UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS GENE THERAPIES, INC. &
NOVARTIS PHARMACEUTICALS CORPORATION,
Petitioners,

v.

GENZYME CORPORATION,
Patent Owner.

IPR2023-00609
Patent 9,051,542 B2

Before JEFFREY N. FREDMAN, SHERIDAN K. SNEDDEN, and JAMES A. TARTAL, *Administrative Patent Judges*.

TARTAL, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation (collectively, "Petitioner")[1] filed a Petition pursuant to 35 U.S.C. §§ 311–319 requesting an *inter partes* review of claims 1, 2, 5, and 6 of U.S. Patent No. 9,051,542 B2 (Ex. 1001, "the '542 patent"). Paper 2 ("Pet."). Genzyme Corporation ("Patent Owner")[2] filed a Preliminary Response. Paper 16. In its Preliminary Response, Patent Owner states that it has disclaimed claims 1 and 2 of the '542 patent. *Id.* at 3 (citing Ex. 2015 (the "Disclaimer"); 37 C.F.R. § 42.107(e)). In light of the Disclaimer, only claims 5 and 6 of the '542 patent remain at issue in this proceeding. *See* 37 C.F.R. § 42.107(e) (stating that "[n]o *inter partes* review will be instituted based on disclaimed claims"). With our prior authorization, Petitioner filed a Reply to Patent Owner's Preliminary Response (Paper 19) and Patent Owner filed a Sur-reply (Paper 20).

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b) (2018); 37 C.F.R. § 42.4(a) (2021). An *inter partes* review may not be instituted "unless . . . the information presented in the petition . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a); *see also PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (stating that the decision whether to institute *inter partes* review requires "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition").

[1] Petitioner identifies no additional real parties in interest related to Petitioner. Pet. 63.
[2] Patent Owner states that Sanofi and Aventis, Inc. are additional real parties in interest. Paper 6, 2.

Upon consideration of the evidence and arguments presented, we conclude that the information does not demonstrate a reasonable likelihood that Petitioner would prevail in showing the unpatentability of either claim 5 or claim 6 of the '542 patent. Accordingly, we do not institute an *inter partes* review.

II. BACKGROUND

A. The '542 Patent

The '542 patent is titled "Compositions and Methods to Prevent AAV Vector Aggregation," and issued on June 9, 2015, from U.S. Patent Application No. 12/661,553, filed March 19, 2010. Ex. 1001, codes (21), (22), (45), (54). The '542 patent "relates to compositions and methods of preparing and storing AAV [(adeno-associated virus)] virions that prevent aggregation." *Id.* at 1:17–19. According to the '542 patent, "[t]he solubility of purified AAV2 virus particles is limited, and aggregation of AAV2 particles has been described as a problem." *Id.* at 1:41–46 (citing, e.g., Wright et al., "Recombinant Adeno-Associated Virus: Formulation Challenges and Strategies for a Gene Therapy Vector," *Curr. Opin. Drug Disc. Dev.* 6(2):174–178 (2003) (Ex. 1007, "Wright"); Croyle, et al., "Development of Formulations That Enhance Physical Stability of Viral Vectors for Gene Therapy," *Gene Ther.*, 8:1281–1290 (2001) (Ex. 1013, "Croyle")).

In particular, the '542 patent discloses high ionic strength solutions that are isotonic with the intended target tissue. *Id.* at code (57). The "combination of high ionic strength and modest osmolarity is achieved using salts of high valency, such as sodium citrate." *Id.*

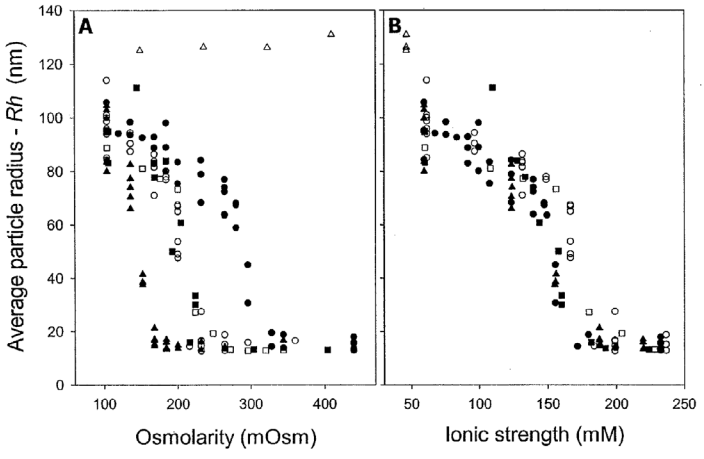
The ’542 patent further explains as follows:

> The present invention is based in part on the observation that solution ionic strength is an important parameter in AAV vector aggregation, implicating the involvement of ionic interactions between virus particles in the aggregation process. The observation that elevated ionic strength increases AAV2 [AAV serotype 2] vector solubility regardless of the identity of the charged excipient supports the hypothesis that ionic strength of solution per se, rather than interactions involving a specific ionic species, is the relevant physico-chemical parameter. A threshold ionic strength of at least 200 mM is required to prevent aggregation at vector particle concentrations examined herein.

Id. at 4:53–64. The ’542 patent additionally states as follows:

> In embodiments of the present invention the exponential relationship of ionic strength with charge valency is used to develop isotonic formulations with high ionic strengths. Salt species with multiple charge valencies (e.g. salts of sulfate, citrate, and phosphate) that are commonly used as excipients in human parenteral formulations can provide the level of ionic strength needed to prevent AAV2 vector aggregation when used at isotonic concentrations. While isotonic (150 mM) sodium chloride has an ionic strength of 150 mM, a value insufficient to maintain AAV2 solubility at high vector concentrations, isotonic sodium citrate, with an ionic strength of ~500 mM, can support AAV2 vector concentrations of at least 6.4×10^{13} vg/mL without aggregation.

Id. at 5:7–20. Figures 1A and 1B of the ’542 patent are reproduced below.



Figures 1A and 1B present the results of a vector aggregation study that tracked aggregation as a function of two parameters, osmolarity (Figure 1A) and ionic strength (Figure 1B) for buffer compositions of sodium chloride (●), sodium citrate (○), sodium phosphate (■), sodium sulfate (□), magnesium sulfate (▲), and glycerol (Δ), and. *Id.* at 6:63–65, 12:33–67 (Example 3), FIGS. 1A, 1B. "Average particle radius is measured by dynamic light scattering (DLS) following vector dilution in varying concentrations of excipients buffered with 10 mM sodium phosphate at pH 7.5." *Id.* at 4:18–28. "Rh values >20 nm are deemed to indicate the occurrence of some level of aggregation." *Id.* at 9:25–27.

The results of Figure 1A, which plots vector aggregation as a function of the osmolarity of selected excipients, are explained as follows:

> For charged species a concentration-dependent inhibition of AAV2 vector aggregation is observed. Salts with multivalent ions achieve a similar degree of inhibition of aggregation at lower concentrations than monovalent sodium chloride. For example, magnesium sulfate prevents aggregation at >200 mOsm whereas sodium chloride requires ≧350 mOsm to achieve a similar effect. Sodium citrate, sodium sulfate, and sodium phosphate are intermediate in their potency to prevent vector aggregation.

Id. at 6:65–7:8.

Figure 1B shows data from the same experiment "plotted as a function of the calculated ionic strength, rather than osmolarity, for each excipient." *Id.* at 7:18–20. Figure 1B's plot of particle radius versus ionic strength shows that "vector aggregation is prevented when ionic strength is ~200 mM or greater regardless of which salt is used." *Id.* at 7:21–22. "These data suggested that the ionic strength (μ) of a solution . . . is the primary factor affecting aggregation." *Id.* at 7:22–25.

The '542 patent discloses the results of a study assessing "the effects of elevated ionic strength and nuclease treatment on AAV2 vector aggregation at a larger scale, using methods to induce and quantify vector aggregation that are relevant to preparative scale vector purification" in Table 2. *Id.* at 8:1–5.

Table 2 of the '542 patent is reproduced, in part, below.

TABLE 2

AAV VECTOR RECOVERY AT PROCESS SCALE

Experiment	Formulation	μ (mM)	Target (vg/mL)	Actual (vg/mL)	Yield % (RSD)
1	CF	160	2.5E13	1.93E13	77 (6.6)
1	TF1	310	2.5E13	2.38E13	95 (7.4)
1	TF2	510	2.5E13	2.33E13	93 (7.4)
2	CF	160	6.7E13	3.98E13	59 (6.0)
2	TF2	510	6.7E13	6.42E13	96 (4.4)

Table 2 shows the results for three solutions of AAV2-AADC vectors filtered through a 0.22 μm filter. *Id.* at 8:1–10, 11:53–12:29. The three solutions are as follows:

> Control Formulation (CF: 140 mM sodium chloride, 10 mM sodium phosphate, 5% sorbitol, pH 7.3); Test Formulation 1 (TF1: 150 mM sodium phosphate, pH 7.5); and Test Formulation 2 (TF2: 100 mM sodium citrate, 10 mM Tris, pH 8.0).

Id. at 11:66–12:3. In Experiment 1, the samples contained 2.5×10^{13} vg/ml vector, and, in Experiment 2, the samples contained 6.7×10^{13} vg/ml vector. *Id.* at 12:4–12. Table 2 shows recoveries exceeded 90% following filtration in formulations TF1 and TF2 having ionic strengths greater than 200 mM, whereas recovery from CF formulations, having ionic strength of 160 mM, was only 77% and 59% for experiments 1 and 2, respectively. *Id.* at 8:19–56.

The '542 patent also discloses the results of a study assessing "stability after storage or freeze-thaw (F/T) cycling is assessed in buffers of

the present invention." *Id.* at 9:19–27. Particle radius was measured by dynamic light scattering (DLS) to determine the presence of aggregates. *Id.*

Table 3, reproduced below, summarizes the results of the study.

TABLE 3

STABILITY OF AAV2 VECTORS

	Particle radius - Rh (nm)							
Formu-		4° C.	−20° C.			−80° C.		
lation	Pre	5 d	1 F/T	5 F/T	10 F/T	1 F/T	5 F/T	10 F/T
CF	14.5	27.0	22.4	56.1	94.5	20.6	57.5	141
TF1	13.8	16.3	TH	TH	TH	TH	TH	TH
TF2	13.8	14.4	14.2	14.0	14.1	13.8	21.3	50.9

Pre: DLS radius measured immediately following 0.2 μm filtration.
Vector concentrations (vg/mL): CF: 1.93E13, TF1: 2.38E13, TF2: 2.33E13.
TH: signal intensity is too high to measure because of extensive aggregation.

According to the '542 patent, Table 3 provides data showing as follows:

> AAV2-AADC vector prepared in CF shows some aggregation after 5 days of storage at 4° C., as well as following one or more F/T cycles at −20 or −80° C. For vector prepared in TF1, no aggregation occurs after 5 days at 4° C., but aggregation occurs following a single F/T cycle at −20 or −80° C. as indicated by a DLS signal intensity that is too high to measure. Visual inspection of these samples reveals slight cloudiness, which is consistent with aggregation. For vector prepared in TF2, no aggregation is observed at 4° C., or following up to 10 F/T cycles at −20° C. Some aggregation is observed following 5 and 10 F/T cycles at −80° C.

Id. at 9:29–55. According to Patent Owner, the results of the studies disclosed in the '542 patent "confirmed the importance of increased ionic strength in preventing aggregation." Prelim. Resp. 12 (citing Ex. 1001, 10:29–43 (stating "[t]he effect of ionic strength [] on virus particle interactions is determined to elucidate the mechanism of vector aggregation")).

B. Claims at Issue

Claims 5 and 6 of the '542 patent are at issue in this proceeding. Claims 5 and 6 each depend directly from disclaimed claim 1. Ex. 1001, 14:34–41. Claims 5 and 6 are reproduced below, along with disclaimed independent claim 1 from which they each depend.

> 1. A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising:
>
> > purified, recombinant AAV vector particles at a concentration exceeding 1×10^{13} vg/ml up to 6.4×10^{13} vg/ml;[3]
> >
> > a pH buffer, wherein the pH of the composition is between 7.5 and 8.0; and
> >
> > excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate; wherein the ionic strength of the composition is greater than 200 mM, and wherein the purified AAV vector particles are stored in the composition without significant aggregation.
>
> 5. The composition of claim 1, wherein the purified, recombinant AAV vector particles have an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering.
>
> 6. The composition of claim 1, wherein recovery of the purified, recombinant virus particles is at least about 90% following

[3] The units of measurements used in the art to measure the titer of AAV compositions are explained in the Petition as follows:

> The titer of AAV compositions can be measured in vector genomes (vg)/ml, genome copies (gc)/ml, capsid particles (cp)/ml, or virus particles (vp)/ml. Ex.1025, ¶35. The first two are used interchangeably, since both represent the number of functional vectors containing the therapeutic gene. *Id.*, ¶¶36–37. By contrast, the latter two measurements include particles that are incomplete, damaged, or lacking genetic material. Ex.1009, [00281]; Ex.1025, ¶36.

Pet. 12.

filtration of the composition of said AAV vector particles through a 0.22 μm filter.

Ex. 1001, 14:15–28, 34–41.

C. Asserted Grounds of Unpatentability

In the Petition, Petitioner asserts that claims 1, 2, 5, and 6 of the '542 patent are unpatentable. Pet. 4. As noted above, after the Petition was filed, Patent Owner explained that it disclaimed claims 1 and 2 of the '542 patent. Prelim. Resp. 3 (citing Ex. 2015). Accordingly, our determination of whether to institute *inter partes* review is based on Petitioner's allegations directed to claims 5 and 6. *See* 37 C.F.R. § 42.107(e). Petitioner challenges claims 5 and 6 on the following grounds:

Claim(s) Challenged	35 U.S.C. §[4]	Reference(s)/Basis
5, 6	103	Liu,[5] Huang,[6] Mingozzi[7]
5, 6	103	Lochrie,[8] Huang, Mingozzi, Johnson,[9] Liu

[4] The Leahy-Smith America Invents Act ("AIA") included revisions to 35 U.S.C. §103 that became effective on March 16, 2013. We apply the pre-AIA version of §103 here, because the application identified in the '542 patent was filed before the effective date of the AIA. *See* Ex. 1001, code (22).

[5] WO 03/039459 A2, published May 15, 2003 (Ex. 1009, "Liu").

[6] Huang J, Gao, 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," MOL THER. 1:S286 (2000) (Ex. 1005, "Huang").

[7] Mingozzi, et al., "Improved Hepatic Gene Transfer by Using an Adeno-Associated Virus Serotype 5 Vector," J VIROL. 76:10497–502 (2002) (Ex. 1006, "Mingozzi").

[8] WO 03/046142 A2, published May 6, 2003 ("Ex. 1010, "Lochrie").

[9] F. B. Johnson and A. S. Bodily, *Effects of Environmental pH on Adenovirus-Associated Virus (39085)*, Procs. of the Soc. for Experimental Biology and Med., pp. 585-90 (1975) (Ex. 1019, "Johnson").

Pet. 4. Petitioner relies on the supporting Declaration of Mansoor M. Amiji, R.Ph., Ph.D., dated February 22, 2023. Ex. 1025. Patent Owner relies on the Declaration of Martyn C. Davies, dated June 15, 2023. Ex. 2004.

D. Related Proceedings

The Parties indicate that the '542 patent is asserted against Petitioner in *Genzyme Corporation et al. v. Novartis Gene Therapies, Inc. et al.*, Case No. 1:21-cv-01736 (D. Del.), filed December 10, 2021. Pet. 63; Paper 6, 2. Petitioner also filed a petition for *inter partes* review in IPR2023-00608 seeking to challenge claims of the '542 patent on other grounds. *Id.*

III. ANALYSIS

A. Legal Standards for Obviousness

A patent claim is unpatentable for obviousness if the differences between the claimed subject matter 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. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). In *Graham v. John Deere Co.*, 383 U.S. 1 (1966), the Supreme Court set out a framework for assessing obviousness that requires consideration of four factors: (1) the "level of ordinary skill in the pertinent art," (2) the "scope and content of the prior art," (3) the "differences between the prior art and the claims at issue," and (4) "secondary considerations" of nonobviousness such as "commercial success, long felt but unsolved needs, failure of others, etc." *Id.* at 17–18; *KSR*, 550 U.S. at 407.

"Whether an ordinarily skilled artisan would have been motivated to modify the teachings of a reference is a question of fact." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1327 (Fed. Cir. 2016) (citations omitted). The

Supreme Court made clear that we apply "an expansive and flexible approach" to the question of obviousness. *KSR*, 550 U.S. at 415. Whether a patent claiming the combination of prior art elements would have been obvious is determined by whether the improvement is more than the predictable use of prior art elements according to their established functions. *Id.* at 417. To support this conclusion, however, it is not enough to show merely that the prior art includes separate references covering each separate limitation in a challenged claim. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). Rather, obviousness additionally requires that a person of ordinary skill at the time of the invention "would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Id.*

In determining whether there would have been a motivation to combine prior art references to arrive at the claimed invention, it is insufficient to simply conclude the combination would have been obvious without identifying any reason why a person of skill in the art would have made the combination. *Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358, 1366 (Fed. Cir. 2017). Moreover, in determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 164 (Fed. Cir. 1985) ("It is elementary that the claimed invention must be considered as a *whole* in deciding the question of obviousness."); *see also Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1537 (Fed. Cir. 1983) ("[T]he question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious. Consideration of differences, like each of the findings set

forth in Graham, is but an aid in reaching the ultimate determination of whether the claimed invention as a whole would have been obvious."). "[W]here a party argues a skilled artisan would have been motivated to combine references, it must show the artisan 'would have had a reasonable expectation of success from doing so.'" *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1360–61 (Fed. Cir. 2017) (quoting *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068–69 (Fed. Cir. 2012)).

B. Level of Ordinary Skill in the Art

In determining the level of ordinary skill in the art, various factors may be considered, including the "type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field." *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (citation omitted). Petitioner proposes that a person of ordinary skill in the art at the time of the invention would have possessed the following level of skill:

> at least a BS in biology, chemistry, chemical engineering, biochemistry, pharmaceutical science, or a related discipline, with ≥4 years of industry, laboratory, and/or clinical experience in formulating or developing dispersions for therapeutic biologics, such as proteins or vectors for gene delivery. Such person may be familiar with, or consult with someone familiar with, the development and/or administration of viral vectors for gene therapy. Ex.1025, ¶82.

Pet. 16–17. Patent Owner does not dispute Petitioner's proposed level of ordinary skill in the art. Prelim. Resp. 2 n.2.

We find that the '542 patent and the cited prior art references reflect a level of skill at the time of the claimed invention that is consistent with the

level of skill proposed by Petitioner. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). Accordingly, for purposes of this Decision, we adopt Petitioner's proposed definition for a person of ordinary skill in the art.

C. Claim Construction

We apply the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.100(b). Under that standard, claim terms "are generally given their ordinary and customary meaning" as would have been understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). "In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" *Phillips*, 415 F.3d at 1317.

Petitioner asserts that "[f]or this proceeding, no terms require express construction," states that the Petition "analyzes the claim terms under their 'plain and ordinary meaning.'" Pet. 17. Patent Owner does not challenge Petitioner's position. Prelim. Resp. 13. We agree that it is not otherwise necessary to address the express interpretation of any claim term for purposes of this Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))). To the

extent further discussion of the meaning of any claim term is necessary to this Decision, we provide that discussion below in our analysis of the asserted grounds of unpatentability.

D. Alleged Obviousness Over Liu, Huang, and Mingozzi

Petitioner contends the subject matter of claims 5 and 6 would have been obvious over Liu, Huang, and Mingozzi. Pet. 22–43. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 14–36. For the reasons set forth below, we determine that Petitioner has not shown a reasonable likelihood of establishing that either claim 5 or claim 6 is unpatentable as obvious over Liu, Huang, and Mingozzi.

1. Summary of Liu

Liu, titled "Viral Vector Production Methods and Compositions," describes methods of preparing viral vector particles and compositions, including "storage compositions" that "effectively maintain a stable population of adenoviral vector particles during the viral vector particle production and/or purification process." Ex.1009 ¶ 365. Under the heading "Example 17," Liu teaches "an adenoviral vector particle composition comprising a population of adenoviral vector particles in a temporary storage buffer (25mM Tris, 300mM NaCl, 5mM MgCl2, 0.0025% polysorbate 80, 5% trehalose, pH 7.5)." *Id.* ¶ 366. According to Liu, the composition was maintained at about 4°C for 7 days in the temporary storage buffer and "showed no signs of settling or precipitation" and "no significant decrease in particle number over the 7 day test period." *Id.* ¶ 368.

2. Summary of Huang

Huang, an abstract titled "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," states that "[t]o 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." Ex. 1005, S286. According to Huang, "at high concentrations, AAV virions form aggregates of different sizes in a range of different buffer systems and storage conditions." *Id.* Huang states that "when the vector titer reached 5-10 x 10^{13} GCs/ml, gene transfer efficiency was 10-100 folds lower at the same dose as compared to the vector whose titer was 1-5 x 10^{12} GCs/ml." *Id.* Huang states that "a series of formulation studies were performed to prevent and dissolve AAV aggregation," and reported "a 30–50% reduction in the size of aggregates size at high vector concentrations" for some of the compositions. *Id*.

3. Summary of Mingozzi

Mingozzi, titled "Improved Hepatic Gene Transfer by Using Adeno-Associated Virus Serotype 5 Vector," states that "AAV vectors do not contain viral coding sequences and have been shown to efficiently transfer genes to nondividing target cells," and that "[a]n excellent safety profile combined with reduced potential for activation of inflammatory or cellular immune responses has made this vector system attractive for clinical application and treatment of genetic disorders." Ex. 1006, 10497. According to Mingozzi, purification of AAV-2 and AAV-5 vectors "by repeated CsCl gradient centrifugation" yielded concentrations of >10^{13} vg/ml. *Id.*

4. Claims 5 and 6

Claim 5 recites a composition of claim 1, "wherein the purified, recombinant AAV vector particles have an average particle size radius (Rh) of less than about 20 nm as measured by dynamic light scattering [DLS]"

(the "average particle radius limitation"). Ex. 1001, 14:34–37. Claim 6 recites a composition of claim 1, "wherein recovery of the purified, recombinant virus particles is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22μm filter" (the "percent filtration limitation"). *Id.* at 14:38–41. Together, the average particle radius limitation and the percent filtration limitation are referred to as the "aggregate limitations."

Petitioner's contentions are based in part on the composition described in Liu's Example 17, described above, which Petitioner concedes does not teach the "recombinant AAV vector particles at a concentration exceeding 1×10^{13} vg/ml," as required by claim 1. Pet. 29 ("Assuming that 100% of the particles contained vector genomes, Liu's composition had an initial concentration of $3.24x10^{8}$ vg/mL") (citing Ex. 1025 ¶ 285). Petitioner reasons that a person of ordinary skill in the art would have had reason to increase "Liu's vector production and concentration" in light of the teachings of Mingozzi and Huang, with a reasonable expectation of success in attaining the concentration required by claim 1. *Id.* at 30–33. Petitioner relies on "Liu's Example 17 composition, as modified by Huang and Mingozzi" in its contentions directed to the aggregate limitations of claims 5 and 6. Pet. 40–43.

In particular, Petitioner asserts that Patent Owner stated in a filing in district court that the aggregate limitations "provide different methods of ensuring that there is no substantial aggregation." *Id.* at 39, 41 (quoting Ex. 1023, 72). From this, Petitioner asserts that "[i]f true," then "because Liu's compositions prevent aggregation," the limitations of claims 5 and 6 provide "no patentable weight." *Id.* at 39, 41. Further, according to Petitioner, during prosecution the Examiner concluded that the aggregate

limitations were inherent characteristics of the purified viral composition. *Id.* at 39, 41–42 (citing Ex. 1002, 86–88, 91, 146, 151, 154, 188, 191, 220, 318). Petitioner maintains that Patent Owner's failure to dispute the Examiner's conclusions during prosecution "constitutes a binding admission." *Id.* (citing *TorPharm, Inc. v. Ranbaxy Pharms., Inc.*, 336 F.3d 1322, 1330 (Fed. Cir. 2003)).

Petitioner further argues with regard to claim 5 as follows:

> The '542 patent admits that AAV2 particles have a diameter of ~26nm (Ex.1001, 1:29-38); thus, a [person of ordinary skill in the art] would have reasonably expected that, because Liu's compositions prevented aggregation, AAV particles stored therein and in obvious variants of Liu's Example 17 composition also have an Rh of less than about 20nm measured by DLS. Indeed, the '542 patent does not identify anything critical about the recited radius range other than it being exemplary of no aggregation. Ex.1001, 9:25-27 ("Rh values >20 nm are deemed to indicate the occurrence of some level of aggregation.").

Pet. 39–40. Petitioner contends that a person of ordinary skill in the art would have been motivated to minimize any potential aggregation in Liu's composition "through routine optimization of known stabilization factors," because it was known that virus aggregation reduced gene transfer efficiency and caused potentially deleterious consequences. *Id.* at 40 (citing Ex. 1005, S286; Ex. 1007, 176). Petitioner also argues as follows:

> A [person of ordinary skill in the art] would have reasonably expected success in minimizing particle size based on Huang's teaching that formulation optimization "could lead to a 30-50% reduction in the size of aggregates at high vector concentrations." Ex.1005, S286. Indeed, Liu taught that its experiments "demonstrate that viral vector compositions can be stably stored in the temporary storage buffers of the invention for extended periods of time" and that reduced aggregation can be achieved by "addition of surfactants." Ex.1009, [00371],

> [00263]. And a [person of ordinary skill in the art] would have understood that AAV "is significantly more stable than the adenovirus." Ex.1013, 1283. Thus, at most, only routine optimization would be required to obtain an average AAV Rh <20nm using the obvious variants of Liu's Example 17 composition discussed above. Ex.1025, ¶¶320-322.

Pet. 41 (citing *Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1353 (Fed. Cir. 2015) (invalidating a claim directed to "a product of routine optimization that would have been obvious to one of skill in the art")).

With regard to claim 6, Petitioner argues as follows:

> Since the inventors acknowledged in Wright that "loss of rAAV following a 0.2-μm filtration step correlates with the extent of vector aggregation" (Ex.1007, 175), a [person of ordinary skill in the art] would have reasonably expected that at least 90% of the AAV particles stored without observable aggregation in Liu's Example 17 composition, as modified by Huang and Mingozzi, will be recovered following filtration through a 0.22μm filter. Ex.1025, ¶324.

Pet. 41–42. Petitioner contends that the '542 patent "does not identify anything critical about the recited recovery rate," and that a person of ordinary skill in the art "would have been motivated to minimize any potential aggregation in Liu's modified Example 17 composition," because "Wright and Huang linked aggregation to reduced functional activity of AAV vectors." *Id.* at 42–43 (citing Ex. 1005, S286; Ex. 1007, 176). Petitioner reasons that 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 known stabilization factors," and would reasonably have expected success through "only routine optimization" for the following reasons:

> Huang taught optimized formulations "could lead to a 30-50% reduction in the size of aggregates at high vector concentrations" (Ex.1005, S286), Liu observed "no signs of settling or

> precipitation" for adenovirus particles stored in a high ionic strength buffer over a 7 day period (Ex.1009, [00369]), and Croyle taught that AAV "is significantly more stable than the adenovirus" (Ex.1013, 1283).

Id. at 43.

In opposition, Patent Owner argues, in part, that Petitioner fails to show the asserted combination of references teaches: "(1) the rAAV 'concentration exceeding $1x10^{13}$vg/ml up to $6.4x10^{13}$vg/ml'; (2) 'the ionic strength of the composition is greater than 200 mM'; and (3) the respective aggregate limitations of claims 5 and 6." Prelim. Resp. 13. According to Patent Owner, Liu's compositions have a viral particle concentration several orders of magnitude below the claimed vector genome concentration and a person of ordinary skill in the art would have understood that "Liu's visual assessment would be unable to detect significant aggregation to the levels recited in claims 5 and 6." *Id.* at 14 (citing Pet. 24, 29; Ex. 1009 ¶¶ 126, 186, 369, 371; Ex. 1025 ¶ 285; Ex. 2004 ¶¶ 64–65). With regard to Huang, Patent Owner argues that the reported 30–50% reduction in the size of aggregates "does not explain what this size reduction means in terms of particle radius or any other metric, does not disclose any information about its formulations, and never suggests that its stored rAAV compositions could remain free of significant aggregation." *Id.* at 14–15 (citing Ex. 2004 ¶ 67). Patent Owner further argues that Mingozzi does not addresses aggregation, rAAV formulations, or storage. *Id.* at 15 (citing Ex. 2004 ¶ 68).

First, we agree with Patent Owner that Petitioner fails to sufficiently show a reasonable likelihood of prevailing in its assertion that the aggregate limitations carry no patentable weight. *See* Prelim. Resp. 31–32; Pet. 39, 41. As Patent Owner explains, the aggregate limitations "'provide[] the criteria by which the' composition for the storage of purified rAAV vector particles

'is analyzed.'" *Id.* (quoting *In re Jasinski*, 508 F. App'x 950, 952 (Fed. Cir. 2013) (citing *Vizio, Inc. v. Int'l Trade Comm'n*, 605 F.3d 1330, 1340 (Fed. Cir. 2010) (holding that claims language going to "the essence or a fundamental characteristic of the claimed invention" was "properly construed as a limitation")). The "wherein" clauses in claims 5 and 6 are reasonably assigned patentable weight because they impose structural limitations that requires the AAV vectors to have particular aggregation properties. *See Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002) (stating that "the Board did not err in giving limiting effect to the 'wherein' clauses" because they give "meaning and purpose to the manipulative steps"). As Patent Owner explains, the aggregate limitations "relate to the quantification of rAAV aggregation (or the absence of aggregates) more accurately than other methods of detection, including visual inspection and analytical methods such as A320/A260 absorbance." Prelim. Resp. 32 (citing Ex. 2005 ¶¶ 45–50; Ex. 2009).

Second, we agree with Patent Owner that Petitioner fails to sufficiently show a reasonable likelihood of prevailing in its assertion that Patent Owner's decision not to dispute the Examiner's conclusion that the aggregate limitations were inherent characteristics of the purified viral composition during prosecution constitutes a binding admission. Pet. 39, 41–42; Prelim. Resp 32–33. Patent Owner explains that it disputed the Examiner's rejection, was not obligated to advance redundant arguments for patentability before the Examiner, and is not limited in subsequent proceedings to advancing only arguments in support of patentability previously made during prosecution. Prelim. Resp. 33 (citing *Woods v. DeAngelo Marine Exhaust, Inc.*, 692 F.3d 1272, 1287 (Fed. Cir. 2012); *Tor Pharm*, 336 F.3d at 1330).

Third, we agree with Patent Owner that Petitioner fails to sufficiently show a reasonable likelihood of prevailing in its assertion that the aggregate limitations were inherently taught by the asserted art. Pet. 38–43; Prelim. Resp. 34–36. To prove inherency in the context of obviousness, a party must "meet a high standard" and establish that "the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014).

In regard to claim 5, we agree with Patent Owner that Petitioner "*fails* to produce any evidence that for the claimed composition 'the purified, recombinant AAV vector particles' would necessarily and inevitably have had 'an average particle radius (Rh) of less than about 20 nm as measured by [DLS].'" Prelim. Resp. 34–35. Petitioner offers no testing or other persuasive evidence in support of its contentions, arguing instead that a person of ordinary skill in the art "would have reasonably expected" Liu's compositions to meet the average particle radius limitation of claim 5. *See* Pet. 39–40.

In regard to claim 6, we also agree with Patent Owner that Petitioner offers no sufficient evidence to show "Liu's Example 17 composition, as modified by Huang and Mingozzi," would necessarily and inevitably result in "at least about 90%" recovery of the "purified, recombinant virus particles following filtration of the composition of said AAV vector particles through a 0.22μm filter." Prelim. Resp. 35–36. Patent Owner argues that Petitioner "cannot possibly meet the high standard for inherency relying on Liu's Example 17, which applies only visual methods that the [person of ordinary skill in the art] would have understood could not determine the presence (or absence) of significant aggregation to the degree of claim 6's product

recovery following filtration requirement." Prelim. Resp. 36 (citing Ex. 2004 ¶ 42). In support, Patent Owner explains that the '542 patent discloses "compositions having ionic strength greater than 200 mM surprisingly resulted in recoveries exceeding 90%, whereas compositions having ionic strengths below 200 mM resulted in recoveries below 80%" and that "[w]ithin the variability of the assays used, vector was recovered fully at both target concentrations using TF2, indicating that aggregation was prevented." Prelim. Resp. 35–36 (quoting Ex. 1001, 8:19–46) (emphasis omitted). Petitioner offers no testing or other persuasive evidence in support of its contentions, arguing instead that a person of ordinary skill in the art "would have reasonably expected that, because Liu's compositions prevented aggregation, AAV particles stored therein and in obvious variants of Liu's Example 17 composition also have an Rh of less than about 20nm measured by DLS." Pet. 39–40.

Petitioner fails to submit sufficient persuasive evidence that either the average particle radius limitation of claim 5 or the percent filtration limitation of claim 6 would necessarily be present in, or the natural result of, the asserted combination of teachings in Liu, Huang, and Mingozzi. Merely asserting a person of ordinary skill in the art "would have reasonably expected" Liu's composition, as modified by Huang and Mingozzi, to meet the aggregation limitations of either claim 5 or claim 6 does not sufficiently support a finding of inherency as to those limitations and the evidence relied upon by Petitioner is not sufficient to show the alleged "expectation" would have been reasonable.

Fourth, we find insufficient and not persuasive Petitioner's conclusory assertions that "only routine optimization" with a reasonable expectation of success in light of the asserted art would have been required to obtain a

composition meeting the aggregation limitations. *See* Pet. 41 ("only routine optimization would be required to obtain an average AAV Rh <20nm using the obvious variants of Liu's Example 17 composition") (citing Ex. 1025 ¶¶ 320–322), 43 ("only routine optimization would be required to improve AAV recovery following filtration of Liu's modified Example 17 composition through a 0.22μm filter") (citing Ex. 1025 ¶¶ 326–329). Petitioner offers scant evidence or explanation of what "optimization" was necessary, or why it would have been obvious to do so at the time of the invention. *See* Pet. 40 ("To the extent modifications to Lin's composition" would have been "required to achieve the features of claim 5," a person of ordinary skill in the art "would have been motivated to make *such changes*") (emphasis added). Petitioner then suggests "such changes" are merely "optimization of known stabilization factors." *Id.* Neither the Petition nor Dr. Amiji on behalf of Petitioner adequately explains what such optimization would have entailed or whether it would have been within the ability of a person of ordinary skill in the art at the time of the invention. *See* Ex. 1025 ¶ 319 (referring to "known aggregation reduction tools" without citation to any supporting prior art and asserting Liu taught "reducing potential aggregation by addition of surfactants"). In regard to the alleged expectation of success, we also find persuasive the testimony of Dr. Davies who notes that a person of ordinary skill in the art would have understood that "rAAV undergoes concentration-dependent aggregation," and that the "nature of the interparticle interactions that result in aggregation has not been well characterized." Ex. 2004 ¶¶ 97, 100 (quoting Ex. 1007, 17, 176).

Petitioner's contentions and supporting evidence fail to show a reasonable likelihood that the aggregate limitations of claims 5 and 6 would have been attainable with a reasonable expectation of success merely based

on a desire to optimize Liu's composition, as allegedly already modified by the teachings of Huang and Mingozzi.

5. Showing of a Reasonable Likelihood of Success

For at least the reasons discussed above, we are not persuaded that Petitioner has shown a reasonable likelihood of establishing that either claim 5 or claim 6 is unpatentable as obvious over Liu, Huang, and Mingozzi

E. Alleged Obviousness Over Lochrie, Huang, Mingozzi, Johnson, and Liu

Petitioner contends the subject matter of claims 5 and 6 would have been obvious over Lochrie, Huang, Mingozzi, Johnson, and Liu. Pet. 43–57. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 36–50. For the reasons set forth below, we determine that Petitioner has not shown a reasonable likelihood of establishing that either claim 5 or claim 6 is unpatentable as obvious over Lochrie, Huang, Mingozzi, Johnson, and Liu.

1. Summary of Lochrie

Lochrie, titled "Methods for Producing Stocks of Recombinant AAV Virons," is directed to "efficient and commercially viable methods for producing stocks of rAAV [recombinant adeno-associated virus] virions with reduced amounts of empty capsids." Ex. 1010, 5:2–4. Lochrie explains that "[a]fter culturing the host cells with the necessary components for rAAV production, the host cell is harvested and a crude extract is produced." *Id.* at 4:5–6. According to Lochrie, "[t]he resulting preparation will contain, among other components, AAV capsids with genomes containing the heterologous gene (i.e., 'packaged capsids') and AAV capsids lacking genomes (i.e., 'empty capsids')." *Id.* at 4:6–9. Lochrie states that in some embodiments "the method produces a stock of rAAV virions

substantially free of empty AAV capsids, such as a stock wherein at least 75 % to about 99 % or more of the AAV virions present are packaged AAV capsids." *Id.* at 7:1–4. In one example of a specific embodiment, Lochrie states that "[h]uman embryonic kidney-293 cells . . . were used as host cells for the production of rAAV virions" and "72 hr post-transfection, 293 cells were disrupted by microfluidization," the crude lysate was collected and subjected to a two-step filtration, and then "the clarified lysate" was purified using column chromate chromatography. *Id.* at 28:28–29, 29:1–6; *see also* Pet. 21. According to Lochrie, "[t]he rAAV virions were eluted with buffer containing 20 mM NaH2PO4 and 350 mM NaCl," and "[t]he eluant was formulated in 20 mM NaH2PO4, 150 mM NaCl, 5% sorbitol, and 0.1 % Tween-80, at pH 7.4 at a concentration of 4 x 10^{12} vector genomes/milliliter (vg/mL)." Ex. 1010, 29:6–9.

2. Summary of Johnson

Johnson, titled "Effects of Environmental pH on Adenovirus-Associated Virus (39085)," describes a study that found that "AAV infectivity titrations, virus production, and induction of FA stainable antigen regions are all influenced by environmental pH." Ex. 1019, 589. Johnson states that "t]he greatest effect of pH appeared to be its influence on the aggregation of the viral particles." *Id.* Johnson states that the effect of pH on the aggregation of AAV particles was examined by exposing purified AAV particles to preparations of PTA [phosphotungstic acid]." *Id.* Johnson reports that at pH 7.5 "the virus particles occurred singly and were evenly distributed," and that at pH 7.2 and all lower pH's tested "the particles were aggregated and were not evenly distributed in the field but were found in clumps, between which were large empty spaces." *Id.* at 589. According to

Johnson, AAV particles "associate into increasingly large aggregates as the environmental pH is lowered." *Id.* at 585.

3. Claims 5 and 6

With regard to claim 1, from which claims 5 and 6 depend, according to Petitioner, "Lochrie's Example 2 provides an rAAV composition meeting all but three of the limitations of challenged claim 1, each of which differ only slightly in value than the recited elements." Pet. 44 (citing Ex. 1025 ¶ 331). Petitioner further argues that "Huang and Mingozzi describe AAV compositions having the recited concentration ("a concentration exceeding $1x10^{13}$vg/ml"), Johnson teaches the recited pH (pH "between 7.5 and 8.0"), and Liu teaches the recited ionic strength (ionic strength "greater than 200mM"). *Id.* More particularly in regard to claims 5 and 6, Petitioner concedes that the aggregation limitations are not expressly taught by Lochrie or any other of the asserted references. Pet. 55–57. Instead, as with the first ground based on Liu discussed above, Petitioner maintains without persuasive supporting evidence that the limitations were inherent and that a person of ordinary skill in the art "would have reasonably expected" the aggregate limitations to have been satisfied and would have arrived at a composition satisfying the limitation through "routine optimization." Pet. 55–57 (substantially relying on Petitioner's arguments set forth in the Petition under the first ground based on Liu). Patent Owner argues, in part, that Petitioner's contentions in the second ground based on Lochrie fail for

the same reasons as Petitioner's contentions in the first ground based on Liu, which we addressed above.[10] Prelim. Resp. 49–50.

4. Showing of a Reasonable Likelihood of Success

We agree with Patent Owner and find, for substantially the same reasons discussed above in regard to Petitioner's contentions based on Liu in the first ground, that Petitioner's contentions and supporting evidence fail to show a reasonable likelihood of establishing that either claim 5 or claim 6 is unpatentable as obvious over Lochrie, Huang, Mingozzi, Johnson, and Liu. *See supra* III.D.

IV. CONCLUSION

For the foregoing reasons, we determine that Petitioner does not demonstrate a reasonable likelihood of prevailing with respect to either

[10] Patent Owner also argues that Petitioner fails to demonstrate the ionic strength was a recognized result effective variable. Prelim. Resp. 40–42 (citing Pet. 52 (Petitioner arguing that a person of ordinary skill in the art would have been motivated to increase the ionic strength of Lochrie's composition to prevent aggregation)). We recognize that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). We also recognize, however, an "exception" to this *Aller* rule where "the parameter optimized was not recognized to be a result-effective variable." *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). Here, Petitioner fails to establish a known relationship between ionic strength and viral particle aggregation. Rather, the evidence of record teaches that "[t]he mechanism of vector aggregation is not well understood," and while buffer ionic strength is identified as a condition that may affect aggregation, the evidence of record does to show a known relationship between vector aggregation and buffer ionic strength. *See* Prelim. Resp. 41; Ex. 1007, 175; Ex. 2001 ¶ 120. Accordingly, on this record, we agree with Patent Owner that Petitioner fails to sufficiently show for purposes of institution that ionic strength was recognized as a result-effective variable for rAAV aggregation.

claim 5 or claim 6 of the '542 patent.[11] Accordingly, we do not institute *inter partes* review of the '542 patent.

IV. ORDER

Upon consideration of the record before us, it is:

ORDERED that the Petition is *denied* and no trial is instituted.

[11] Because we deny the Petition on the merits, we do not reach Patent Owner's argument for discretionary denial under 35 U.S.C. § 314(a). *See* Prelim. Resp. 51–57.

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