stable stored, purified virus meeting the pH, multivalent ion, and ionic strength limitations of claim 1. A person of ordinary skill in the art would have been motivated to use the Liu (2003) composition in formulating a rAAV composition because Liu (2003) discloses that its teachings are not limited to

adenoviral compositions but are also suitable for AAV particle compositions; the ’542 patent likewise admits that its rAAV compositions may be suitable for formulating adenoviruses. Liu (2003) at [0008]; ’542 patent at 1:65-2:8. It was also appreciated that AAV was of interest for use in human gene therapy because AAV can efficiently transduce a variety of postmitotic cells, resulting in long-lived, robust gene expression. *See, e.g.*, Wright (2003) at 174; Lochrie (2003) at 2:26-30. A person of ordinary skill in the art would have further been motivated to use AAV in Liu (2003)’s compositions based on Mingozzi (2002)’s statement that “[a]n excellent safety profile combined with reduced potential for activation of inflammatory or cellular immune responses has made this vector [AAV] system attractive for clinical application and treatment of genetic disorders.” Mingozzi (2002) at 10497; *see also* Wright (2003) at 175 (teaching AAV has “shown significant promise for human gene therapy”); Clark (2002) at S-9 (touting AAV’s ability “to mediate long-term, robust in vivo gene expression in numerous cell types”).

A person of ordinary skill in the art would have been motivated to increase the concentration of particles in Liu (2003)’s compositions and remove empty capsids because, as discussed above, Liu (2003) discloses that its purified particle compositions can comprise about $1x10^{15}$ particles or more. Liu (2003) at [00271]; *see also id.* at [0006]. Moreover, prior to the filing of the ’542 patent, a person of ordinary skill in the art would have known that high concentrations of AAV vector are required in therapeutic compositions, both because of the large dosages required for successful phenotypic correction of a subject (10^{12}-10^{14} particles) and the inherent constraints on volume in the various administration routes for gene therapies. *See* Clark (2002) at S-9 (“[A] clinical dose in humans will require 10^{12} to 10^{14} rAAV vector particles . . . . Therefore, the ability to produce high titer rAAV is critical for clinical applications….”); Gatlin (1999) at 405, 417-418 (teaching that most parenteral compositions have an injection volume limit of only a few

milliliters). Indeed, the ’542 patent admits as much in its “Background” section. ’542 patent at 2:10-14 (“in vivo administration of AAV2 vectors to certain site, such as the central nervous system, may require small volumes of highly concentrated vector”); *see also* Wright (2003) at 175 (“AAV vectors are typically prepared at final purified concentrations in the range of 10^{11} to 10^{13} vg/ml.”); Liu (2003) at [00157]-[00158]; Huang (2000) at S268 (“To achieve high level of gene transfer and ensure the safety of vector administration it is desirable to deliver high doses of vector in small volumes.”). For example, Mingozzi (2002) reported that AAV vector doses of 10^{12} vg/kg resulted in sustained transgene expression in a large-animal (canine) model, which corresponds to doses of $7x10^{13}$ vector genomes for a 70kg human. Mingozzi (2002) at 10497. Pre-clinical trials using rAAV vector had also used relatively small dosage volumes. *See, e.g.,* Mount (2002) at 2671 (using a 10 ml dosage for mesenteric vein administration); Ye (1999) at 90 (using a 10 ml dosage for intramuscular administration).

A person of ordinary skill in the art also would have been motivated to use an elution buffer in Liu (2003)’s Example 18 that has a pH between 7.5 and 8.0, multivalent ions selected from magnesium, and an ionic strength of at least ~750 mM, because Liu (2003) teaches that divalent salts are contemplated for use to load and elute the SEC column, including with a composition comprising at least about 250-600 mM of a divalent salt, for example magnesium chloride. Liu (2003) at [00223]; *see also* claim 192. Liu (2003) also discloses that Tris buffers, for example, 25mM Tris, 10mM NaCl, 5mM MgCl2, 0.0025% polysorbate 80, at pH 7.5-8 are “capable of maintaining a pH at a range of temperatures used in the production and storage of the viral vector composition that is compatible with retaining the activity of viral gene transfer vectors (particularly adenoviral gene transfer vectors).” *Id.* at [00138].

A person of ordinary skill in the art would have had a reasonable expectation of success in arriving at the composition recited in Claim 1 of the ’542 patent based on the teachings of Liu (2003) alone or in combination with the other references discussed above. A person of ordinary skill in the art would have expected to successfully incorporate AAV into Liu (2003)’s compositions instead of adenovirus because Liu (2003) discloses that the “basic construction of recombinant viral vectors is well understood in the art,” including construction of adeno-associated viral vectors. *Id.* at [0009] (citing Laughlin (1983)). Moreover, the ’542 patent admits that its rAAV compositions may be suitable for formulating adenoviruses. ’542 patent at 5:67-6:4.

A person of ordinary skill in the art would have reasonably expected success in concentrating the virus in Liu (2003)’s compositions and removing empty capsids, since Liu (2003) discloses that its purified particle compositions can comprise about $1x10^{15}$ particles or more. Liu (2003) at [00271]; *see also id.* at [0006]. Moreover, by June 2004, methods of generating high yields of rAAV vectors were well-known, as were methods of removing empty capsids and concentrating rAAV vectors with techniques such as cesium chloride density centrifugation and tangential flow filtration. *See* Clark (2002) at S-12 (disclosing that stable cell lines can yield between 1×10^{14} to 1×10^{15} rAAV particles per large-scale preparation); Liu (2003) at [00157]-[00158]; ’542 patent at 7:49-8:18 and 11:7-12:29. Additionally, prior art references had demonstrated that the claimed concentrations were possible. For instance, Huang (2000) describes rAAV vector titers of $5\text{-}10x10^{13}$ genomes/ml, which exceeds the claimed “$1x10^{13}$ vg/ml.” Huang (2000) at S286. Although Huang (2000) discloses that AAV can aggregate at $5\text{-}10x10^{13}$ genomes/ml, Huang (2000) teaches that its formulations reduced aggregation and that PEGylation of AAV efficiently dissolves AAV aggregates, thus teaching a person of ordinary skill in the art that high concentration AAV formulations (e.g., $5\text{-}10x10^{13}$ genomes/ml) could have been achieved

and were desirable for delivering high doses of viral vector in small volumes. Likewise, Sommer (2003) discloses vector genome copy titers of $1.06x10^{13}$ genomes/ml (measured by absorbance) and titers of $9.76x10^{12}$ genomes /ml ± $2.88x10^{12}$ (measured by Q-PCR), which encompasses a range of values from $6.88x10^{12}$ genomes/ml to $1.26x10^{13}$ genomes/ml. Sommer (2003) at 125. Thus, Sommer (2003) also discloses AAV-2 formulations that include concentrations exceeding the claimed "$1x10^{13}$ vg/ml." Thus, a person of ordinary skill in the art would have had a reasonable expectation of success in concentrating the particles in Liu (2003)'s compositions to fall within the claimed range using methods of concentrating viral preparations, such as tangential flow filtration that were well known in the art. Indeed, Mingozzi (2002) proved as much by preparing compositions of purified AAV-2 and AAV-5 having concentrations "$>10^{13}$ vg/ml as determined by quantitative slot blot analysis," and successfully utilizing those compositions for gene transfer in mice. Mingozzi (2002) at 10497-98.

A person of ordinary skill in the art also would have reasonably expected success in using an elution buffer in Liu (2003)'s Example 18 to recover a composition having the claimed pH, multivalent ion, and ionic strength ranges, since Liu (2003) teaches that Tris buffers at pH 7.5-8 are "capable of maintaining a pH at a range of temperatures used in the production and storage of the viral vector composition that is compatible with retaining the activity of viral gene transfer vectors (particularly adenoviral gene transfer vectors)." *Id.* at [00138]. Liu (2003) also teaches that divalent salts such as magnesium chloride may be used to load and elute SEC columns, using at least about 250-600 mM of a divalent salt. *Id.* at [00223]; *see also* claim 192. Thus, a person of ordinary skill in the art would have had a reasonable expectation of success in eluting the particles using a sufficient amount divalent salt to meet the ionic strength limitation and buffering the eluate with Tris within the claimed range. Indeed, protocols for the large-scale production of rAAV had

been described that involved eluting and storing the resulting rAAV stocks in a high-ionic strength (500mM NaCl) buffer. Potter (2002) at 417-419, 429.

Regarding the claimed stability feature, as the ’542 patent admits, “[i]t is known that high salt concentrations increase AAV2 vector solubility” and that “vector aggregation is prevented when ionic strength is ~200 mM or greater regardless of which salt is used.” ’542 patent at 4:67-5:2; 7:20-22. Moreover, Croyle (2001) taught that AAV “is significantly more stable than adenovirus.” Croyle (2001) at 1283; *see also* Wright (2003) at 175 (reporting that highly purified AAV vector preparations at concentrations of $5x10^{13}$ capsid particles/ml “are stable in a non-aggregated, monomeric state when stored at 2 to 8°C”). Thus, a person of ordinary skill in the art would have understood and expected that formulations having an ionic strength ≥ 200 mM, such as those described in Liu (2003), are necessarily and inevitably stored “without significant aggregation.” Thus, Liu (2003), alone or in combination with the other references discussed above, renders obvious rAAV compositions that inherently meet the stability limitation of claim 1.

ii. Frei (1999) alone or in combination with Clark (2002), Huang (2000), Lochrie (2003), Wright (2003), Mingozzi (2002), Croyle (2001), Potter (2002), Gatlin (1999), and/or Sommer (2003), the admissions in the ’542 patent, and the knowledge of a person of ordinary skill in the art

Claim 1 of the ’542 patent is obvious over Frei (1999) alone, or over Frei (1999) in combination with Clark (2002), Huang (2000), Lochrie (2003), Wright (2003), Mingozzi (2002), Croyle (2001), Potter (2002), Gatlin (1999), and/or Sommer (2003), the admissions in the ’542 patent, and the knowledge of a person of ordinary skill in the art. Frei (1999) describes compositions and formulations for storing purified, recombinant adenoviruses, as well as methods for concentrating and purifying virus preparations. Frei (1999) at 8:18-34; 9:11-15. Frei (1999) discloses multiple high titer ($>10^{13}$ particles/ml) buffered compositions (Examples D-1, D-3, and

S-1) comprising the multivalent ions Mg^{2+} and or PO_4^{3-}, and a pH of 8 that are stored without detectable aggregation by A_{320}/A_{260} UV absorbance analysis. *Id.* at 22:24- 23:20. Frei (1999)'s Example D-1 discloses an adenoviral composition comprising 20mM NaPi, 100 mM NaCl, 2mM $MgCl_2$, 2% sucrose, 10% glycerol, pH 8 at 2-10°C and having a viral concentration of 1.6 $x10^{13}$ particles/ml and an ionic strength of ~160mM. Frei's Example D-3 discloses an adenoviral composition comprising 20mM NaPi, 100 mM NaCl, 2mM $MgCl_2$, 2% sucrose, 10% glycerol, pH 8 at 2-10°C and having a viral concentration of 1.5 $x10^{13}$ particles/ml and an ionic strength of ~160mM. Frei (1999)'s Example S-1 discloses an adenoviral composition comprising 16mM NaPi, 80 mM NaCl, 1.6mM $MgCl_2$, 1.6% sucrose, 20% glycerol, pH 8 at 2-10°C and having a viral concentration of 1.66 $x10^{13}$ particles/ml and an ionic strength of ~127mM. Frei (1999) also discloses elution of recombinant viral particles from a DEAE anion exchange column performed with a 6% to 100% linear gradient between Buffer A (50mM sodium phosphate, 260mM NaCl, 2mM $MgCl_2$, 2% sucrose, pH 7.5) (ionic strength 0.266M) and Buffer B (50mM sodium phosphate, 600mM NaCl, 2mM $MgCl_2$, 2% sucrose, pH 7.5) (ionic strength 0.606 mM). *Id.* at 19:41-20:17. Glycerol was added to 30% (v/v) and the pool was subsequently concentrated using tangential flow filtration to 1.0 to 2.0 x 10^{13} particles/ml, and no significant aggregation was observed by A_{320}/A_{260} UV absorbance analysis. *Id.* at 20:17-32. Frei (1999) thus discloses that its DEAE pool is an adenoviral composition, comprising $MgCl_2$, sodium phosphate, pH 7.5, having a viral concentration of to 1.0 to 2.0 x 10^{13} particles/ml, and an ionic strength of at least ~266mM.

Although the '542 patent claims viral titers in terms of viral genomes or "vg," a person of ordinary skill in the art would have recognized that the factors contributing to concentration-induced virus aggregation are independent of whether or not a particle contains a viral genome. Thus, virus compositions comprising particle/ml concentrations exceeding $1x10^{13}$ up to $6.4x10^{13}$

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Exhibit 2011

will have similar aggregation properties as the claimed compositions comprising genome/ml concentrations within that range. *See also* '542 patent at 1:46-48 ("In commonly used buffered-saline solutions, significant aggregation occurs at concentrations of 10^{13} particles/mL."); 1:60-64 ("The effective vector concentration limit may be even lower for vectors purified using column chromatography techniques because excess empty capsids are co-purified and contribute to particle concentration."); *see also id.* 1:46-48, 4:65-67, 7:13-17 (discussing aggregation in the context of concentrations measured in particles/ml). Indeed, in Wright (2003), the inventors "[a]ssum[ed] that full vector particles and empty capsids aggregate by a similar mechanism." Wright (2003) at 175.

Frei (1999) discloses that its invention "is particularly well suited for stabilizing a recombinant virus, such as a live recombinant adenovirus (or 'viral vector'), for therapeutic use in gene therapy." *Id.* at 8:27-29, 16:28-30 ("The present invention is particularly useful for concentrating recombinant viruses carrying a heterologous transgene for use in gene therapy."), claim 2, 18, 19. Frei (1999) discloses that anion exchange chromatography produces a "purified" product. *See, e.g., id.* at 19:29-30 ("the adenovirus product is first purified by anion exchange chromatography."). Frei (1999) also discloses that size exclusion chromatography is a "subsequent purification step." *See, e.g., id.* at 3:27-29; *see also id.* at 22:19-21 ("The preparations were then subjected to further purification by Superdex-200 gel filtration chromatography to obtain the final formulation for testing.").

Frei (1999) discloses storage of the formulations in examples D-1 to D-3 and S-1. *See, e.g., id.* at 1:16-17 ("The compositions of the present invention are useful in maintaining the stability of viruses during storage …"). Furthermore, Frei (1999) discloses that the final formulation of examples D-1 to D-3 and S-1 are maintained at 2-10°C, which corresponds to refrigeration and

would thus have been understood by a person of ordinary skill in the art to correspond to a storage temperature. *See also id.* at 12:18-19 ("The temperatures listed in the second column of the tables under 'condition' represent the storage temperature."). Frei (1999) also discloses stable storage of the salt-containing DEAE pool for over 10 days at 2-10°C. *See, e.g., id.* at 22:10-12. Thus, Frei (1999) discloses that the formulations following both the anion exchange chromatography and size exclusion chromatography steps as well as the DEAE pool following anion exchange chromatography produce compositions comprising purified, recombinant adenoviral particles which are stored. Frei (1999) also explicitly discloses that sodium chloride can stabilize the composition and can "preferably" be included in a range of concentrations up to 171.1mM (10mg/ml). *Id.* at 5:37-6:6, claim 28.

A person of ordinary skill in the art would have been motivated to modify the compositions described in Frei (1999) to arrive at the Claim 1 composition. The '542 patent admits that the challenges and motivations regarding AAV aggregation are similar to those encountered when formulating other viruses, including adenovirus, and when developing protein therapeutics. '542 patent at 2:58-65 ("As is well established for protein therapeutics, an important aspect of vector stability is solubility during preparation and storage, and vector aggregation is a problem that needs to be fully addressed.") (internal citations omitted); 1:65-2:8 ("the composition and methods of the present invention may also be useful with other AAV serotypes/variants, or other viral vectors such as adenoviruses, lentiviruses and retroviruses"). Thus, the '542 patent admits that prior art teachings directed to stability of other viruses, including adenoviruses, and protein stability are relevant to developing rAAV formulations, motivating a person of ordinary skill in the art to rely on such teachings when addressing aggregation in rAAV compositions.

As discussed above, Frei (1999) expressly discloses compositions of stable stored, purified virus meeting the viral titer, pH, multivalent ion, and ionic strength limitations of Claim 1. A person of ordinary skill in the art would have been motivated to use the Frei (1999) compositions in formulating an rAAV composition because Frei (1999) discloses that its teachings are not limited to adenoviral compositions but are also suitable for AAV particle compositions, as well as recombinant viral compositions; the ’542 patent likewise admits that its rAAV compositions may be suitable for formulating adenoviruses. Frei (1999) at 8:18-33; ’542 patent at 5:67-6:4. It was also appreciated that AAV was of interest for use in human gene therapy because AAV can efficiently transduce a variety of postmitotic cells, resulting in long-lived, robust gene expression. *See, e.g.*, Wright (2003) at 174; Lochrie (2003) at 2:26-30. A person of ordinary skill in the art would have further been motivated to use AAV in Frei (1999)’s compositions based on Mingozzi (2002)’s statement that “[a]n excellent safety profile combined with reduced potential for activation of inflammatory or cellular immune responses has made this vector [AAV] system attractive for clinical application and treatment of genetic disorders.” Mingozzi (2002) at 10497; *see also* Wright (2003) at 175 (teaching AAV has “shown significant promise for human gene therapy”); Clark (2002) at S-9 (touting AAV’s ability “to mediate long-term, robust in vivo gene expression in numerous cell types”).

A person of ordinary skill in the art would have been motivated to remove any empty capsids from Frei (1999)’s formulations while maintaining Frei (1999)’s purified virus concentration because it was understood that high concentrations of vector-containing particles are required for therapeutic use. *See* Huang (2000) at S286 (“To achieve high level of gene transfer and ensure the safety of vector administration it is desirable to deliver high doses of vector in small volumes.”). The ’542 patent admits as much. *See, e.g.*, 2:11-14 (“in vivo administration of AAV2

vectors to certain sites, such as the central nervous system, may require small volumes of highly concentrated vector"). For example, Mingozzi (2002) reported that AAV vector doses of 10^{12} vg/kg resulted in sustained transgene expression in a large-animal (canine) model, which corresponds to doses of $7x10^{13}$ vector genomes for a 70kg human. Mingozzi (2002) at 10497; *see also* Clark (2002) at S-9 ("a clinical dose in humans will require 10^{12} to 10^{14} rAAV vector particles"). Moreover, it was known that most parenteral compositions have an injection volume limit of only a few milliliters. Gatlin (1999) at 405, 417-418. Thus, to deliver clinically relevant amounts of AAV particles via parenteral administration, a person of ordinary skill in the art would have been motivated to develop compositions having vector genome concentrations exceeding 10^{13} vg/ml.

A person of ordinary skill in the art also would have been motivated to increase the ionic strength of Frei (1999)'s Example D-1, D-3, or S-1 compositions to greater than 200mM through the addition of a monovalent salt stabilizer such as sodium chloride since Frei (1999) teaches that such additives "may suppress the rate and existence of by-products of fermentation, resulting in a more pharmaceutically elegant presentation that may have reduced antigenicity potential due to protein aggregates." Frei (1999) at 5:38-6:10. Specifically, Frei (1999) instructs that sodium chloride may be present up to "10.0 mg/ml," which corresponds to an ionic strength contribution of 172mM. *Id.* at 6:5. Increasing the sodium chloride concentration to 172mM for the formulations in D-1, D-3, and S-1 would result in buffers with an overall ionic strength greater than 200mM.

A person of ordinary skill in the art would have had a reasonable expectation of success in arriving at the composition recited in Claim 1 of the '542 patent based on the teachings of Frei (1999) alone or in combination with the other references discussed above. A person of ordinary skill in the art would have had a reasonable expectation of success in using the Frei (1999)

compositions in formulating an rAAV composition because Frei (1999) discloses that its teachings are not limited to adenoviral compositions but are also suitable for AAV particle compositions, as well as recombinant viral compositions; the ’542 patent likewise admits that its rAAV compositions may be suitable for formulating adenoviruses. Frei (1999) at 8:18-33; ’542 patent at 5:67-6:4.

A person of ordinary skill in the art also would have had a reasonable expectation of success in achieving the claimed vg/mL vector concentrations because methods of generating high yields of AAV were well-known, as were methods for removing empty capsids and concentrating genome-containing vectors. *See, e.g.*, Clark (2002) at S-12 (reporting that stable cell lines can yield between $1x10^{14}$ to $1x10^{15}$ AAV particles per large-scale preparation); Wright (2003) at 175 (discussing cesium chloride and iodixanol gradient ultracentrifugation for separating “genome-containing[] vector particles from the lighter empty capsids”); Huang (2000) at S286 (reporting that “the same vector prep was concentrated to different concentrations”). In fact, by June 2004, the prior art had already achieved AAV compositions exceeding $1x10^{13}$ vg/ml. For example, Huang (2000) described AAV compositions having concentrations of $5\text{-}10x10^{13}$ genome copies/ml. Huang (2000) at S286. Although Huang (2000) states that gene transfer efficiency was lower with such compositions compared to corresponding compositions having concentrations of 1 $5x10^{12}$ genome copies/ml, Huang (2000) also taught that certain formulation techniques “could lead to a 30-50% reduction in the size of aggregates at high vector concentrations.” *Id.* Thus, based on Huang (2000), a person of ordinary skill in the art would have reasonably expected that high concentration AAV compositions (e.g, $5\text{-}10x10^{13}$ vg/ml) could be achieved and utilized for successful gene transfer. Indeed, Mingozzi (2002) proved as much by preparing compositions of purified AAV-2 and AAV-5 having concentrations “$>10^{13}$ vg/ml as determined by quantitative

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slot blot analysis," and successfully utilizing those compositions for gene transfer in mice. Mingozzi (2002) at 10497-98.

A person of ordinary skill in the art also would have had a reasonable expectation of success of using a buffer with 172mM NaCl in Frei (1999)'s Example D-1, D-3, and S-1 compositions because Frei (1999) discloses that such a concentration of sodium chloride can be used in the formulations of its invention. *Id.* at 5:37-6:11. Moreover, protocols for the large-scale production of rAAV had been described that involved eluting and storing the resulting rAAV stocks in a high-ionic strength (500mM NaCl) buffer. Potter (2002) at 417-419, 429. Thus, Frei (1999), alone or in combination with the other references discussed above, renders obvious rAAV compositions that inherently meet the ionic strength limitation of claim 1.

Regarding the claimed stability feature, as discussed above, Frei (1999) teaches that its Example D-1, D-3, and S-1 compositions are stored without detectable aggregation. A person of ordinary skill in the art would understand that the disclosed A_{320}/A_{260} ratios of 0.22-0.26 are characteristic of a composition wherein the viral particles do not exhibit significant aggregation. *See, e.g.*, Tang (2001) at 6:62-63 ("Purified, free virus particles display a light scattering ratio of about 0.22–0.30:1."). As the '542 Patent admits, "[i]t is known that high salt concentrations increase AAV2 vector solubility" and that "vector aggregation is prevented when ionic strength is ~200 mM or greater regardless of which salt is used." '542 Patent at 4:67-5:2; 7:20-22. Moreover, Croyle (2001) taught that AAV "is significantly more stable than adenovirus." Croyle (2001) at 1283; *see also* Wright (2003) at 175 (reporting that highly purified AAV vector preparations at concentrations of $5x10^{13}$ capsid particles/ml "are stable in a non-aggregated, monomeric state when stored at 2 to 8°C"). Thus, a person of ordinary skill in the art would have understood and expected that all prior art virus compositions having an ionic strength ≥ 200 mM, such as those

rendered obvious by Frei (1999), are necessarily and inevitably stored "without significant aggregation."

iii. Evans (2001) alone or in combination with Clark (2002), Huang (2000), Lochrie (2003), Wright (2003), Mingozzi (2002), Croyle (2001), Potter (2002), Gatlin (1999), and/or Sommer (2003), the admissions in the '542 patent, and the knowledge of a person of ordinary skill in the art

Claim 1 of the '542 patent is obvious over Evans (2001) alone, or Evans (2001) in combination with Clark (2002), Huang (2000), Lochrie (2003), Wright (2003), Mingozzi (2002), Croyle (2001), Potter (2002), Gatlin (1999), and/or Sommer (2003), the admissions in the '542 patent, and the knowledge of a person of ordinary skill in the art. Evans (2001) specifically claims a virus formulation and comprising: a purified virus from about 1 x 10^7 particles/mL to about 1 x 10^{13} particles/mL;[17] a buffer acceptable for human parenteral use at a pH from about 7.5 to about 8.5; sodium chloride from about 25 mM to about 250 mM; a divalent cation selected from $MgCl_2$ and $CaCl_2$ in an amount from about 0.1 mM to about 5 mM; and a non-ionic detergent. Evans (2001) at Claim 5. Accepting the high end of each range, for a formulation of Evans (2001)'s claim 5 comprising 250 mM of NaCl and 5 mM of $MgCl_2$, the formulation of claim 5 has an ionic strength of ~265 mM. Thus, Evans (2001) teaches compositions comprising purified adenovirus particles at concentrations to about 1 x 10^{13} particles/mL, having a pH between about 7.5 and about 8.5, multivalent ions in the form of magnesium, and ionic strengths of up to 265 mM. Evans (2001) also exemplifies a formulation for purified adenovirus particles, A115, comprising 5mM Tris pH 8.0, 75mM NaCl, 5% sucrose, 1mM $MgCl_2$, 0.005% PS-80, and 10mM sodium citrate. *Id.* at 16:14-18.

[17] A person of ordinary skill in the art would understand that the term "about 1 x 10^{13} particles/mL" includes concentrations that exceed 1 x 10^{13}.

Although the ’542 patent claims viral titers in terms of viral genomes or “vg,” a person of ordinary skill in the art would have recognized that the factors contributing to concentration-induced virus aggregation are independent of whether or not a particle contains a viral genome. Thus, virus compositions comprising particle/ml concentrations exceeding $1x10^{13}$ up to $6.4x10^{13}$ will have similar aggregation properties as the claimed compositions comprising genome/ml concentrations within that range. *See also* ’542 patent at 1:46-48 (“In commonly used buffered-saline solutions, significant aggregation occurs at concentrations of 10^{13} particles/mL.”); 1:60-64 (“The effective vector concentration limit may be even lower for vectors purified using column chromatography techniques because excess empty capsids are co-purified and contribute to particle concentration.”); *see also id.* 1:46-48, 4:65-67, 7:13-17 (discussing aggregation in the context of concentrations measured in particles/ml). Indeed, in Wright (2003), the inventors “[a]ssum[ed] that full vector particles and empty capsids aggregate by a similar mechanism.” Wright (2003) at 175.

Evans (2001) describes “viral formulations and related pharmaceutical products for use in gene therapy and/or vaccine applications.” Evans (2001) at 1:15-16. Evans (2001) explains that “[a]n ongoing challenge in the field of gene therapy and vaccine research is to generate liquid virus formulations which are stable for longer periods of time within a useful temperature range, such as from about 2° C to about 8° C.” *Id.* at 1:28-30. Thus, Evans (2001) discloses its formulations are stored. Like the ’542 patent, Evans (2001) is concerned with maintaining the buffer conditions of its disclosed formulations so that it is acceptable for human parenteral administration. *See* ’542 patent at Abstract.

Evans (2001) discloses a number of viral compositions that enhance viral stability and teaches that “[t]he recombinant viruses of the present invention which show enhanced storage

stability include but are not limited to adenovirus, adeno-associated virus, retroviruses, herpes virus, vaccinia virus, rotovirus, pox viruses." Evans (2001) at 3:12-14. Evans (2001) discloses exemplary formulations in Example 1 that used Adenovirus type 5 containing the FL HIV-gag transgene. *Id.* at 21:9-13. Evans (2001) discloses that this virus is "a recombinant virus" which was "purified by column chromatography." *Id.* Thus, Evans (2001) discloses a composition comprising purified, recombinant adenoviral particles. *Id.* at 1:15-25, 3:12-18, 21:9-13. Evans (2001) discloses that its formulation comprises a divalent cation as well as additional components such as an inhibitor of free radical oxidation. *See, e.g., id.* at 7:8-12. Evans (2001) discloses that a preferred divalent cation is magnesium chloride at a concentration ranging from about 0.1mM to about 5mM. *Id.* at 9:6-9. Evans (2001) also claims formulations containing divalent cations, including magnesium chloride and calcium chloride. *Id.* at claims 1, 5, 7, 8, 10, 14, 17, 18, 22, 23, 25, 29, 31, 32, 35, 39. Evans (2001) also discloses that the one or more components which inhibits free radical oxidation includes sodium citrate at a concentration ranging from about 1mM to about 100mM. *Id.* at 1:19-31. Evans (2001) also discloses that sodium chloride can be used in its formulations at a concentration of about 25mM to about 250mM, and that sodium citrate can be added at a concentration from about 1mM to about 100mM, preferably in a range from about 5 mM to about 25 mM. *Id.* at 14:15-28, 15:19-31.

The ionic strength of the A115 formulation in Evans (2001) is ~138mM. However, Evans (2001) discloses that sodium citrate can be used at about 1mM to about 100mM, preferably in a range from about 5 mM to about 25 mM. *Id.* at 15:19-31 (teaching that sodium citrate can be used at a concentration up to 100mM, and that about 5mM to about 25mM is a preferred range). Evans (2001) also discloses that sodium chloride can be used at about 25mM to about 250mM. *Id.* at 14:15-28.

A person of ordinary skill in the art would have been motivated to modify the compositions described in Evans (2001) to arrive at the claim 1 composition. The ’542 patent admits that the challenges and motivations regarding AAV aggregation are similar to those encountered when formulating other viruses, including adenovirus, and when developing protein therapeutics. ’542 patent at 2:58-65 (“As is well established for protein therapeutics, an important aspect of vector stability is solubility during preparation and storage, and vector aggregation is a problem that needs to be fully addressed.”) (internal citations omitted); 1:65-2:8 (“the composition and methods of the present invention may also be useful with other AAV serotypes/variants, or other viral vectors such as adenoviruses, lentiviruses and retroviruses”). Thus, the ’542 patent admits that prior art teachings directed to stability of other viruses, including adenoviruses, and protein stability are relevant to developing rAAV formulations, motivating a person of ordinary skill in the art to rely on such teachings when addressing aggregation in rAAV compositions.

As discussed above, Evans (2001) expressly discloses a composition of stable stored, purified virus meeting the titer, pH, multivalent ion, and ionic strength limitations of claim 1. A person of ordinary skill in the art would have been motivated to apply the methods and compositions of Evans (2001) to AAV, because Evans (2001) expressly discloses that its methods and formulations can be applied to AAV as well as adenovirus. *See* Evans (2001) at 3:12-18, 7:16-18. It was also appreciated that AAV was of interest for use in human gene therapy because AAV can efficiently transduce a variety of postmitotic cells, resulting in long-lived, robust gene expression. *See, e.g.*, Wright (2003) at 174; Lochrie (2003) at 2:26-30. A person of ordinary skill in the art would have further been motivated to use AAV in Evans (2001)’s compositions based on Mingozzi (2002)’s statement that “[a]n excellent safety profile combined with reduced potential for activation of inflammatory or cellular immune responses has made this vector [AAV] system

attractive for clinical application and treatment of genetic disorders." Mingozzi (2002), 10497; *see also* Wright at 175 (teaching AAV has "shown significant promise for human gene therapy"); Clark (2002) (touting AAV's ability "to mediate long-term, robust in vivo gene expression in numerous cell types").

As discussed above, Evans (2001)'s Claim 5 specifically claims a virus formulation comprising a purified virus from about 1 x 10^7 particles/mL to about 1 x 10^{13} particles/mL. A person of ordinary skill in the art would understand that "about" 1x10^{13} vp/ml encompasses variation that would result in values that are both above and below 1x10^{13} vp/ml. Moreover, a person of ordinary skill in the art would have been motivated to further increase the particle concentration in Evans (2001)'s compositions and remove empty capsids. Prior to the filing of the '542 patent, a person of ordinary skill in the art would have known that high concentrations of AAV vector are required in therapeutic compositions, both because of the large dosages required for successful phenotypic correction of a subject (10^{12}-10^{14} particles) and the inherent constraints on volume in the various administration routes for gene therapies. Clark, (2002) at S9 ("[A] clinical dose in humans will require 10^{12} to 10^{14} rAAV vector particles . . . . Therefore, the ability to produce high titer rAAV is critical for clinical applications…"); Gatlin (1999) at 405, 417-418 (teaching that most parenteral compositions have an injection volume limit of only a few milliliters). Indeed, the '542 patent admits as much in its "Background" section. '542 patent at 2:10-14 ("in vivo administration of AAV2 vectors to certain site, such as the central nervous system, may require small volumes of highly concentrated vector"); *see also* Wright (2003) at 175 ("AAV vectors are typically prepared at final purified concentrations in the range of 10^{11} to 10^{13} vg/ml."); Liu (2003) at [00157]-[00158]; Huang (2000) at S268 ("To achieve high level of gene transfer and ensure the safety of vector administration it is desirable to deliver high doses of vector

in small volumes.”). For example, Mingozzi (2002) reported that AAV vector doses of 10^{12} vg/kg resulted in sustained transgene expression in a large-animal (canine) model, which corresponds to doses of $7x10^{13}$ vector genomes for a 70kg human. Mingozzi (2002) at 10497. Pre-clinical trials using AAV vector had also used relatively small dosage volumes. *See, e.g.,* Mount (2002) at 2671 (using a 10 ml dosage for mesenteric vein administration); Ye (1999) at 90 (using a 10 ml dosage for intramuscular administration).

A person of ordinary skill in the art also would have been motivated to modify Evans (2001)’s A115 formulation to have a sodium citrate concentration of 25 mM and/or a sodium chloride concentration of 250 mM because Evans (2001) teaches that 25 mM is a preferred sodium citrate concentration and that the amount of sodium chloride can range from about 25 mM to about 250 mM. Evans (2001) at 11:22-27; 14:15-28, 15:19-31. Evans (2001) further teaches that the inclusion of sodium chloride can “enhance viral stability” and that sodium citrate is a component that inhibits free radical oxidation. *Id.* at 9:16-19, 13:28-31. Modifying Evans (2001)’s A115 formulation to have a sodium citrate concentration of 25mM would yield an ionic strength exceeding 200mM. Likewise, modifying Evans (2001)’s A115 formulation to have a sodium chloride concentration of 250 mM would also yield an ionic strength exceeding 200 mM.

A person of ordinary skill in the art would have had a reasonable expectation of success in arriving at the composition recited in Claim 1 of the ’542 patent based on the teachings of Evans (2001) alone or in combination with the other references discussed above. A person of ordinary skill in the art would have expected to successfully incorporate AAV into Evans (2001)’s compositions instead of adenovirus because Evans (2001) discloses that its invention is particularly useful for virus formulations for use in gene therapy, including AAV; the ’542 patent

likewise admits that its rAAV compositions may be suitable for formulating adenoviruses. Evans (2001) at 3:2-3; ’542 patent at 5:67-6:4.

As discussed above, Evans (2001) specifically claims a virus formulation comprising a purified virus from about 1 x 10^7 particles/mL to about 1 x 10^{13} particles/mL. Moreover, a person of ordinary skill in the art would have reasonably expected success in further concentrating the virus in Evans (2001)’s compositions and removing empty capsids. By June 2004, methods of generating high yields of rAAV vectors were well-known, as were methods of removing empty capsids and concentrating rAAV vectors with techniques such as cesium chloride density centrifugation and tangential flow filtration. Clark (2002) at S-12 (disclosing that stable cell lines can yield between 1 x 10^{14} to 1 x 10^{15} rAAV particles per large-scale preparation); Liu (2003) at [00157]-[00158]; ’542 patent at 7:49-8:18 and 11:7-12:29. Additionally, prior art references had demonstrated that the claimed concentrations were possible. For instance, Huang (2000) describes rAAV vector titers of 5-10x10^{13} genomes/ml, which exceeds the claimed “1x10^{13} vg/ml.” Huang (2000) at S268. Although Huang (2000) discloses that AAV can aggregate at 5-10x10^{13} genomes/ml, Huang (2000) teaches that its formulations reduced aggregation and that PEGylation of AAV efficiently dissolves AAV aggregates, thus teaching a person of ordinary skill in the art that high concentration AAV formulations (e.g., 5-10x10^{13} genomes/ml) could have been achieved and were desirable for delivering high doses of viral vector in small volumes. Likewise, Sommer (2003) discloses genome titers of 1.06x10^{13} genomes/ml (measured by absorbance) and titers of 9.76x10^{12} genomes/ml ± 2.88x10^{12} (measured by Q-PCR), which encompasses a range of values from 6.88x10^{12} genomes/ml to 1.26x10^{13} genomes/ml. Sommer (2003) at 125. Thus, Sommer (2003) also discloses AAV-2 formulations that include concentrations exceeding the claimed “1x10^{13} vg/ml.” Thus, a person of ordinary skill in the art would have had a reasonable expectation

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of success in concentrating the particles in Evans's (2001)'s compositions to fall within the claimed range using methods of concentrating viral preparations, such as tangential flow filtration that were well known in the art. Indeed, Mingozzi (2002) proved as much by preparing compositions of purified AAV-2 and AAV-5 having concentrations "$>10^{13}$ vg/ml as determined by quantitative slot blot analysis," and successfully utilizing those compositions for gene transfer in mice. Mingozzi (2002) at 10497-98.

A person of ordinary skill in the art also would have had a reasonable expectation of success in modifying Evans (2001)'s A115 formulation to contain 25 mM sodium citrate and/or 250 mM because Evans (2001) itself discloses that its formulations can comprise up to 100 mM of sodium citrate and up to 250 mM sodium chloride. *Id.* at 14:15-28, 15:19-31. In addition, Evans (2001) claims formulations having such sodium citrate and sodium chloride concentrations in its claim 5. Moreover, protocols for the large-scale production of rAAV had been described that involved eluting and storing the resulting rAAV stocks in a high-ionic strength (500mM NaCl) buffer. Potter (2002) at 417-419, 429.

Regarding the claimed stability feature, as the '542 patent admits, "[i]t is known that high salt concentrations increase AAV2 vector solubility" and that "vector aggregation is prevented when ionic strength is ~200 mM or greater regardless of which salt is used." '542 patent at 4:67-5:2; 7:20-22. Moreover, Croyle (2001) taught that AAV "is significantly more stable than adenovirus." Croyle (2001) at 1283; *see also* Wright (2003) at 175 (reporting that highly purified AAV vector preparations at concentrations of $5x10^{13}$ capsid particles/ml "are stable in a non-aggregated, monomeric state when stored at 2 to 8°C"). Thus, a person of ordinary skill in the art would have understood and expected that formulations having an ionic strength ≥ 200 mM, such as those described in Evans (2001)'s Claim 5, and those containing the obvious modifications of

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Evans (2001)'s A115 formulation discussed above, are necessarily and inevitably stored "without significant aggregation." Thus, Evans (2001), alone or in combination with the other references discussed above, renders obvious rAAV compositions that inherently meet the stability limitation of claim 1.

iv. Lochrie (2003) and Johnson (1975) alone, or in combination with Clark (2002), Huang (2000), Wright (2003), Mingozzi (2002) , Croyle (2001), Potter (2002), Gatlin (1999), and/or Sommer (2003), the admissions in the '542 patent, and the knowledge of a person of ordinary skill in the art.

Claim 1 of the '542 patent is obvious over Lochrie (2003) and Johnson (1975) alone, or in combination with Clark (2002), Huang (2000), Wright (2003), Mingozzi (2002), Croyle (2001), Potter (2002), Gatlin (1999), and/or Sommer (2003), the admissions in the '542 patent, and the knowledge of a person of ordinary skill in the art. Lochrie (2003) describes efficient and commercially viable methods for producing stocks of recombinant AAV virions with reduced amounts of empty capsids. Lochrie (2003) at 1:10-13. Lochrie (2003) discloses the elution of rAAV at $4x10^{12}$ genomes/ml into a buffer containing 20 mM NaH_2PO_4, 150 mM NaCl, 5% sorbitol, and 0.1% Tween-80 at a pH of 7.4, with an ionic strength of ~200.8 mM. *Id.* at 29:7-9. Lochrie (2003) further discloses that empty capsids can be removed via cesium chloride density centrifugation or by preferentially denaturing empty capsids with destabilizing agents, thermal stress, and/or pH changes. *Id.* at 4:11-14; 5:15-18. Thus Lochrie (2003) teaches a composition comprising purified rAAV at $4x10^{12}$ genomes/ml, having a pH of 7.4, multivalent ions in the form of phosphate, and an ionic strength of ~200.8 mM. Lochrie (2003) also teaches that there is "a need to eliminate or reduce the number of empty capsids from stocks of packaged capsids so that manufacturing capability is increased" in the production of AAV stocks. *Id.* at 4:24-26.

A person of ordinary skill in the art would have been motivated to modify the composition described in Lochrie (2003) to arrive at the claim 1 composition. As discussed above, Lochrie (2003) expressly discloses a composition of stable stored, purified rAAV meeting the multivalent ion and ionic strength limitations of claim 1.

A person of ordinary skill in the art would have been motivated to increase the rAAV concentration in Lochrie (2003)'s composition because prior to the filing of the '542 patent, a person of ordinary skill in the art would have known that high concentrations of AAV vector are required in therapeutic compositions, both because of the large dosages required for successful phenotypic correction of a subject (10^{12}-10^{14} particles) and the inherent constraints on volume in the various administration routes for gene therapies. Clark (2002) at S-9 ("[A] clinical dose in humans will require 10^{12} to 10^{14} rAAV vector particles . . . . Therefore, the ability to produce high titer rAAV is critical for clinical applications…"); Gatlin (1999) at 405, 417-418 (teaching that most parenteral compositions have an injection volume limit of only a few milliliters). Indeed, the '542 patent admits as much in its "Background" section. '542 patent at 2:10-14 ("in vivo administration of AAV2 vectors to certain site, such as the central nervous system, may require small volumes of highly concentrated vector"); *see also* Wright (2003) at 175 ("AAV vectors are typically prepared at final purified concentrations in the range of 10^{11} to 10^{13} vg/ml."); Liu (2003) at [00157]-[00158]; Huang (2000) at S268 ("To achieve high level of gene transfer and ensure the safety of vector administration it is desirable to deliver high doses of vector in small volumes."). For example, Mingozzi (2002) reported that AAV vector doses of 10^{12} vg/kg resulted in sustained transgene expression in a large-animal (canine) model, which corresponds to doses of $7x10^{13}$ vector genomes for a 70kg human. Mingozzi (2002) at 10497. Pre-clinical trials using AAV vector had also used relatively small dosage volumes. *See, e.g.,* Mount (2002) at 2671 (using a 10 ml

dosage for mesenteric vein administration); Ye (1999) at 90 (using a 10 ml dosage for intramuscular administration).

As of June 2004, it was also appreciated that removing empty capsids from rAAV preparations before administration to a subject would be desirable for safety and efficacy reasons, and methods for removing empty capsids were well known. Lochrie (2003) at 4:24-26 (there is "a need to eliminate or reduce the number of empty capsids from stocks of packaged capsids so that manufacturing capability is increased" in the production of AAV stocks). Indeed, the '542 patent admits as much in its "Background" section. '542 patent at 1:60-64 (empty capsids contribute to particle concentration). Thus, a person of ordinary skill in the art who was preparing stocks of purified virus for administration to a subject would have been motivated to remove all or most empty capsids to minimize safety and efficacy concerns, to ideally achieve a ratio of genomes to particles in the final composition of ~1/1 while keeping concentration constant. Lochrie (2003) at 4:11-14; 5:15-18.

A person of ordinary skill in the art would have been motivated to increase the pH of the composition disclosed in Lochrie to 7.5 because Johnson (1975) discloses that AAVs have the potential to aggregate below that value. Johnson (1975) at 589; '542 patent at 1:41-46. Johnson (1975) discloses that AAV particles "associate into increasingly large aggregates as the environmental pH is lowered," and that no aggregates were observed at a pH of 7.5. Johnson (1975) at 585, 589. Moreover, as the '542 patent admits, AAV aggregation was known to be undesirable, as it compromises stability, effectiveness, and testing protocols, and increases the potential for an immunogenic reaction upon administration to a subject. *Id.* at 2:15-47.

A person of ordinary skill in the art would have had a reasonable expectation of success in arriving at the composition recited in Claim 1 of the '542 patent based on the teachings of Lochrie

(2003) alone or in combination with the other references discussed above. As recited above, Lochrie (2003) expressly discloses compositions of stored, purified rAAV virions meeting the multivalent ion and ionic strength limitation of Claim 1.

A person of ordinary skill in the art would have had a reasonable expectation of success in increasing the pH values of Lochrie (2003)'s formulation from 7.4 to a pH of 7.5 in view of the teachings of Johnson (1975). Johnson (1975) discloses that AAV particles "associate into increasingly large aggregates as the environmental pH is lowered." Johnson (1975) at 585. To examine this aggregation, Johnson (1975) mixed purified AAV virus dialyzed in physiological saline without buffers. *Id.* at 586. Johnson (1975) discloses that the maximum titers of stock were seen at a pH above 7.3, and that "[a]s the pH increased, the titers registered in the cultures increased regardless of whether the pH adjustment was due to increased sodium bicarbonate or addition of sodium hydroxide with no sodium bicarbonate in the medium." *Id.* Johnson (1975) further discloses that aggregates were observed at a pH of 7.2, however, no aggregates were observed at a pH of 7.5. *Id.* at 589. Moreover, a person of ordinary skill in the art would have appreciated that an increase to pH 7.5, as taught in Johnson (1975), would cause further disassociation of Lochrie (2003)'s sodium phosphate buffer, raising the ionic strength to ~202mM. A person of ordinary skill in the art would have reasonably expected success from using such a buffer since protocols for the large-scale production of rAAV had been described that involved eluting and storing the resulting rAAV stocks in a high-ionic strength (500mM NaCl) buffer. Potter (2002) at 417-419, 429. Thus, Lochrie (2003) in view of Johnson (1975) renders obvious rAAV compositions that also meet the pH limitations of claim 1.

A person of ordinary skill in the art would have reasonably expected success in concentrating the AAV in Lochrie (2003)'s composition and removing empty capsids, because by

June 2004, methods of generating high yields of rAAV vectors were well-known, as were methods of concentrating rAAV vectors and removing empty capsids with techniques such as cesium chloride density centrifugation and tangential flow filtration. Clark (2002) at S-12 (disclosing that stable cell lines can yield between 1 x 10^{14} to 1 x 10^{15} rAAV particles per large-scale preparation); Liu (2003) at [00157]-[00158]; '542 patent at 7:49-8:18 and 11:7-12:29. Additionally, prior art references had demonstrated that the claimed concentrations were possible. For instance, Huang (2000) describes rAAV vector titers of 5-10x10^{13} genomes/ml, which exceeds the claimed "1x10^{13} vg/ml." *Id.* Although Huang (2000) discloses that AAV can aggregate at 5-10x10^{13} genomes/ml, Huang (2000) teaches that its formulations reduced aggregation and that PEGylation of AAV efficiently dissolves AAV aggregates, thus teaching a person of ordinary skill in the art that high concentration AAV formulations (e.g., 5-10x10^{13} genomes/ml could have been achieved and were desirable for delivering high doses of viral vector in small volumes. Likewise, Sommer (2003) discloses genome titers of 1.06x10^{13} genomes/ml (measured by absorbance) and titers of 9.76x10^{12} genomes/ml ± 2.88x10^{12} (measured by Q-PCR), which encompasses a range of values from 6.88x10^{12} genomes/ml to 1.26x10^{13} genomes/ml. Sommer (2003) at 125. Thus, Sommer (2003) also discloses AAV-2 formulations that include concentrations exceeding the claimed "1x10^{13} vg/ml." Thus, a person of ordinary skill in the art would have had a reasonable expectation of success in concentrating the rAAV in Lochrie (2003)'s composition to fall within the claimed range using methods of concentrating viral preparations, such as tangential flow filtration that were well known in the art. Indeed, Mingozzi (2002) proved as much by preparing compositions of purified AAV-2 and AAV-5 having concentrations ">10^{13} vg/ml as determined by quantitative slot blot analysis," and successfully utilizing those compositions for gene transfer in mice. Mingozzi (2002) at 10497-98.

Regarding the claimed stability feature, as the ’542 patent admits, “[i]t is known that high salt concentrations increase AAV2 vector solubility” and that “vector aggregation is prevented when ionic strength is ~200 mM or greater regardless of which salt is used.” ’542 patent at 4:67-5:2; 7:20-22. Moreover, Croyle (2001) taught that AAV “is significantly more stable than adenovirus.” Croyle (2001) at 1283; *see also* Wright (2003) at 175 (reporting that highly purified AAV vector preparations at concentrations of $5x10^{13}$ capsid particles/ml “are stable in a non-aggregated, monomeric state when stored at 2 to 8°C”). Thus, a person of ordinary skill in the art would have understood and expected that all prior art virus compositions having an ionic strength ≥ 200 mM, such as those described in Lochrie (2003), are necessarily and inevitably stored “without significant aggregation.” Thus, Lochrie (2003), alone or in combination with the other references discussed above, renders obvious rAAV compositions that inherently meet the stability limitation of claim 1.

2. Dependent Claims 2, 5, and 6

The dependent claims of the ’542 patent are additionally invalid over the prior art, at least based on the references and combinations set forth in Appendix F. As set forth in Appendix F, the prior art discloses, expressly or inherently, each and every limitation of the dependent claims, which merely recite additional features that provide no meaningful narrowing of independent claim 1. The dependent claims therefore are obvious for the same reasons set for above for claim 1, as well as for the additional reasons discussed below.

Claim 2 of the ’542 patent is obvious over the above references and combinations, further in view of Croyle (2001), Sommer (2003), and Wright (2003). For example, Liu (2003) discloses that the temporary storage composition comprises a non-ionic surfactant and exemplifies in Example 17 the use of 0.0025% polysorbate 80. Liu (2003) at [00189], [00369]. Liu (2003) discloses that alternative non-ionic surfactants are known in the art and include Pluronic® F68. *Id.*

at [00189]. Frei (1999) discloses that the compositions of its invention can further comprise a non-ionic detergent, including Pluronic® F68. Frei (1999) at 7:22-8:10. Evans (2001) discloses that its formulations "comprise[] a minimal amount of at least one non-ionic surfactant added to reduce adsorption to container surfaces as well as possibly providing increased virus stabilization." Evans (2001) at 1:15-25. Evans (2001) discloses "the Pluronic series of non-ionic surfactants" as a non-ionic surfactant for use in its formulations. *Id.* at 8:30-9:5. Sommer (2003) teaches that Pluronic F-68 used in a composition containing AAV particles "prevents loss of AAV due to nonspecific adsorption during storage and vector manipulations at concentrations as low as 0.001%." Sommer (2003) at 123-124. Wright (2003) teaches that surfactants such as Pluronic® F68 can be included to minimize non-specific binding of AAV-2 to plastic or glass surfaces. Wright (2003) at 175. Croyle (2001) teaches that AAV compositions comprising Pluronic® F68 have an expiration date of 240 days when stored at 4°C. Croyle (2001) at 1284 (Table 3, composition comprising "0.01% Pluronic"), 1288 (identifying detergent as "Pluronic block copolymer F68"). Accordingly, a person of ordinary skill in the art would have been motivated to add Pluronic® F68 to the obvious rAAV compositions of claim 1 to prevent vector loss due to adsorption. A person of ordinary skill in the art would have had a reasonable expectation of success in making such modifications at least because Sommer (2003), Croyle (2001), and Wright (2003) teach the successful use of such surfactants in viral formulations.

Claim 5 of the '542 patent is obvious over the above references and combinations, further in view of the admissions in the '542 patent. According to the '542 patent, prior art compositions having an ionic strength of ≥ 200mM inherently have an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering. '542 patent at Table 1. The '542 patent discloses that dynamic light scattering is a measurement of aggregation and that Rh values greater

than 20nm are "deemed to indicate the occurrence of some level of aggregation." '542 patent at 6:14-15, 9:25-27, 12:36-38. The '542 patent does not identify anything critical about the recited radius of less than about 20nm other than it being indicative of monomeric AAV. A person of ordinary skill in the art would have been motivated to develop compositions for storing monomeric AAV particles, since Huang (2000) linked virus aggregation to reduced gene transfer efficiency and Wright (2003) taught that a "potentially deleterious consequence of vector aggregation is inconsistency in the functional activity of AAV vectors following their administration in vivo" (Wright (2003) at 176). Thus, a person of ordinary skill in the art would have been motivated to reduce AAV aggregation by stabilizing AAV monomers through routine optimization of the formulations described in Liu (2003), Frei (1999), Evans (2001), and Lochrie (2003). A person of ordinary skill in the art would have had a reasonable expectation of successfully reducing vector aggregation, and thereby minimizing particle size in view of Huang (2000)'s teaching that certain compositions "could lead to a 30-50% reduction in the size of aggregates at high vector concentrations." Indeed, "no signs of settling or precipitation" were observed for adenovirus compositions stored in a high ionic strength buffer over a 7 day period (Liu (2003) at [00369]) and Croyle (2001) taught that AAV "is significantly more stable than the adenovirus." Croyle (2001) at 1283. Thus, only routine optimization would be required to store monomeric AAV particles in the formulations described in Liu (2003), Frei (1999), Evans (2001), and Lochrie (2003). Thus, as disclosed by the '542 patent, the limitation of claim 5 is an inherent characteristic of purified AAV-2 particles stored in a composition meeting the limitations of claim 1.

Claim 6 of the '542 patent is obvious over the above references and combinations, further in view of the admissions of the '542 patent and Wright (2003). The '542 patent discloses that vector recovery after filtration through a 0.22μm filter is a measurement of aggregation. '542

patent at 8:8-9, 8:19-26, 8:41-50, Table 2. The ’542 patent discloses that its test formulations TF1 and TF2, which the ’542 patent characterizes as resulting in unaggregated AAV-2, have over 90% recovery following filtration of the composition through a 0.22μm filter. *Id.* Thus, as disclosed by the ’542 patent, the limitation of claim 6 is an inherent characteristic of purified AAV-2 particles stored in a composition meeting the limitations of claim 1. Furthermore, Wright (2003) also discloses that recovery of AAV following a 0.2μm filtration step “correlates with the extent of vector aggregation.” Wright (2003) at 175. And since both Wright and Huang linked aggregation to reduced functional activity of AAV vectors (Wright (2003) at 176; Huang (2000) at S286), a person of ordinary skill in the art would have been motivated to maximize virus recovery from a 0.22μm filter through routine optimization of the formulations described in Liu (2003), Frei (1999), Evans (2001), and Lochrie (2003). A person of ordinary skill in the art would have had a reasonable expectation of successfully minimizing vector aggregation, and thereby maximizing particle recovery after filtration, in view of Huang (2000)’s teaching that certain compositions “could lead to a 30-50% reduction in the size of aggregates at high vector concentrations.” Indeed, “no signs of settling or precipitation” were observed for adenovirus particles stored in a high ionic strength buffer over a 7 day period (Liu (2003) at [00369]), and Croyle (2001) taught that AAV “is significantly more stable than the adenovirus” (Croyle (2001) at 1283). Thus, only routine optimization would be required to improve recovery of AAV particles following filtration through a 0.22 μm filter. Thus, according to the ’542 patent, that prior art composition meeting the limitations of claim 1 inherently exhibits a recovery of at least about 90% following filtration of the composition of said AAV particles through a 0.22 μm filter.

B. The ’542 Patent Claims Are Invalid under 35 U.S.C. § 112

In addition, or in the alternative, Novartis contends that the Asserted Claims of the ’542 patent do not satisfy one or more requirements of 35 U.S.C. § 112. Novartis identifies the below

grounds upon which the Asserted Claims of the ’542 patent are invalid based on lack of written description under 35 U.S.C. § 112, first paragraph, lack of enablement under 35 U.S.C. § 112, first paragraph, and indefiniteness under 35 U.S.C. § 112, second paragraph.

1. Invalidity under 35 U.S.C. § 112, First Paragraph for Inadequate Written Description

As discussed *supra*, a patent’s specification must contain a written description of the claimed invention. 35 U.S.C. § 112, ¶ 1. The description must “clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*) (citations omitted). In other words, the specification must reasonably convey that the inventor had possession of the claimed subject matter as of the filing date. *Id.* For at least the reasons discussed herein, and outlined in more detail for specific claim limitations below, the Asserted Claims of the ’542 patent are invalid under 35 U.S.C. § 112, ¶ 1 for failing to satisfy the written description requirement.

a. Independent Claim 1

i. “recombinant adeno-associated virus (AAV) vector particles”

Independent claim 1 of the ’542 patent (and its dependent claims) is directed to compositions of purified “recombinant adeno-associated virus (AAV) vector particles” that are stored without significant aggregation. There is no indication in the specification of the ’542 patent that the inventors knew how to create compositions for storage of all AAV particles without significant aggregation, much less those at the recited concentration. By June 2004, there were at least seven different AAV serotypes as well as six phylogenetically distinct clades which varied significantly in their characteristics. *See, e.g.*, Gao (2002); Gao (2003); Vanderberghe (2004). Moreover, methods employing both rational and directed evolution approaches have been used to produce variants that have changes in their capsid protein sequence and structures, to alter cell

tropisms or to reduce immunogenic potential, further adding to the wide variety of adeno-associated viruses. The AAV2 serotype itself, which is the focus of the ’542 patent, had been subjected to extensive site-directed mutagenesis in its capsid coding regions, resulting in numerous functional differences. Wu (2000) (reporting the generation of 93 AAV mutants at 59 different positions and corresponding infectivity phenotypes). Thus, the Asserted Claims of the ’542 patent, which are not limited to any particular type of “recombinant adeno-associated virus (AAV) vector particles,” cover an unknown (and unknowable) number of recombinant adeno-associated virus species. Yet the ’542 patent contains data for compositions employing only two AAV2 vectors that differ only by their non-capsid transgene (human coagulation factor IX (FIX) or human amino acid decarboxylase (AADC)). ’542 patent at 10:56-60.

A person of ordinary skill in the art would not understand that the patentee possessed compositions for the storage of any and all purified “recombinant adeno-associated virus[es]” purportedly encompassed by the Asserted Claims at the time of filing. The ’542 patent echoes this uncertainty: “Although data were obtained using AAV2 vectors, the composition and methods of the present invention *may* also be useful with other AAV serotypes/variants . . . .” ’542 patent at 5:67-6:3(emphasis added). Accordingly, the ’542 patent “claim[s] a broader invention than that set forth in the written description contained in [the] specification.” *Application of Sus*, 306 F.2d 494, 505, (C.C.P.A. 1962) (affirming rejection of claims to chemical compound that sought to claim all types of “aryl and substituted aryl radicals” because although numerous examples of the invention with *certain* types of aryl and substituted aryl radicals were disclosed in the Patent specification, the specification did not contain any disclosure or teach that *all* types of aryl and substituted aryl radicals could be used); *see also Regents of Univ. of California v. Eli Lilly,* 1919 F.3d 1559, 1568 (Fed. Cir. 1997) (“a description of rat insulin cDNA is not a description of the

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broad classes of vertebrate or mammalian insulin cDNA").

Thus, independent claim 1 (and its dependent claims) is invalid under § 112 for a lack of written description.

ii. "at a concentration exceeding $1x10^{13}$ vg/ml up to $6.4x10^{13}$ vg/ml"

Independent claim 1 of the '542 patent (and its dependent claims) recites a composition containing purified, recombinant AAV vector particles "at a concentration exceeding $1x10^{13}$ vg/ml up to $6.4x10^{13}$ vg/ml" that is stored without significant aggregation. The specification provides no disclosure of any composition having purified AAV vector particles at the low end of the claimed range, i.e., between $1x10^{13}$ vg/ml and $2.33x10^{13}$ vg/ml, or the high end of the claimed range, i.e., between $2.38x10^{13}$ vg/ml and $6.4x10^{13}$ vg/ml, much less demonstrate that compositions having particles at these concentrations can be stored without significant aggregation. While Table 2 discloses compositions having $2.33x10^{13}$ vg/ml, 2.38 $x10^{13}$ vg/ml, and 6.42 $x10^{13}$ vg/ml, these compositions have not been stored and thus fail to provide written description support for the claims. Thus, independent claim 1 (and its dependent claims) is invalid under § 112 for a lack of written description.

iii. "for the storage of" and "stored . . . without significant aggregation"

Independent claim 1 of the '542 patent (and its dependent claims) is directed to compositions "for the storage of" purified, recombinant AAV vector particles at the recited vg concentration that are "stored in the composition without significant aggregation." The specification only discloses a limited number of compositions which are purported to be suitable for storing AAV particles under a few exemplary storage conditions. For example, the '542 patent refers to compositions comprising particles "stored…at -20° C. or at -80° C," particles after "5 days of storage at 4° C.," and particles "stored for 45 days at 4° C." Yet, the claims are not limited

to storage at such time periods or temperatures and there is no disclosure in the specification to suggest the inventors were in possession of compositions for storage of AAV particles without significant aggregation under all claimed storage conditions, including, for example, particles stored at room temperature for 120 days, at 4° C for 90 days, at -20° C for 14 days, or -80° C for 7 days. Thus, independent claim 1 (and its dependent claims) is invalid under § 112 for a lack of written description.

iv. "purified"

Independent claim 1 of the '542 patent (and its dependent claims) requires that the composition contains "purified" recombinant AAV vector particles. To the extent Plaintiffs argue that this term requires a certain level of purity be obtained, the claim lacks adequate written description. The '542 patent describes certain "AAV purification methods" suitable for the invention including for example column chromatography, cesium chloride ("CsCl") ultracentrifugation, and column chromatography followed by CsCl ultracentrifugation. '542 patent at 4:28-32; 10:51-11:50. As admitted by the '542 patent specification, these purification methods result in compositions with remaining impurities, such as host cell and plasmid DNA. '542 patent at 5:45-60. Furthermore, different impurity profiles are observed depending on the chosen purification method. '542 patent at 7:49-52 ("Recombinant AAV2 purified using different methods (e.g. density gradient purification versus ion-exchange chromatography) would be expected to have different impurity profiles."). However, the '542 patent is silent on what impurities need to be measured, how to measure them, and the acceptable levels before an AAV is considered "purified."

During prosecution, the patentee amended independent claim 1 to recite that the purified rAAV virions are "at a concentration exceeding $1x10^{13}$ vg/ml up to $6.4x10^{13}$ vg/ml," which was maintained in the issued claims. '542 patent file history January 17, 2013 Submission under 37

CFR 1.114 at 2. Notwithstanding patentee's assertion that "all claims now define the purity level of the rAAV particles in the composition," a person of ordinary skill in the art would recognize the vector concentration as a measure of strength, not a measure of purity. *Id.* at 7. The '542 patent explicitly recognizes that vector concentration is not a measure of purity in its description of the assessment of aggregation at process scale. There, "purified AAV vectors are diafiltered into solutions of various ionic strengths [and] the volume is reduced to achieve high vector concentrations." ranging from the 2.33×10^{13} to 6.42×10^{13} values reported in Table 2.

Thus, independent claim 1 (and its dependent claims) is invalid under § 112 for a lack of written description.

v. "ionic strength of the composition is greater than 200 mM"

Independent claim 1 of the '542 patent (and its dependent claims) requires that the "ionic strength of the composition is greater than 200 mM," and wherein the recombinant AAV vector particles are stored in the composition without significant aggregation. The specification, however, provides very limited disclosure regarding the relationship between the ionic strength of the composition and aggregation upon storage. For example, there is no disclosure of any composition having an ionic strength at the low end of the claimed range, i.e., between 200 mM and 310 mM, within 310 mM and 510 mM, or the high end of the claimed range, i.e., above 510 mM, wherein the recombinant AAV vector particles are stored without significant aggregation. "In the case of a claimed range, a skilled artisan must be able to reasonably discern a disclosure of that range." *Indivior UK Ltd. v. Dr. Reddy's Lab'ys S.A.*, 18 F.4th 1323, 1328 (Fed. Cir. 2021).

For example, the disclosure of AAV stability following storage as reported in Table 3 is not sufficient written description even for the 310 mM and 510 mM ionic strengths notwithstanding the reported ionic strength of the TF1 and TF2 formulations (having an ionic

strength of 310 and 510 mM, respectively). A person of ordinary skill in the art would recognize that these values do not represent the ionic strength of the compositions in Table 3. Specifically, the patent states that the AAV2 vector is diafiltered in formulations TF1 or TF2 (having an ionic strength of 310 and 510 mM, respectively) but that the volume of each formulation is reduced prior to filtration to achieve the target vg concentration. This concentration step will necessarily increase the ionic strength of the composition to some unreported and unknowable value.

Additionally, while Fig 1B purports to disclose compositions having ionic strength around 200 mM, there is no disclosure suggesting these compositions are compositions of claim 1 (e.g., having the claimed pH or having purified, recombinant AAV vectors within the claimed vg concentration) or whether these compositions been stored within the meaning of the claims. "The written description requirement is not met when, as here, the specification provides at best disparate disclosures that an artisan might have been able to combine in order to make the claimed invention." *Flash-Control, LLC v. Intel Corp.*, No. 2020-2141, 2021 WL 2944592, at *4 (Fed. Cir. July 14, 2021) (citing *Ariad Pharms.*, 598 F.3d at 1352.). Thus, Fig. 1B fails to provide written support for the claims.

Thus, independent claim 1 (and its dependent claims) is invalid under § 112 for a lack of written description.

b. Dependent Claim 6

Claim 6 depends from claim 1 and limits the composition of claim 1 (which has been stored without significant aggregation), to those "wherein recovery of the purified, recombinant virus particles is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22 µm filter."

The '542 specification provides no disclosure of any composition having purified AAV vector particles wherein recovery is at least 90% after storage. While the '542 patent discloses

three examples comprising two test formulations (TFs) where recovery of the purified, recombinant virus particles prior to storage is measured to be 95% (±7.4), 93% (±7.4), or 96% (±4.4), this would not suggest to a person of ordinary skill in the art that the inventors were in possession of the "at least 90%" limitation following storage, particularly given the reported relative standard deviation in vector recovery can be as large as 12% in such experiments. '542 patent at Table 2.

Thus, for at least the reasons explained herein and above for claim 1, a person of ordinary skill in the art would not reasonably have understood that the '542 patent inventors had possession of the composition of claim 6 at the time of filing.

2. Invalidity under 35 U.S.C. § 112, First Paragraph for Lack of Enablement

As discussed *supra*, "[t]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *ALZA Corp. v. Andrx Pharms.*, LLC., 603 F.3d 935, 940 (Fed. Cir. 2010) (quoting *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997)). For similar reasons discussed above, the Asserted Claims of the '542 patent are not enabled. A person of ordinary skill in the art would be required to engage in undue experimentation to achieve a composition for the storage of each purified "recombinant adeno-associated virus" species covered by the scope of each Asserted Claim of the '542 patent. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). *See In re Fisher*, 427 F.2d 833, 839 (CCPA 1970) ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved."); *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

For at least the reasons discussed herein, and outlined in more detail for specific claim

limitations below, the Asserted Claims of the ’542 patent are invalid under 35 U.S.C. § 112, ¶ 1 for failing to satisfy the enablement requirement.

a. Independent Claim 1

i. “recombinant adeno-associated virus (AAV) vector particles”

Independent claim 1 of the ’542 patent (and its dependent claims) is directed to compositions of purified “recombinant adeno-associated virus (AAV) vector particles” that are stored without significant aggregation. For reasons similar to those discussed above, a person of ordinary skill in the art would not have been able to make and use the full scope of the claimed invention without undue experimentation. By June 2004, there were at least seven different AAV serotypes as well as six phylogenetically distinct clades which varied significantly in their characteristics. *See, e.g.*, Gao (2002); Gao (2003); Vanderberghe (2004). Moreover, methods employing both rational and directed evolution approaches have been used to produce variants that have changes in their capsid protein sequence and structures, to alter cell tropisms or to reduce immunogenic potential, further adding to the wide variety of adeno-associated viruses. The AAV2 serotype itself, which is the focus of the ’542 patent, had been subjected to extensive site-directed mutagenesis in its capsid coding regions, resulting in numerous functional differences. Wu (2000) (reporting the generation of 93 AAV mutants at 59 different positions and corresponding infectivity phenotypes). Thus, the Asserted Claims of the ’542 patent, which are not limited to any particular type of “recombinant adeno-associated virus (AAV) vector particles,” cover an unknown (and unknowable) number of recombinant adeno-associated virus species. Yet the ’542 patent contains data for compositions employing only two AAV2 vectors that differ only by their non-capsid transgene (human coagulation factor IX (FIX) or human amino acid decarboxylase (AADC)). ’542 patent at 10:56-60. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

Further, the ’542 patent does not provide any information regarding how a person of ordinary skill in the art should vary the composition, storage conditions, or both, when using AAV vector particles other than the two AAV2 vectors exemplified to obtain a composition wherein said particles are stored without significant aggregation. Additionally, to the extent Plaintiffs take the position that the prior art does not teach the claimed compositions, or that the art is unpredictable, these factors further suggest undue experimentation would be required to make and use the full scope of the claimed invention.

Thus, independent claim 1, and all subsequent dependent claims, are invalid under § 112 for a lack of enablement.

ii. “at a concentration exceeding $1x10^{13}$ vg/ml up to $6.4x10^{13}$ vg/ml”

Independent claim 1 of the ’542 patent (and its dependent claims) recites a composition containing purified, recombinant AAV vector particles “at a concentration exceeding $1x10^{13}$ vg/ml up to $6.4x10^{13}$ vg/ml” that is stored without significant aggregation. The specification provides no disclosure of any composition for storage having purified AAV vector particles at the low end of the claimed range, i.e., between $1x10^{13}$ vg/ml and $2.33x10^{13}$ vg/ml, or the high end of the claimed range, i.e., between $2.38x10^{13}$ vg/ml and $6.4x10^{13}$ vg/ml. While Table 2 discloses compositions having $2.3x10^{13}$ vg/ml, 2.38 $x10^{13}$ vg/ml, and 6.42 $x10^{13}$ vg/ml, these compositions have not been stored or shown to be “stored…without significant aggregation.”

The ’542 patent also does not provide any information regarding how a person of ordinary skill in the art should vary the composition when using formulations having between $1x10^{13}$ vg/ml and $2.33x10^{13}$ vg/ml or between $2.38x10^{13}$ vg/ml and $6.4x10^{13}$ vg/ml to obtain a composition wherein said particles are stored without significant aggregation. This is particularly problematic given the substantial differences in, for example, aggregation at low versus high vector

concentrations. Additionally, to the extent Plaintiffs take the position that the prior art does not teach the claimed compositions, or that the art is unpredictable, these factors further suggest undue experimentation would be required to make and use the full scope of the claimed invention.

Thus, independent claim 1, and all subsequent dependent claims, are invalid under § 112 for a lack of enablement.

iii. "for the storage of" and "stored . . . without significant aggregation"

Independent claim 1 of the '542 patent (and its dependent claims) is directed to compositions "for the storage of" purified, recombinant AAV vector particles at the recited concentration that are "stored in the composition without significant aggregation." The specification only discloses a limited number of compositions which are purported to be suitable for storing AAV particles under a few exemplary storage conditions. For example, the '542 patent refers to "non-frozen storage," "refrigerated storage," "stored…at -20° C. or at -80° C," "5 days of storage at 4° C." and "stored for 45 days at 4° C." Yet, the claims are not limited to such time periods or temperatures and there is no disclosure in the specification on how a person of ordinary skill in the art should vary the composition to obtain compositions for storage of AAV particles without significant aggregation under all claimed storage conditions. Notably, even compositions purported to meet the limitations of claim 1 (i.e., ionic strength > 200 mM) were shown to result in significant aggregation under certain storage conditions. *See* Table 3.

Additionally, to the extent Plaintiffs take the position that the prior art does not teach the claimed compositions, or that the art is unpredictable, these factors further suggest undue experimentation would be required to make and use the full scope of the claimed invention.

Thus, independent claim 1, and all subsequent dependent claims, are invalid under § 112 for a lack of enablement.

iv. "ionic strength of the composition is greater than 200 mM"

Moreover, claim 1 of the '542 patent (and its dependent claims) requires that "the ionic strength is greater than 200 mM," and wherein the recombinant AAV vector particles are stored in the composition without significant aggregation. The specification, however, provides very limited disclosure regarding the relationship between the ionic strength of the composition and aggregation upon storage. For example, there is no disclosure of any composition having an ionic strength at the low end of the claimed range, i.e., between 200 mM and 310 mM, within 310 mM and 510 mM, or the high end of the claimed range, i.e., above 510 mM, wherein the recombinant AAV vector particles are stored without significant aggregation. Although a specification does not need to "describe how to make and use every possible variant of the claimed invention, when a range is claimed, there must be reasonable enablement of the scope of the range." *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 (Fed. Cir. 2020) (citing *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003)) (internal citations omitted).

For example, the specification fails to indicate whether virus formulations having ionic strengths above 510 mM are even attainable, let alone whether they are suitable "for the storage of purified, recombinant adeno-associated virus (AAV) vector particles." '542 patent at Claim 1. For example, it is well-known that in a protein solubilization context, the addition of some salt to a solution can help solubilize and stabilize a protein ("salting in"), while at some point further increasing salt will cause the protein to crash out of solution ("salting out"). *See, e.g.*, Arakawa (1984) at 5912. There is no teaching in the specification regarding such "salting out" considerations, let alone the ionic strength level at which this might occur. The '542 patent additionally recognizes that ionic strength levels present enablement concerns since "[a]n important question is whether preparation and storage of the vector in high ionic strength TF2

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[buffer] would adversely affect its functional activity" and reports the results of an infectivity assay designed to confirm that high ionic strength compositions do not compromise virion function. '542 patent at 9:60-63; Fig. 3.

The '542 patent specification also fails to indicate whether a composition falling within the scope of the claimed ionic strength would actually work for its intended purpose. Despite teaching that "ionic strength…is the relevant physiochemical parameter" and that "[a] threshold ionic strength of at least 200 mM is required to prevent aggregation of vector particle concentrations examined herein," the '542 patent discloses a composition with an ionic strength of >200 mM (TF1; μ = 310 mM) that fails to prevent aggregation during certain storage conditions, despite purportedly meeting all of the other claim parameters (i.e., virus concentration, pH, and presence of multivalent ions). '542 patent at 4:59-64, 9:19-55, Table 3. A claim is invalid for lack of enablement "if it reads on a significant number of inoperative embodiments." *Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1381 (Fed. Cir. 2002) (internal citations omitted). A person of ordinary skill in the art would be required to engage in undue experimentation to identify compositions with ionic strengths greater than 200mM that would achieve the claimed absence of significant aggregation in all claimed storage conditions.

Further, the '542 patent does not provide any information regarding how a person of ordinary skill in the art should vary the composition, storage conditions, or both, when using a composition having an ionic strength other than 310 mM or 510 mM to obtain a composition wherein AAV particles are stored without significant aggregation. Additionally, to the extent Plaintiffs take the position that the prior art does not teach the claimed compositions, or that the art is unpredictable, these factors further suggest undue experimentation would be required to make and use the full scope of the claimed invention.

Thus, independent claim 1, and all subsequent dependent claims, are invalid under § 112 for a lack of enablement.

b. Dependent Claim 5

Claim 5 depends from claim 1 and limits the composition of claim 1 (which has been stored without significant aggregation), to those "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."

The '542 patent discloses fourteen examples comprising two test formulations (TFs), a single AAV vector (i.e., AAV2-AADC vector), and two vector concentrations (i.e., 2.3×10^{13} vg/ml and 2.38×10^{13} vg/ml) where the average particle radius of recombinant, purified particles is measured by dynamic light scattering (DLS) following storage (two at 4° C, six at -20° C, and six at -80° C). '542 patent, Table 3. However, a person of ordinary skill in the art would not be able to replicate even these examples without undue experimentation not to mention the full scope of the claimed compositions because there is insufficient information regarding the DLS method or conditions for those examples.[18] In particular, the specification discloses limited information concerning the measurement of vector aggregation by dynamic light scattering, stating only that "aggregation is assessed by DLS using undiluted samples," "vectors are analyzed for aggregation by dynamic light scattering (DLS) using a Protein Solutions DynaPro 99 (λ = 825.4 nm)" and that "average value [is] measured over 30 cycles, 10 cycles/min" '542 patent at 9:25; 12:36-40. The specification does not disclose any additional information regarding the DLS method or conditions suitable in the claimed invention and it was known in the art as of June 1, 2004 that different DLS

[18] For the twelve of fourteen examples where aggregation is measured by DLS following storage at -20° C or -80° C, there is also insufficient information regarding the length of storage or the freeze/thaw process to replicate those examples.

methods and conditions can result in different observed average particle radius values.

Further, while Figures 1B and 2 disclose the average particle radii of AAV-2 compositions as measured by dynamic light scattering, a person of ordinary skill in the art would not understand these compositions to fall within the scope of the claims because they lack at least the viral genome, pH, and in some instances, ionic strength requirements, and because they have not been stored within the meaning of the claims.

Thus, the specification fails to enable a person of ordinary skill in the art to make and use compositions of claim 5 without undue experimentation. For at least the reasons explained herein and above for claim 1, dependent claim 5 is invalid for lack of enablement.

c. Dependent Claim 6

Claim 6 depends from claim 1 and limits the composition of claim 1 (which has been stored without significant aggregation), to those "wherein recovery of the purified, recombinant virus particles is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22 µm filter."

The '542 patent discloses only three examples comprising two test formulations (TFs) and a single AAV vector (i.e., AAV2-AADC vector) where recovery of the purified, recombinant virus particles is measured. However, a person of ordinary skill in the art would not be able to replicate even these three examples much less all compositions within the scope of the claim without undue experimentation because there is insufficient information regarding the filtration conditions and filter for those examples. In particular, the specification discloses limited information concerning the filtration, stating only that "[t]he samples are filtered through a 0.22 um filter." The specification does not disclose any additional information regarding the filtration conditions or filter suitable in the claimed invention and it was known in the art as of June 1, 2004 that different filtration methods and conditions, and the specification of the filter, can result in different percent

recovery.

Further, the specification provides no disclosure of any composition having purified AAV vector particles at the claimed concentration wherein recovery is at least 90% after storage. While Table 2 discloses compositions having $2.3x10^{13}$ vg/ml, 2.38 $x10^{13}$ vg/ml, and 6.42 $x10^{13}$ vg/ml, these compositions have not been stored within the meaning of the claims. Additionally, the specification states that, prior to filtration, the AAV2 vector is diafiltered in formulations TF1 or TF2 (having an ionic strength of 310 and 510 mM, respectively) and each formulation is reduced to achieve the target vg concentration (and consequently an unknown ionic strength). *See* '542 patent at 8:19-44.

Thus, the specification fails to enable a person of ordinary skill in the art to make and use compositions of claim 6 without undue experimentation. For at least the reasons explained herein and above for claim 1, dependent claim 6 is invalid for lack of enablement.

3. Invalidity under 35 U.S.C. § 112, Second Paragraph for Indefiniteness

As discussed *supra*, under 35 U.S.C. § 112, ¶ 2, a patent "is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig. Instruments, Inc.*, 572 U.S. 898, 901 (2014).

i. "for the storage of" and "stored . . . without significant aggregation"

Claim 1 of the '542 patent (and its dependent claims) is directed to compositions "for the storage of" purified, recombinant AAV vector particles that are "stored in the composition without significant aggregation." Yet neither the specification nor its prosecution history provides any direction or guidance regarding the parameters of the "storage," what constitutes "significant aggregation," or how to measure "significant aggregation." A person of ordinary skill in the art

cannot determine the metes and bounds of the claims and, therefore, cannot determine whether a composition that exhibits at least some aggregation when stored for an unspecified time and under unspecified conditions infringes the claims.

The prosecution history sheds no light on the parameters of the storage period, such as length, temperature, agitation, or freeze-thaw cycles, let alone what is meant by without "significant aggregation" or how to measure it. The only potential guidance regarding what constitutes "significant aggregation" in the '542 patent is in a discussion of Experiments 1 and 2.[19] *Id.* at 8:19-56. Specifically, the '542 patent characterizes yields of 59% and 77% after filtration through a 0.22 µm filter as "significant aggregation," and characterizes yields of 93% and 96% after filtration through a 0.22 µm filter as "indicating that aggregation was prevented." *Id.* at 8:41-50. However, the '542 patent provides no guidance for determining what % recovery between 93% and 77% qualifies as without "significant aggregation." Nor does the patent provide any information regarding how long and under what conditions the formulations were stored (if at all) before being subjected to the filtration assay.[20] And without such guidance, claim 1 fails to "inform, with reasonable certainty, those skilled in the art about the scope of the invention," because it is not possible to determine values within that range that fall within the scope of the claims. *See Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

Moreover, the '542 patent itself teaches that aggregation depends on the storage conditions and the methods used to assess aggregation. *See, e.g.*, 2:5-8 (disclosing that aggregation can occur

[19] Column 1, lines 46-49, column 3, lines 46-63, and column 9, lines 5-55, discuss circumstances in which significant aggregation may or may not occur, but do not discuss what level of aggregation is considered "significant."

[20] The patent also does not disclose the ionic strength of the formulations filtered through the 0.22 µm filter. Notably, the patent states that the AAV2 vector is diafiltered in formulations CF, TF1, or TF2 (having an ionic strength of 160, 310, and 510 mM, respectively) but that the volume of each formulation is reduced prior to filtration. *See* '542 patent at 8:19-44.

under a variety of storage conditions), Table 3 (demonstrating that different formulations experience aggregation under certain conditions but not others), 8:44-56 (teaching that "significant aggregation was observed at both target concentrations using CF" and that "[v]ector concentrated in CF contains obvious amounts of visible material"), 9:25-27 (teaching that when "[a]ggregation is assessed by DLS using undiluted samples, [ ] Rh values >20 are deemed to indicate the occurrence of *some level* of aggregation."), 9:50-52 (teaching that visual inspection of TF1 samples with "DLS signal intensity that is too high to measure" "reveals slight cloudiness, which is consistent with aggregation"). Thus, for these additional reasons, claim 1 of the '542 patent (and its dependent claims) are indefinite. *See Forest Labs., Inc. v. Teva Pharm. USA, Inc.*, 716 Fed. App'x 987, 994 (Fed. Cir. 2017) (finding claims indefinite "where the claims require measured quantities (absolute or relative), different techniques for such measurements are known in the art and some produce infringing results and others not, the intrinsic evidence does not adequately specify the technique or techniques to use and extrinsic evidence does not show that a relevant skilled artisan would know what technique or techniques to use"); *see also Dow Chemical Co. v. Nova Chemicals Corp. (Canada)*, 803 F.3d 620, 634 (Fed. Cir. 2015) (same).

The asserted dependent claims of the '542 patent (claims 2, 5, and 6) do not resolve the indefiniteness problems of independent claim 1, and therefore lack definiteness for the same reasons. Claim 2 fails to provide any further guidance regarding "storage . . . without significant aggregation." Although claim 5 recites an "average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering" and claim 6 recites a recovery of "at least about 90% following filtration" through a 0.22 µm filter, as discussed above, the '542 patent does not equate either of those parameters as being indicators of "storage . . . without significant aggregation." At best, these claims recite particular methods for analyzing the "purified, recombinant adeno-

associated virus (AAV) vector particles." However, those claims fail to define the length of time the formulation needs to be stored (if at all) or the conditions of the storage (such as temperature, length, agitation, or freeze-thaw cycles) before the measurements are made. Thus, the dependent claims fail to provide any meaningful guidance regarding whether the "storage" and without "significant aggregation" limitations from claim 1 are met for any given composition.

ii. "dynamic light scattering"

Claim 5 of the '542 patent depends from claim 1 and further requires that the purified, recombinant AAV vector particles after storage "have an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering." This language is indefinite (as applied) at least with respect to the term "dynamic light scattering" (DLS). It would not be possible for a person of ordinary skill in the art to determine, with reasonable certainty, whether the purified, recombinant AAV vector particles in a particular composition fall within or outside of the average particle radius claimed in claim 5 because the claim 5 does not define what DLS method or conditions are to be used, and it was known in the art as of June 1, 2004 that different DLS methods and conditions can result in different observed average particle radius values. *See Forest Labs.*, 716 Fed. App'x at 994; *see also Dow Chemical*, 803 F.3d at 634.

iii. "filtration . . . through a 0.22 µm filter"

Claim 6 of the '542 patent depends from claim 1 and further requires that "recovery of the purified, recombinant virus particles" from the composition of claim 1 following storage "is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22 µm filter." This language is indefinite (as applied) at least with respect to the phrase "filtration … through a 0.22 um filter." It would not be possible for a person of ordinary skill in the art to determine, with reasonable certainty, whether the recovery of purified, recombinant virus particles in a particular composition falls within or outside of the claimed percent recovery following

filtration in claim 6 because the claim does not define what filtration methods or conditions or the specification of the filter, are to be used, and it was known in the art as of June 1, 2004 that different filtration methods and conditions, and the specification of the filter, can result in different percent recovery." *See Forest Labs.*, 716 Fed. App'x at 994; *see also Dow Chemical*, 803 F.3d at 634.

C. The '542 Patent Claims Are Invalid for Obviousness-Type Double Patenting

Each Asserted Claim of the '542 patent is invalid for obviousness-type double patenting over claims 1-11 ("the reference claims") of U.S. Patent No. 7,704,721 ("the '721 patent) because the Asserted Claims and the reference claims are not patentably distinct from each other.

Claim 1 of the '721 patent is directed to a method of preventing aggregation of purified rAAV virion preparations by adding "one or more salts of multivalent ions selected from the group consisting of citrate, phosphate, sulfate and magnesium to said purified virions to produce a preparation of virions with an ionic strength of at least 200 mM, wherein the concentration of purified rAAV virions in said preparations exceeds $1x10^{13}$ vg/ml up to $6.4x10^{13}$ vg/ml; and wherein the pH of the purified preparation of rAAV virions is between 7.5 and 8.0." Thus, the method recited in claim 1 of the '721 patent uses the composition recited in claim 1 of the '542 patent, rendering that asserted claim obvious. *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008) (a "claim to a method of using a composition is not patentably distinct from an earlier claim to the identical composition in a patent disclosing the identical use.").

Claim 2 of the '542 patent depends from claim 1 and adds that the composition further comprises Pluronic® F68. As explained supra, the addition of Pluronic® F68 to purified rAAV virion preparations would have been obvious over the teachings of at least Liu (2003), Frei (1999), Evans (2001), Lochrie (2003), Wright (2003), and Sommer (2003). Thus, asserted claim 2 would have been obvious over claim 1 of the '721 patent for the reasons discussed above in view of the

teachings of Liu (2003), Frei (1999), Evans (2001), Lochrie (2003), Wright (2003), and Sommer (2003).

Claim 6 of the ’721 patent depends from claim 1 and recites that “the average particle radius (Rh) of the virions in the preparation of virions is less than about 20 nm as measured by dynamic light scattering.” Thus, the method recited in claim 6 of the ’721 patent uses the composition recited in claim 5 of the ’542 patent, rendering that asserted claim obvious. *See Pfizer*, 518 F.3d at 1363.

Claim 7 of the ’721 patent depends from claim 1 and recites that “recovery of the virions is at least about 90% following filtration of the preparation of virions through a 0.22 µm filter.” Thus, the method recited in claim 7 of the ’721 patent uses the composition recited in claim 6 of the ’542 patent, rendering that asserted claim obvious. *See Pfizer*, 518 F.3d at 1363.

Since the application that led to the ’542 patent was filed as a continuation of the application that led to the ’721 patent, the safe harbor protection against obviousness-type double patenting provided under 35 U.S.C. § 121 does not apply. *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1353 (Fed. Cir. 2009) (“[t]he statute on its face applies only to divisional applications, and a continuation application . . . is not a divisional application.”). Thus, the Asserted Claims of the ’542 patent are invalid for obviousness-type double patenting.

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Novartis Gene Therapies, Inc. et al. v. Genzyme Corporation
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Exhibit 2011