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.

Case No. IPR2023-00609
Patent No. 9,051,542

PETITION FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

In the early 2000's, years before the alleged priority date of U.S. Patent No. 9,051,542 ("the '542 patent"),[1] compositions had been developed to improve storage stability of virus particles for use in gene therapy. One reference, Liu, provided processes for high-yield virus production of $1x10^{15}$ particle units/cell, improved virus purification, and storage compositions that could be used to stably store AAV for extended periods of time. One particular composition stored $1.62x10^{10}$ viral particle units of purified adenovirus in a buffer comprising 25mM Tris, 300mM NaCl, 5mM $MgCl_2$ (ionic strength of ~315mM), 0.0025% polysorbate 80, 5% trehalose, pH7.5 at ~4°C for 7 days. This composition showed no signs of settling or precipitation and no significant change in the number of infectious viral particles during the storage period. Another reference, Lochrie, exemplified a stock composition comprising purified rAAV in 20mM NaH_2PO_4, 150mM NaCl, 5% sorbitol, and 0.1% Tween-80, at pH7.4 and a virus concentration of $4x10^{12}$vg/mL.

The challenged claims are obvious variants of Liu's and Lochrie's compositions. For instance, challenged claim 1 is drawn to compositions comprising a known buffer (*i.e.*, having a pH "between 7.5 and 8.0," excipients comprising

[1] For purposes of this Petition, Petitioners do not challenge the alleged priority date of the '542 patent, but reserves the right to do so in this or other proceedings.

"multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate," and an "ionic strength…greater than 200mM") for storing a known recombinant virus (*i.e.*, "purified, recombinant adeno-associated virus (AAV) vector particles") at known concentrations (*i.e.*, "exceeding $1x10^{13}$vg/ml") and under known preferred conditions (*i.e.*, "without significant aggregation"). Ex.1001, 14:15-26 (claim 1).

To the extent one could argue any differences between the claims and Liu's compositions, it could only be the recited virus concentration. Similarly, Lochrie exemplified an rAAV composition comprising only minor differences in the recited parameters in challenged claim 1: purified rAAV, multivalent ions, a vg/ml concentration just under the recited "exceeding $1x10^{13}$vg/ml" (i.e., $4x10^{12}$vg/ml), a pH just under the recited pH7.5 (i.e., pH7.4), and an ionic strength just under the recited "greater than 200mM" (i.e., 194mM). But nothing of record indicates that these trivial differences between Lochrie's composition and the claims were critical or inventive. Rather, the art of record, Patent Owner's admissions, and expert testimony indicate that modifying Liu's and Lochrie's compositions to achieve the claimed composition would have merely been a matter of routine optimization.

Long before the '542 patent was filed, the prior art (Mingozzi and Huang) had produced purified AAV preparations having concentrations of $>10^{13}$ and $5\text{-}10x10^{13}$vg/ml, and Mingozzi had successfully used such preparations to deliver

transgenes in mice. The prior art also taught that AAV aggregation is pH dependent, with particles agglomerating into increasingly large aggregates as pH is lowered, but observing no aggregation at pH7.5 (Johnson). Additionally, Liu observed no signs of settling or precipitation or changes in infectious particle numbers after storing its composition at an ionic strength of ~315mM and pH7.5 for 7 days. Thus, the recited virus concentration, pH, ionic strength, and lack of "significant aggregation" are not inventive, with the latter merely recognizing a natural event flowing from Liu's and Lochrie's compositions and obvious variants thereof. Because a POSA would have been motivated and reasonably expected success from modifying Liu's and Lochrie's compositions to develop storage-stable rAAV compositions, the rAAV composition recited in claim 1 of the '542 patent is unpatentable.

The challenged dependent claims do not recite any patentable distinctions over the prior art. Instead, they merely recite additional limitations that were either well-known (Pluronic® F68) and/or the result of routine optimization (an average particle radius of less than about 20nm and recovery of at least about 90% following filtration through a 0.22μm filter). Thus, challenged claims 2, 5, and 6 are also unpatentable.

Petitioners respectfully submit there is a reasonable likelihood it will prevail in showing the challenged claims are unpatentable. That position is supported by the art of record, the POSA's knowledge, Patent Owner's admissions in the '542 Patent

and during prosecution, and by the declaration of Dr. Amiji (Ex.1025), an expert in formulating dispersions of therapeutic biologics.

II. REQUIREMENTS FOR *INTER PARTES* REVIEW UNDER 37 C.F.R. §42.104

A. Grounds for Standing

Petitioners certify that (1) the '542 patent is available for *inter partes* review ("IPR") based on its March 19, 2010, filing date (Ex.1001, (22)), and (2) Petitioners are not barred or estopped from requesting review on the grounds identified.

B. Identification of Challenges

Pursuant to 37 C.F.R. §§42.104(b) and 42.22(a)(1), Petitioners request review and cancellation of claims 1, 2, 5, and 6 of the '542 patent on the following grounds:

Ground	Claim(s)	Basis	References
1	1, 2, 5, and 6	§103	Liu in view of Huang and Mingozzi
2	1, 2, 5, and 6	§103	Lochrie in view of Huang, Mingozzi, Johnson, and Liu

III. THE '542 PATENT

The '542 patent purports to have developed isotonic compositions with high ionic strength to solve the "problem" of concentration-induced viral aggregation. Ex.1001, 1:41-66, 5:7-10; Ex.1025, ¶78. The patent purports to provide "[c]ompositions and methods…for preparation of concentrated stock solutions of AAV virions without aggregation" and, in particular, "high ionic strength solutions…that are nonetheless isotonic with the intended target tissue…achieved

using salts of high valency." Ex.1001, Abstract. But the relationship between high-valency salts and ionic strength was well-known in the art by June 2004, and isotonic solutions having high ionic strength had already been used in virus compositions. Ex.1025, ¶¶66-71, 79.

A. The Challenged Claims

Independent Claim 1 recites:

> A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising:
>
> purified, recombinant AAV vector particles at a concentration exceeding $1x10^{13}$ vg/ml up to $6.4x10^{13}$ vg/ml;
>
> a pH buffer, wherein the pH of the composition is between 7.5 and 8.0; and
>
> excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate; wherein the ionic strength of the composition is greater than 200 mM, and wherein the purified AAV vector particles are stored in the composition without significant aggregation.

Ex.1001, 14: 5-26; Ex.1025, ¶80. Dependent claim 2 recites that the composition further comprises Pluronic® F68. Ex.1001, 14:27-28. Dependent claim 5 recites that the AAV particles have an average particle radius of less than about 20nm as

measured by dynamic light scattering. *Id.*, 14:34-37. Dependent claim 6 recites that recovery of the AAV particles is at least about 90% following filtration of the composition through a 0.22μm filter. *Id.*, 14:38-41; Ex.1025, ¶81.

B. Patent Owner's Admissions in the Specification

"Admissions in the specification regarding the prior art are binding on the patentee for the purposes of a later inquiry into obviousness." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007); *see also* "Updated Guidance on the Treatment of Statements of the Applicant in the Challenged Patent in Inter Partes Reviews Under §311," June 9, 2022, at 4 ("If an IPR petition relies on admissions in combination with reliance on one or more prior art patents or printed publications, those admissions do not form 'the basis' of the ground and must be considered by the Board in its patentability analysis."). The '542 patent admissions relate to elements of the challenged claims that were known in the art, the motivation to develop the claimed compositions, and a reasonable expectation of success in doing so.

The patent admits that the problem of concentration-induced AAV aggregation was well-known by June 2004. *See* Ex.1001, 1:41-64 (citing references from the early 2000s, including Huang, Wright, and Croyle). The patent admits that such aggregation was known to be undesirable, as it compromises stability, effectiveness, and testing protocols, and increases the potential for immunogenic

reactions upon administration to a subject. *Id.*, 2:9-47. The patent admits that "in vivo administration of AAV2 vectors to certain sites, such as the central nervous system, may require small volumes of highly concentrated vector." *Id.*, 2:10-14. These admissions acknowledge a motivation to develop concentrated AAV compositions for storage that prevent aggregation. *Id.*, 14:26; *see* Ex.1025, ¶¶48-54.

The patent admits that empty capsids contribute to concentration-induced aggregation. Ex.1001, 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."). The patent admits that "4.4 to 18x10^{14} ***particles***/ml" are "very high concentrations" and that "[i]n commonly used buffered-saline solutions, significant aggregation occurs at concentrations of 10^{13} ***particles***/mL." *Id.* 1:46-48, 7:13-17 (emphases added); *see also* 4:65-67 (discussing vector aggregation in terms of virus ***particles***/ml) (emphasis added). These admissions acknowledge that virus titers measured in particles/ml were considered relevant for assessing concentration-induced AAV aggregation. *See* Ex.1025, ¶47.

The patent admits "[i]t is known that high salt concentrations increase AAV2 vector solubility." Ex.1001, 4:67-5:4 ("highly concentrated AAV2 vectors recovered from gradients generally remain soluble in concentrated CsCl"). The patent admits the prior art "reported that at concentrations exceeding 0.1 mg/mL, AAV2 vectors

require elevated concentrations of salt to prevent aggregation." *Id.*, 1:52-55. And the patent admits that "[s]alt species with multiple charge valences…are commonly used as excipients in human parenteral formulations…." *Id.*, 5:10-15. These admissions acknowledge that a POSA would have reasonably expected success in storing purified AAV particles in high ionic strength buffers using multivalent salt species without observable aggregation. Ex.1001, 14:25-26; *see* Ex.1025, ¶¶66-71.

The patent admits that "the compositions and methods of the present invention may also be useful with other AAV serotypes/variants, or other viral vectors such as adenoviruses." Ex.1001, 5:67-6:4; *see also* 1:65-2:8 (analogizing to prior adenovirus research), 9:7-18 (same). The patent admits that the challenges and motivations regarding AAV aggregation are similar to those encountered when developing compositions for storing other protein therapeutics. *Id.*, 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). These admissions acknowledge that prior art teachings directed to stability of adenoviruses and therapeutic proteins are relevant to developing AAV compositions.

The patent admits that AAV aggregation may be assessed by, for example, dynamic light scattering (DLS), and that average particle radius ("Rh") "values >20nm are deemed to indicate the occurrence of some level of aggregation."

Id., 9:25-27. This admission acknowledges that an average particle radius (Rh) of less than about 20nm as measured by DLS merely indicates aggregation was prevented.

C. Prosecution of the '542 Patent

Prosecution of the '542 patent took over five years and involved five substantive Office Actions (two final and three non-final), one Request for Continued Examination, and an Examiner Interview. Ex.1002, 82, 143, 162, 181, 212, 310, 323. The extended length of time for prosecution of this patent was a direct result of Patent Owner's erroneous belief that it had provided the first disclosure of high ionic strength, isotonic solutions using multivalent ions (*see*, Ex.1001, Abstract; Ex.1002, 36 (original claim 1)), and its attempts to gain allowance through the piecemeal inclusion of additional limitations.

For instance, in rejecting the original claims for anticipation and obviousness, the Examiner relied on Vihinen-Ranta's canine parvovirus compositions and Zolotukhin's use of buffers comprising 1M NaCl during AAV purification. Ex.1002, 85-87. The Examiner also cited Andersson, Zhang, and Chen for their teachings of virus concentration, Pluronic® F68, pH, and/or various salts for reducing protein aggregation. *Id.*, 89-92, 148-54, 184-91, 216-24. Patent Owner argued Zolotukhin was not relevant because its high ionic strength buffer was only used while AAV

was "in the process of being purified," and the other references do not relate to AAV. *Id.*, 130-31, 152-53, 169, 171.

The Examiner rejected those arguments (*id.*, 145-48), so Patent Owner added the virus concentration limitation to overcome the §102 rejection over Zolotukhin. *Id.*, 166. The Examiner maintained the §103 rejections over Zolotukhin (*id.*, 183-191), so Patent Owner continued limiting the claims. Patent Owner first added the pH range, which failed to overcome the rejections, so Patent Owner then limited the claims to "recombinant" AAV particles and argued that Zolotukhin only teaches preventing aggregation between virus particles and host-cell proteins, and did not recognize or solve virus self-aggregation. *Id.*, 200, 216-224, 240-243.

The Examiner ultimately capitulated after Patent Owner agreed to further modify the claims by an Examiner's Amendment. *Id.*, 340 (limiting to AAV "vector" particles, adding specific multivalent ions, and replacing "wherein aggregation…is prevented" with "wherein the purified AAV vector particles are stored in the composition without significant aggregation"). But even the issued claims merely combine limitations that were known in the art. As further explained in §XI *infra*, the challenged claims were allowed because the Examiner (1) overlooked critical teachings in the cited art; (2) was not aware of the highly relevant asserted art; and (3) was led astray by Patent Owner's irrelevant arguments concerning causes of virus self-aggregation.

IV. BACKGROUND

A. AAV Was One of the Most Actively Investigated Gene Therapy Vehicles by June 2004

AAV is a replication-defective, non-enveloped parvovirus consisting of a protein shell surrounding a single-stranded DNA genome. Ex.1025, ¶30. Years before the '542 patent was filed, AAV had "received considerable attention in the field of gene therapy, because of [its] ability to mediate long-term gene transfer in the absence of significant toxicity." Ex.1007, 174; Ex.1025, ¶31. AAV was touted as "a promising vector for human gene transfer" due to its ability to "infect both dividing and non-dividing cells and establish a latent state with high frequency." Ex.1007, 174. AAV vectors were also known to be less immunogenic than other viral vectors, "a factor which may contribute to enhanced duration of therapeutic gene expression in vivo." *Id.* Other well-known attributes of AAV vectors include their "high affinity for the target tissue," and "the ability to accommodate the desired transgene of interest." Ex.1013, 1281. By June 2004, AAV vectors had been successfully formulated for use in investigative studies. Ex.1006, 10497; Ex.1007, 174; Ex.1009, [0002]; Ex.1012, Abstract, S-9; Ex.1005, S286; Ex.1025, ¶¶32-33.

It was also known that "because AAV and adenovirus are both non-enveloped viruses developed as gene transfer vectors, studies on the latter can provide guidance for AAV vector formulation development." Ex.1007, 174. Researchers had initiated

side-by-side studies with both adenovirus and AAV, and reported AAV to be "significantly more stable than the adenovirus." Ex.1013, 1281, 1283. Thus, skilled artisans would have understood that compositions capable of storing adenovirus without aggregation should produce similar results for AAV particles, which are significantly more stable. Ex.1025, ¶34.

B. Gene Therapy Requires High Virus Concentrations

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. By June 2004, however, density-based methods, such as cesium chloride or iodixanol gradient ultracentrifugation, were routinely used to separate full (genome-containing) vector particles from lighter-weight empty capsids. Ex.1007, 175; Ex.1025, ¶38.

By June 2004, it was known that high AAV vector titer is required for therapeutic efficacy. Ex.1025, ¶39. And since viral-based gene therapies are typically delivered by parenteral injection, which require small volumes, it was understood that "[t]o achieve high level of gene transfer and ensure the safety of vector administration it is desirable to deliver high doses of [AAV] vector in small

volumes." Ex.1005, S286; *see also* Ex.1008, 405, 410; Ex.1025, ¶40. As Wright explained, "AAV vectors are typically prepared at final purified concentrations in the range of 10^{11} to 10^{13} vg/ml." Ex.1007, 176. Thus, there was a recognized desire in the art to achieve high-concentration AAV vector compositions to maximize vector doses and gene transfer safety and efficiency. Ex.1025, ¶¶39-41.

Advances in vector production technology before June 2004 had resulted in the routine isolation of therapeutically useful amounts of rAAV particles, permitting "widespread use of this technology for clinical applications." Ex.1012, Abstract, S-9; Ex.1025, ¶¶42-46. Researchers had also routinely achieved high titers of AAV in the final virus composition using known purification and concentration methods. Ex.1025, ¶¶42-43 For instance, Clark reported that improved chromatography-based purification methods had increased AAV "vector purity, biological potency, and process throughput" and that by using such techniques, "[r]ecoveries were on average >70% with purity in excess of 95%." Ex.1012, S12-13. Potter likewise described "an improved protocol adapted for large-scale production of a preclinical grade rAAV" in a high ionic strength (500mM NaCl) buffer "consisting of three sequential chromatography purification steps resulting in highly purified (99.9% pure) and infectious (particle-to-infectivity ratios less than 10) vector preparations." Ex.1011, 429; *see also id.*, 417-419. Additionally, Mingozzi used repeated CsCl

gradient centrifugation to purify genome-containing AAV-2 and AAV-5 vectors and achieved yields of $>10^{13}$vg/ml. Ex.1006, 10497.

Thus, by 2004, researchers had developed technologies to achieve stable, high-titer purified AAV vector compositions at concentrations of $>10^{13}$vg/ml. Ex.1025, ¶¶42-46.

C. Aggregation at High Virus Concentration was a Recognized Problem with Known Solutions

As the '542 patent admits, aggregation of AAV particles at higher AAV vector concentrations was a recognized problem before June 2004. Ex.1001, 1:41-55. The patent acknowledges that aggregation causes losses during purification, inconsistencies in testing, adverse immune responses, and negatively influences biodistribution following administration. *Id.*, 2:9-17; *see also* Ex.1007, 175-76. What the patent ignores, however, was that by the early 2000s researchers understood the factors contributing to aggregation and had already developed successful approaches to reduce aggregation and improve virus stability. Ex.1025, ¶48.

For instance, Huang acknowledged that "at high concentrations, AAV virions form aggregates of different sizes in a range of different buffer systems and storage conditions" and that "[t]he size of aggregates appears to be concentration dependent." Ex.1005, S286. Huang then developed new compositions to tackle that problem,

noting "[o]ur preliminary finding indicated that some of our formulations could lead to a 30-50% reduction in the size of aggregates at high vector concentrations." *Id.* Furthermore, Wright taught that "empty capsids, whose size and surface characteristics are similar to that of genome-containing vector particles, contribute to particle aggregation." Ex.1007, 175; Ex.1025, ¶¶37. 47. Wright also described "highly purified vector preparations at concentrations of 5×10^{13} cp/ml that are stable in a non-aggregated, monomeric state when stored at 2 to 8°C." Ex.1007, 175.

With high-concentration compositions of AAV having been achieved, it opened the door for skilled artisans to optimize other components known to stabilize high-concentration virus preparations. Ex.1025, ¶¶49-60. Those components, including pH, divalent cations, and ionic strength, had been successfully used in Liu, Lochrie, and other prior art. *Id.* For instance, Wright taught that "purification conditions that may affect aggregation include buffer ionic strength and pH, shear and vector concentration." Ex.1007, 175. Wright also taught that initial aggregation "could be reversed by adjusting buffer pH" (*id.*, 176), and Johnson observed that "aggregates of virus were present at pH 7.2 and below, but at pH 7.5 no aggregates were seen" (Ex.1019, 589. Liu demonstrated successful storage of adenovirus particles at an ionic strength >300mM (Ex.1009, Example 17), and Potter's "improved protocol" for production of preclinical grade rAAV involved eluting and storing the stocks in a high ionic strength buffer (500mM NaCl) (Ex.1011, 417-419).

Building on these developments, Liu taught the desirability of stably storing viral vectors during large-scale production/purification in compositions that maintain the activity of the virus for extended periods of time. Ex.1009, [00186]-[00187]. Liu taught that its purification and storage compositions contain high ionic strength, a divalent metal salt, such as calcium chloride, magnesium chloride, and magnesium sulfate, pH7.5, and can contain a nonionic surfactant, such as Pluronic F68. *Id.*, [00189], [00191], and [00366]. Similarly, Lochrie examined the impact of pH and temperature on stability of empty AAV particles, and developed methods for producing stable stocks of genome-containing particles. Ex.1010, 5:2-7:3, Examples 3-4.

Thus, before the alleged priority date of the ’542 patent, skilled artisans had developed robust techniques to achieve stable, high-concentration virus compositions. Ex.1025, ¶¶49-59.

V. LEVEL OF ORDINARY SKILL IN THE ART

A POSA working in the field of the ’542 patent on June 1, 2004, would have possessed 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.

VI. CLAIM CONSTRUCTION

The Board construes claims per *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). 37 C.F.R. §42.100(b). Claims should only be construed to the extent necessary to resolve a controversy. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). For this proceeding, no terms require express construction, because the prior art's disclosures are commensurate with the '542 patent disclosures and Patent Owner's admissions during prosecution. Thus, the prior art covers the claims under any construction consistent with *Phillips*. For purposes of this proceeding, the petition analyzes the claim terms under their "plain and ordinary meaning."[2]

[2] Patent Owner's infringement and validity positions in the co-pending litigation may raise controversies that need to be resolved through claim constructions not implicated here given the similarities between the prior art and the '542 patent. Specifically, Petitioners reserve the right to argue in an appropriate forum that certain limitations in the challenged claims are indefinite as applied, including the term "significant aggregation." *See e g.*, Ex.1023, 73-74.

VII. ASSERTED ART

A. Liu

Liu is a PCT Publication of International Application Number PCT/US02/35049. Ex.1009, (21). Liu was published in May 2003, and qualifies as prior art under 35 U.S.C. §102(b). *Id.*, (43); Ex.1025, ¶101.

Liu describes methods of preparing viral vector particles and compositions. Ex.1009, Abstract; Ex.1025, ¶¶102-105, 107. Example 17 discloses storage compositions that "effectively maintain a stable population of adenoviral vector particles during the viral vector particle production and/or purification process." Ex.1009, [00365]. Adenoviral vector particle-infected cells were processed and the particles were purified "to obtain an adenoviral vector particle composition comprising a population of adenoviral vector particles in a temporary storage buffer (25mM Tris, 300mM NaCl, 5mM $MgCl_2$, 0.0025% polysorbate 80, 5% trehalose, pH 7.5)." Ex.1009, [00365]; Ex.1025, ¶106. The composition was maintained at about 4°C for 7 days in the temporary storage buffer. Ex.1009, [00367].

Liu reports that visual inspection showed "no signs of settling or precipitation," and "no significant decrease in particle number over the 7 day test period." *Id.*, [00369], Table 15. Liu concludes these results demonstrate the stability of the adenoviral particles in the storage composition and the suitability of using such a

composition for storing virus particles during the production process. *Id.*, [00371]; Ex.1025, ¶107.

B. Huang

Huang is an abstract published in 2000, and qualifies as prior art under 35 U.S.C. §102(b). Ex. 1005, S286; Ex.1025, ¶110.

Huang teaches that to achieve high levels of gene transfer and ensure the safety of AAV vector administration, one must deliver high doses of vector in small volumes. Ex. 1005, S286; Ex.1025, ¶111. Huang notes that at high concentrations, AAV virions form aggregates of different sizes and that the size of these aggregates is concentration dependent. Ex. 1005, S286. Huang describes concentrating an AAV vector preparation and observing that when the concentration reached 5-10x10^{13}vg/ml, gene transfer efficiency was 10 to 100-fold lower compared to the same vector administered at the same dose but having a concentration of 1-5x10^{12}vg/ml. *Id.* Huang conducted a series of formulation studies to prevent and dissolve AAV aggregates, and reported a 30-50% reduction in the size of aggregates at high vector concentrations for some of the compositions. *Id.*; Ex.1025, ¶112.

C. Mingozzi

Mingozzi is a scientific article published in 2002, and qualifies as prior art under 35 U.S.C. §102(b). Ex. 1006; Ex.1025, ¶113.

Mingozzi teaches that AAV vectors "have been shown to efficiently transfer genes into 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; Ex.1025, ¶114.. Mingozzi examines the efficiency of gene transfer in mice using AAV-2 and AAV-5 vectors. Ex.1006, 10497; Ex.1025, ¶115. Mingozzi describes the purification of both vectors by repeated CsCl gradient centrifugation, and reports final concentrations of $>10^{13}$ vg/ml. *Id.* Both preparations led to productive hepatic gene transfer. Ex.1006, 10498, FIG. 1; Ex.1025, ¶115.

D. Lochrie

Lochrie is a PCT Publication of International Application Number PCT/US02/37944. Ex.1010, (21); Ex.1025, ¶108. Lochrie qualifies as prior art under 35 U.S.C. §§102(a) and 102(e) based on its publication date of June 5, 2003, and its international filing date of November 26, 2002, respectively. Ex.1010, (22), (43).[3]

[3] Petitioners reserve the right to establish that Lochrie is entitled to an effective prior art date of November 26, 2001, based on its priority data, should Patent Owner attempt to antedate Lochrie's international filing date. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375 (Fed. Cir. 2015).

Lochrie is directed to efficient and commercially viable methods for producing stocks of recombinant AAV virions with reduced amounts of empty capsids. *Id.*, 5:2-4; Ex.1025, ¶109. The methods produce stocks of rAAV virions substantially free of empty capsids in which at least 75% to about 99% or more of the virions present in the stocks contain viral genomes. Ex.1010, 7:1-3. Example 2 describes the production and purification of rAAV virions from human embryonic kidney-293 cells by microfluidization, two-step filtration, and column chromatography. *Id.*, 28:22-29:7. The eluant was formulated in 20mM NaH_2PO_4, 150mM NaCl, 5% sorbitol, and 0.1% Tween-80, at pH7.4 at a concentration of $4x10^{12}$vg/mL. *Id.*, 29:7-9.

E. Johnson

Johnson is an article published by the Proceedings of the Society for Experimental Biology and Medicine in 1975. Ex.1019, 1. Johnson qualifies as prior art under 35 U.S.C. §102(b); Ex.1025, ¶122.

Johnson examined the effects of pH on AAV aggregation and observed that AAV particles "associate into increasingly large aggregates as the environmental pH is lowered." Ex.1019, 585; Ex.1025, ¶123. Specifically, Johnson purified AAV by CsCl gradient, dialyzed against physiological saline at various pHs, and examined particle aggregation by electron microscopy. Ex.1019, 585-86. Johnson discloses that at pH7.5, "the virus particles occurred singly and were evenly distributed" and

"no aggregations were seen," while at pH7.2 and all lower pHs tested, "the particles were aggregated" into clumps "containing thousands of particles." *Id.*, 589; Ex.1025, ¶124. Johnson concludes that "[t]he greatest effect of pH appeared to be its influence on the aggregation of the viral particles" at pH <7.5. Ex.1019, 589; Ex.1025, ¶125.

VIII. GROUND 1: CLAIMS 1, 2, 5, AND 6 ARE OBVIOUS OVER LIU IN VIEW OF HUANG AND MINGOZZI

Each element of claims 1, 2, 5, and 6 of the '542 patent is present in the compositions disclosed in Liu, Huang, and Mingozzi, which are from the same field of endeavor and pertinent to the problem the '542 patent alleges to solve. *See, e.g., Wyers v. Master Lock Co.*, 616 F.3d 1231, 1237 (Fed. Cir. 2010). The '542 patent relates to compositions for AAV preparation and storage that maintain high infectivity titer and transduction efficiency and purportedly reduce concentration-induced viral vector aggregation. Ex.1001, Abstract, 1:41-66, 3:11-15. Liu, Huang, and Mingozzi likewise relate to viral compositions, including AAV compositions, for use in gene therapy. Ex.1009, [0005]-[0006]; Ex.1005, S286; Ex.1006, 10497. Liu teaches that its compositions can stabilize virus during storage (Ex.1009, [00187], [00371]), Huang teaches that its high-titer compositions reduce AAV aggregation (Ex.1005, S286), and Mingozzi teaches that its high-titer compositions achieve successful gene therapy (Ex.1006, 10498). A POSA would have been motivated to combine the teachings of Liu, Huang, and Mingozzi, with a reasonable

expectation of arriving at the challenged claims. This position is consistent with the prior art (*e.g.*, Wright, Clark, Gatlin, and Croyle), Patent Owner's admissions in the '542 patent and during prosecution, and the opinion of Petitioners' expert, Dr. Amiji. Ex. 1025, ¶¶23-25, 274-329. Thus, claims 1, 2, 5, and 6 are unpatentable as obvious.

A. Claim 1 is Obvious Over Liu in View of Huang and Mingozzi

Liu's Example 17 describes a virus composition that expressly meets all but two of the limitations of challenged claim 1. But Liu itself teaches one of the absent limitations ("adeno-associated virus (AAV) vector particles") as being suitable for use in its compositions, and Huang and Mingozzi describe AAV compositions having the recited virus concentration ("a concentration exceeding $1x10^{13}$ vg/ml"). Ex.1025, ¶275.

Claim Limitations	Teachings in Liu/Huang/Mingozzi
A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising: purified, recombinant AAV vector particles	**Liu Example 17**: "demonstrates the ability of the storage compositions of the invention to effectively maintain a stable population of adenoviral vector particles during the viral vector particle production and/or purification processes" (Ex.1009, [00365]). **Liu**: "The invention provides particular methods of producing adenoviral vector particle compositions (particularly replication-deficient recombinant adenoviral vector gene transfer particle compositions), which

	are preferred." *Id.*, [0006]. "Suitable viral vector particles include, for example…adeno-associated viral vector particles (AAV vector particles)" (*id.*, [0008]). **Huang**: describes AAV "Vector Formulations to Prevent and Dissolve Aggregation" (Ex.1005, Title). **Mingozzi**: describes compositions comprising purified AAV-2 and AAV-5. Ex.1006, 10497.
at a concentration exceeding $1x10^{13}$vg/ml up to $6.4x10^{13}$vg/ml	**Liu Example 17**: PU=$1.62x10^{10}$ (Day 0); PU=$8.14x10^{9}$ (Day 7) (Ex.1009, Table 15). **Huang**: "it is desirable to deliver high doses of vector in small volumes." Ex.1005, S286. **Mingozzi**: describes compositions comprising purified AAV-2 and AAV-5 having concentrations >10^{13}vg/ml. Ex.1006, 10497.
a pH buffer, wherein the pH of the composition is between 7.5 and 8.0	**Liu Example 17**: "a population of adenoviral vector particles in a temporary storage buffer (25mM Tris, 300mM NaCl, 5mM $MgCl_2$…pH 7.5)" (Ex.1009, [00366]).
excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate	**Liu Example 17**: "5mM $MgCl_2$" (*id.*).
wherein the ionic strength of the composition is greater than 200mM	**Liu Example 17**: A composition comprising 300mM NaCl and 5mM $MgCl_2$ (*id.*) has an ionic strength of ~315mM. Ex.1025, ¶300.

and wherein the purified AAV vector particles are stored in the composition without significant aggregation.	**Liu Example 17**: "Visual inspection of the glass tubes showed no signs of settling or precipitation over the 7 day period"; "No significant change over the 3 day period in FFU level [number infectious particles] was observed"; "These results demonstrate that viral vector compositions can be stably stored in the temporary storage buffers of the invention for extended periods of time" (Ex.1009, [00369]-[00371]).

The composition of challenged claim 1 is obvious over Liu, Huang, and Mingozzi, when taken with the general knowledge in the field, as evidenced by Wright, Clark, Gatlin, and Croyle, and Patent Owner's admissions. Ex.1025, ¶¶275-311.

1. "A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising: purified, recombinant AAV vector particles"

Liu describes a "storage composition [that] maintains the viral activity of the virus for an extended period of time." Ex.1009, [00187]; Ex.1025, ¶¶276-277. Liu's Example 17 provides "an adenoviral vector particle composition comprising a population of adenoviral vector particles in a temporary storage buffer (25mM Tris, 300mM NaCl, 5mM $MgCl_2$, 0.0025% polysorbate 80, 5% trehalose, pH 7.5)." Ex.1009, [00366]; Ex.1025, ¶278. The adenoviral vector particles were produced by lysing adenovirus-infected cells by microfluidization, and purified by clarifying the cell lysate through a triple-filter system and performing diafiltration by tangential

flow filtration followed by nuclease digestion. Ex.1009, [00366]; Ex.1025, ¶280. Thus, Liu discloses a composition comprising purified virus particles. Ex.1025, ¶¶278-280.

To the extent the preamble of claim 1 is limiting, Liu describes storing its Example 17 composition "at about 4°C for 7 days in the temporary storage buffer" and concludes "[t]hese results demonstrate that the viral vector compositions can be stably stored in the temporary storage buffers of the invention for extended periods of time." Ex.1009, [00367], [00371]. Liu also teaches that "[t]he viral vector particle desirably includes one or more heterologous nucleic acid sequences," and therefore, is recombinant. *Id.*, [0024], Ex.1025, ¶277. Thus, Liu's composition is "for the storage of purified, recombinant" virus vector particles, as recited in challenged claim 1.

During prosecution, Patent Owner argued that compositions obtained at intermediate stages in the purification process, like Liu's Example 17 composition, do not contain a "purified preparation" of virions because the virus is still "in the process of being purified." Ex.1002, 130, 169. The Examiner correctly dismissed these arguments, noting that "the term 'purified' is not specifically defined in the instant disclosure, as being tied to any particular step and/or degree of purification of the AAV particles, or for that matter number of virions associated with such composition as claimed." *Id.*, 147. A POSA would understand that the adenovirus in

Liu's Example 17 composition was purified because the described triple-filter clarification, diafiltration, and nuclease digestion were used to purify the virus, with the purified virus being subsequently placed in a storage composition. Ex.1009, [0005] ("The completely filtered composition can be *further purified* by one or more chromatography steps") (emphasis added), [00154], [00166], [00184]; Ex.1001, 10:44-50 (characterizing nuclease digestion as a "purification method[] to efficiently remove vector surface residual nucleic acids); Ex.1025, ¶280. Thus, Patent Owner's prosecution arguments are inapt.

A POSA would have been motivated to apply Liu's teachings to AAV because Liu disclosed AAV as a "[p]articularly preferred" type of virus to which its methods and compositions should apply. Ex.1009, [0011] ("Particularly preferred types of viral vector particles include adeno-associated viral vector particles"). Moreover, Mingozzi taught that AAV's "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; *see also* Ex.1007, 174 (teaching AAV has "shown significant promise for human gene therapy"); Ex.1012, S-9 (touting AAV's ability "to mediate long-term, robust in vivo gene expression in numerous cell types"); Ex.1025, ¶¶281-282. Thus, a POSA would have been motivated to use purified, recombinant AAV vector particles in Liu's composition. *See PGS Geophysical AS v. Iancu*, 891 F.3d

1354, 1365 (Fed. Cir. 2018) ("The motivation to modify a reference can come from the knowledge of those skilled in the art, from the prior art reference itself, or from the nature of the problem to be solved."); *In re Urbanski*, 809 F.3d 1237, 1244 (Fed. Cir. 2016) (finding a claimed method obvious when prior art provided motivation to modify and suggested desirability of such modification).

During prosecution, Patent Owner argued that adenovirus "is unrelated to AAV," and that "[o]ne of skill in the art of rAAV virion formulations would simply not look to art pertaining to unrelated viruses in order to determine proper conditions to prevent aggregation." Ex.1002, 132 (stating that adenoviruses "are double-stranded DNA viruses, are medium-sized (90-100 nm), and belong to the family *Adenoviridae*" and "cause human respiratory diseases."). But these arguments directly contradict admissions in the '542 patent and the inventors' statement in Wright that prior art teachings directed to adenovirus compositions are relevant to developing AAV compositions. Ex.1001, 1:65-2:8, 5:67-6:4, 9:7-18; Ex.1007, 174 ("because AAV and adenovirus are both non-enveloped viruses developed as gene transfer vectors, studies on the latter can provide guidance for AAV vector formulation development.").

Moreover, Patent Owner's distinctions between adenovirus and AAV lack meaningful differences with respect to "proper conditions to prevent aggregation." Ex.1002, 132. The nature of the viral genome, the family classification of the virus,

and its disease-causing properties (or lack thereof) do not impact the propensity of particles to aggregate. Ex.1025, ¶47. Indeed, years before the '542 patent, Croyle had reported that AAV "is significantly more stable than the adenovirus." Ex.1013, 1283. Thus, even assuming *arguendo* that a POSA would have viewed Liu's Example 17 as being limited to adenovirus, she would have reasonably expected Liu's compositions to provide similar, if not better stability for storing AAV particles. Ex.1025, ¶¶283-284.

Accordingly, Liu renders obvious "[a] composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising: purified, recombinant AAV vector particles," as recited in challenged claim 1. *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (obvious to replace prior art gene with another gene known to lead to protein production, because a POSA would have been able to carry out such a substitution, and the results were reasonably predictable).

2. "at a concentration exceeding $1x10^{13}$vg/ml up to $6.4x10^{13}$vg/ml"

Liu placed 50mL of its Example 17 solution into a sterile bag for storage. Ex.1009, [00367]-[00368]. On day 0, the bag contained $1.62x10^{10}$ viral particle units (PU), corresponding to a concentration of $3.24x10^{8}$vp/mL. Ex.1009, [00126], [00369], Table 15; Ex.1025, ¶285. Assuming that 100% of the particles contained

vector genomes, Liu's composition had an initial concentration of $3.24x10^{8}$vg/mL. Ex.1025, ¶285.

Even if Liu's composition contained a portion of empty viral capsids (i.e., viral particles lacking genomes), a POSA would have been motivated to remove them and increase Liu's virus genome concentration because high concentrations of genome-containing particles are required for therapeutic use. Ex.1005, 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."); *see also* Ex.1009, [00126] (discussing desirability of maximizing recovery of "active viral vector particles"). Patent Owner admitted as much in the '542 patent. *See, e.g.*, Ex.1001, 2:11-14 ("in vivo administration of AAV2 vectors…may require small volumes of highly concentrated vector"). For example, Mingozzi reported that AAV doses of 10^{12}vg/kg resulted in sustained transgene expression in a large-animal (dog) model, which corresponds to doses of $3.2x10^{13}$vg for a 60kg human. Ex.1006, 10497. Moreover, it was known that most parenteral compositions have an injection volume limit of only a few milliliters. Ex.1008, 405, 417-418. Thus, to prepare therapeutically useful amounts of AAV particles via parenteral administration, a POSA would have been motivated to develop compositions having highly-concentrated vector genome. Ex.1025, ¶¶286-288.

A POSA would have been motivated to target concentrations "exceeding $1x10^{13}$ vg/mL," and would have had a reasonable expectation of success in doing so, since the inventors taught in Wright that AAV compositions having such concentrations "are stable in a non-aggregated, monomeric state when stored at 2 to 8°C,"[4] and Mingozzi and Huang both taught that AAV compositions having such concentrations achieve successful gene transfer. Ex.1007, 175 Ex.1006, 10497; Ex.1005, S286; Ex.1025, ¶¶289-290. Although Huang observed lower gene transfer efficiency with such compositions compared to compositions having concentrations of $1\text{-}5x10^{12}$vg/ml, Huang also taught that routine formulation techniques "could lead to a 30-50% reduction in the size of aggregates at high vector concentrations." Ex.1005, S286. Thus, based on Huang, a POSA would have reasonably expected that high-concentration AAV compositions (e.g., $5\text{-}10x10^{13}$vg/ml) could be achieved. Mingozzi proved as much by preparing compositions of purified AAV-2 and AAV-5 having concentrations "$>10^{13}$ vg/ml" and successfully utilizing those compositions for gene transfer in mice. Ex.1006, 10497-98.

A POSA also would have expected success in achieving such concentrations because Liu itself teaches an "advantage of the methods of the invention is in the

[4] *See* §VIII.A.6, *infra*, for role of virus particles in concentration-dependent aggregation.

reduction in the number of empty viral vector particles (viral vector particles that are incomplete, damaged, or lacking genetic material) or 'empty capsids,'" and that the disclosed techniques achieve high-yield production of $1x10^{15}$ particle units/cell having improved purification, concentration, and storage. Ex.1009, [0068], [00271], [0281]; Ex.1025, ¶291. Moreover, by June 2004, methods of generating high yields of AAV, removing empty capsids, and concentrating genome-containing vectors were well-known. *See*, e.g., Ex.1010, 15:15-17:15, 24:5-26:12, Examples; Ex.1012, S-12 (reporting that stable cell lines can yield > $1x10^{14}$ AAV particles per large-scale preparation), Ex.1007, 175 (discussing cesium chloride and iodixanol gradient ultracentrifugation for separating "genome-containing[] vector particles from the lighter empty capsids"); Ex.1005, S286 (reporting that "the same vector prep was concentrated to different concentrations"); Ex.1011, 417-419, 429 (describing "an improved protocol adapted for large-scale production of a preclinical grade rAAV"). A POSA would have understood that such methods could be used to further increase Liu's vector production and concentration. Ex.1025, ¶¶292-293. Indeed, by June 2004, the prior art had already achieved AAV compositions exceeding $1x10^{13}$vg/ml. Ex.1006, 10497; Ex.1005, S286.

Accordingly, "a concentration exceeding $1x10^{13}$vg/ml up to $6.4x10^{13}$vg/ml," as recited in challenged claim 1, was obvious. *Alcon Research, Ltd. v. Apotex Inc.*,

687 F.3d 1362, 1368 (Fed. Cir. 2012) ("if prior art discloses a portion of the claimed range, the entire claim is invalid."); Ex.1025, ¶294.

3. "a pH buffer, wherein the pH of the composition is between 7.5 and 8.0"

Liu's Example 17 composition comprises "a population of adenoviral vector particles in a temporary storage buffer" at "pH 7.5." Ex.1009, [00366]. Thus, the pH of "between 7.5 and 8.0" recited in challenged claim 1 is anticipated. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) ("a disclosure that anticipates under §102 also renders the claim invalid under §103, for 'anticipation is the epitome of obviousness,'") (internal citation omitted); *In re Wertheim*, 541 F.2d 257, 267 (CCPA 1976) ("the disclosure in the prior art of any value within a claimed range is an anticipation of the claimed range."); Ex.1025, ¶¶295-296.

4. "excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate"

Liu's Example 17 composition contains "5mM $MgCl_2$" (Ex.1009, [00366]) and, therefore, contains "excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate," as recited in challenged claim 1. Ex.1025, ¶¶297-298.

5. "wherein the ionic strength of the composition is greater than 200mM"

Liu's Example 17 composition contains "300mM NaCl, 5mM $MgCl_2$," yielding an ionic strength of ~315mM. Ex.1009, [00366]; Ex.1025, ¶¶299-301. Thus, the ionic strength of "greater than 200mM" recited in challenged claim 1 is anticipated. *Connell*, 722 F.2d at 1548; *Wertheim*, 541 F.2d at 267.

6. "wherein the purified AAV vector particles are stored in the composition without significant aggregation"

A POSA would have reasonably expected the obvious variants of Liu's Example 17 composition discussed above to prevent aggregation.[5] Liu reported "no signs of settling or precipitation over the 7 day [storage] period" and "[n]o significant change in the number of viral particles or infectious viral particles." Ex.1009, [00369], [00371]; Ex.1025, ¶302. Liu concludes that "[t]hese results demonstrate that viral vector compositions can be stably stored in the temporary storage buffers of the invention for extended periods of time." Ex.1009, [00371]; Ex.1025, ¶302. A POSA would have reasonably expected AAV particles to exhibit even greater stability than the adenovirus tested in Liu's composition, since Croyle taught that

[5] Preventing aggregation should be evidence of lack of aggregation, but does not inform a POSA of what exactly qualifies as "without significant aggregation." *Supra*, n.2.

AAV "is significantly more stable than the adenovirus." Ex.1013, 1283; Ex.1025, ¶303.

Although Liu's Table 15 reports the number of virus particles, rather than genomes, the '542 patent admits empty capsids also contribute to virus aggregation. Ex.1001, 1:60-64 ("empty capsids…contribute to particle concentration."); *see also* 1:46-48, 4:65-67, 7:13-17 (discussing aggregation in the context of concentrations measured in particles/ml). In Wright, the inventors "[a]ssum[ed] that full vector particles and empty capsids aggregate by a similar mechanism." Ex.1007, 175. This is consistent with the general understanding that the factors contributing to concentration-induced AAV aggregation are independent of whether the particles contain a viral genome. Ex.1025, ¶47. That is, aggregation should not differ between equal AAV concentrations of "vp" versus "vg." Thus, a POSA would have reasonably expected Liu's composition having a concentration of $3.24x10^{8}$***vp***/mL to exhibit levels of aggregation similar to a composition having a concentration of $3.24x10^{8}$***vg***/mL. Ex.1025, ¶¶304-305.

A POSA likewise would have expected Liu's composition to prevent aggregation at even higher virus concentrations, since the inventors themselves had already reported that highly purified AAV vector preparations at concentrations of $5x10^{13}$cp/ml "are stable in a non-aggregated, monomeric state when stored at 2 to 8°C" without a freeze-thaw cycle. Ex.1007, 175. Because particle aggregation was

known to be independent of genome packaging, Wright's $5x10^{13}$ "cp/ml" AAV composition would be expected to exhibit similar levels of aggregation as a $5x10^{13}$ "vg/ml" AAV composition. Ex.1025, ¶¶304-305. Thus, compositions capable of storing purified AAV vector particles at the claimed concentrations "without significant aggregation" were described in Wright and, therefore, cannot form the basis for patentability. *In re Slayter*, 276 F.2d 408, 411 (CCPA 1960) ("A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus.").

To the extent the obvious variants of Liu's composition with AAV at the recited concentration do not prevent aggregation, a POSA would have been motivated to develop such based on Liu's teaching that "[t]he presence of viral vector particle aggregates is unfavorable since the clumping of the viral vector particles could result in an increased host immune response to the viral vector particles." Ex.1009, [00262]. Furthermore, Huang linked virus aggregation to reduced gene transfer efficiency (Ex.1005, S286), and the inventors acknowledged "potentially deleterious" consequences of vector aggregation in Wright (Ex.1007, 176). Indeed, the '542 patent admits it was well known that "vector aggregation is a problem that needs to be fully addressed." *See, e.g.*, Ex.1001, 2:64-65; *see also id.*, 1:41-64 (citing publications from the early 2000s, including Huang, Wright, and Croyle, that discuss AAV aggregation), 2:9-3:4 (discussing known problems caused

by AAV aggregation). Thus, a POSA would have been motivated to store AAV vectors in compositions that minimize particle aggregation. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."); Ex.1025, ¶¶306-307.

Claim 1 of the '542 patent simply recites a composition comprising components that were obvious over the prior art, and a "wherein" clause that describes the natural result flowing form such compositions as being "without significant aggregation." As discussed above, the structural components of the challenged claims were obvious based on the teachings of Liu, Huang, and Mingozzi, and so the natural result flowing from such compositions alone or in combination is also obvious. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) ("[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer."); *see also* Ex.1025, ¶¶308-311.

For at least these reasons, challenged claim 1 is unpatentable.

B. Claim 2 is Obvious Over Liu in View of Huang and Mingozzi

Claim 2 recites a composition of claim 1 "further comprising ethylene propylene oxide block copolymer Pluronic® F68." Ex.1001, 14:27-28. Liu motivated the use of Pluronic® F68 in its compositions with a reasonable expectation of success by teaching that "[i]n another preferred embodiment, the temporary storage composition further comprises a nonionic surfactant," including "Pluronic F68." Ex.1009, [00189].

A POSA would have been further motivated and expected success from including Pluronic® F68 in Liu's Example 17 composition, as modified by Huang and Mingozzi, based on the inventors' teachings in Wright that "addition of the surfactants Polysorbate 80 or Pluronic® F68…effectively prevent losses due to non-specific binding during [virus] vector sampling and transfer," and Croyle's disclosure that AAV compositions comprising this detergent have an expiration date of 240 days when stored at 4°C. Ex.1007, 175, 176; Ex.1013, 1284 (Table 3, composition comprising "0.01% Pluronic"), 1288 (identifying detergent as "Pluronic block copolymer F68"); *see also* Ex.1025, ¶¶312-316.

Accordingly, the composition of challenged claim 2 was obvious.

C. Claim 5 is Obvious Over Liu in View of Huang and Mingozzi

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]." Ex.1001, 14:34-37. Patent Owners admit that claim 5 merely "provide[s] [a] method[] of ensuring that there is no substantial aggregation." Ex.1023, 72; *see also* Ex.1025, ¶¶316-317. If true, and because the Liu compositions prevent aggregation, then this limitation provides no patentable weight to claim 5. Indeed, during prosecution, Patent Owner never disputed the Examiner's conclusion that the "average particle radius" limitation is an "inherent characteristic feature[] of the purified viral composition" disclosed in the cited references. Ex.1002, 86-88, 91, 146, 151, 154, 188, 191, 220, 318.[6] Patent Owner's silence constitutes a binding admission. *TorPharm, Inc. v. Ranbaxy Pharms., Inc.*, 336 F.3d 1322, 1330 (Fed. Cir. 2003) ("in ascertaining the scope of an issued patent, the public is entitled to equate an inventor's acquiescence to the examiner's narrow view of patentable subject matter with abandonment of the rest.").

The '542 patent admits that AAV2 particles have a diameter of ~26nm (Ex.1001, 1:29-38); thus, a POSA would have reasonably expected that, because Liu's compositions prevented aggregation, AAV particles stored therein and in

[6] Patent Owner merely made legally erroneous arguments that inherency is inappropriate in obviousness rejections. Ex.1002, 131, 133, 170, 172, 204, 242; *Univ. of Penn v. Eli Lilly and Co.*, 737 Fed. Appx. 1006 (Fed. Cir. 2018) (affirming Board's decision holding claims unpatentable for inherent obviousness).

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.").

To the extent modifications to Liu's composition, beyond those described above, would be required to achieve the features of claim 5, a POSA would have been motivated to make such changes to minimize any potential aggregation. As explained above, Huang linked virus aggregation to reduced gene transfer efficiency (Ex.1005, S286), and the inventors taught "potentially deleterious consequence of vector aggregation" in Wright (Ex.1007, 176). Thus, a POSA would have been motivated to minimize AAV aggregation through routine optimization of known stabilization factors. Ex.1025, ¶319; *KSR*, 550 U.S. at 421. Patent Owner admitted as much in the '542 patent. *See, e.g.*, Ex.1001, 2:9-47 (discussing known drawbacks to aggregation); *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.").

A POSA 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 POSA 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. *Senju*, 780 F.3d at 1353.

Accordingly, the compositions of challenged claim 5 are obvious.

D. Claim 6 is Obvious Over Liu in View of Huang and Mingozzi

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." Ex.1001, 14:38-41. Patent Owners admits that claim 6 merely "provide[s] [a] method[] of ensuring that there is no substantial aggregation." Ex.1023, 72; *see also* Ex.1025, ¶¶60, 323. If true, because Liu's compositions prevent aggregation (*supra*, § VIII.A.6), then this claim element should provide no patentable weight to claim 6.

Additionally, as discussed above, Patent Owner's silence during prosecution regarding the Examiner's conclusion that this filtration recovery limitation is an "inherent characteristic feature[] of the purified viral composition" disclosed in the

cited references should be viewed as an admission. *TorPharm.*, 336 F.3d at 1330. 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 POSA 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.

The '542 patent does not identify anything critical about the recited recovery rate. The patent merely states that "in various embodiments of the present invention, recovery is improved from less than about 80% to at least about 85%, 90%, 95% or more," suggesting that the critical cutoff (if one exists at all) is greater than 80% recovery. Ex.1001, 9:1-4. The minor advancement of a prior art concept involving only a change of form, proportion, or degree, or the substitution of equivalents doing the same thing by substantially the same means, is not an invention that will sustain a patent, even though the changes may produce better results than prior inventions. *Ex parte Lewin*, No. 2019-003773, 2020 WL 5039330, *11 (PTAB August 17, 2020) (citing *In re Williams*, 36 F.2d 436, 438 (CCPA 1929)).

To the extent claim 6 requires less aggregation than claim 1, a POSA would have been motivated to minimize any potential aggregation in Liu's modified Example 17 composition, since both Wright and Huang linked aggregation to

reduced functional activity of AAV vectors. Ex.1007, 176; Ex.1005, S286. Thus, a POSA would have been motivated to maximize virus recovery from a 0.22μm filter through routine optimization of known stabilization factors. Ex.1025, ¶325; *KSR*, 550 U.S. at 421. Patent Owner admitted as much in the '542 patent. *See, e.g.*, Ex.1001, 2:9-47.

A POSA also would have reasonably expected success in maximizing particle recovery after filtration because she knew that 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). Thus, only routine optimization would be required to improve AAV recovery following filtration of Liu's modified Example 17 composition through a 0.22μm filter. Ex.1025, ¶¶326-329; *Senju*, 780 F.3d at 1353.

Accordingly, the composition of challenged claim 6 was obvious.

IX. GROUND 2: CLAIMS 1, 2, 5, AND 6 ARE OBVIOUS OVER LOCHRIE IN VIEW OF HUANG, MINGOZZI, JOHNSON, AND LIU

Each element of claims 1, 2, 5, and 6 of the '542 patent is present in the combined teachings of Lochrie, Huang, Mingozzi, Johnson, and Liu, which are from the same field of endeavor and pertinent to the problem the '542 patent tried to solve.

See, e.g., Wyers, 616 F.3d at 1237. Lochrie discloses methods for producing rAAV stocks without empty capsids. Ex.1010, 5:2-4. Huang, Mingozzi, and Liu relate to purified viral compositions, including AAV compositions, for use in gene therapy. Ex.1005, S286; Ex.1006, 10497; Ex.1009, [0005]-[0006]. And Johnson teaches that pH7.5 prevents AAV aggregation. Ex.1019, 589. A POSA would have combined the teachings of Lochrie, Huang, Mingozzi, Johnson, and Liu with a reasonable expectation of arriving at the compositions of the challenged claims. This position is consistent with the prior art (*e.g.*, Wright, Clark, Croyle, and Gatlin), Patent Owner's admissions in the '542 patent and during prosecution, and the opinions of Dr. Amiji. Ex.1025, ¶¶26-28, 330-387. Thus, claims 1, 5, and 6 are unpatentable as obvious.

A. Claim 1 is Obvious Over Lochrie in View of Huang, Mingozzi, Johnson, and Liu

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. Ex.1025, ¶331. 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").

Claim Limitations	Teachings in Lochrie/Huang/Mingozzi/Johnson/Liu
A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising: purified, recombinant AAV vector particles	**Lochrie's Example 2**: "Production and Purification of rAAV Virions" "formulated in 20mM NaH_2PO4, 150mM NaCl, 5% sorbitol, and 0.1% Tween-80" (Ex.1010, 28:22-29:9). *See also id.*, 29:13 ("Recombinant AAV stocks purified as in Example 2").
at a concentration exceeding $1x10^{13}$vg/ml up to $6.4x10^{13}$vg/ml	**Lochrie's Example 2**: "at a concentration of 4 x 10^{12} vector genomes/milliliter (vg/mL)" *Id.*, 29:9. **Huang:** "it is desirable to deliver high doses of vector in small volumes." Ex.1005, S286. **Mingozzi**: describes successful gene therapy using compositions comprising purified AAV having concentrations >10^{13}vg/ml. Ex.1006, 10497.
a pH buffer, wherein the pH of the composition is between 7.5 and 8.0	**Lochrie's Example 2**: "formulated in 20 mM NaH_2PO4…at pH 7.4" Ex.1010, 29:8-9. **Johnson**: "At pH 7.5, [AAV] virus particles occurred singly and were evenly distributed" but "showed increasingly large aggregates of particles as the pH was lowered" Ex.1019, 589, 590.
excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate	**Lochrie's Example 2**: "formulated in 20mM NaH_2PO4" (Ex.1010, 29:8).

wherein the ionic strength of the composition is greater than 200mM	**Lochrie's Example 2**: Lochrie's Example 2 has an ionic strength of ~194mM at pH7.4 and ~196mM at pH7.5. Ex.1010, 29:7-9; Ex.1025, ¶¶357-359. **Liu**: reported "[n]o significant change in the number of viral particles or infectious viral particles" after storing virus compositions having an ionic strength of ~315mM. Ex.1009, [00369], [00371]; Ex.1025, ¶300.
and wherein the purified AAV vector particles are stored in the composition without significant aggregation.	**Johnson**: "at pH 7.5 no aggregates were seen." Ex.1019, 589. **Liu**: reported "no signs of settling or precipitation over the 7 day [storage] period" (Ex.1009, [00369], [00371]).

The composition of challenged claim 1 is obvious over Lochrie, Huang, Mingozzi, Johnson, and Liu when taken with the general knowledge in the field, as evidenced by Wright, Clark, Croyle, Gatlin, and Patent Owner's admissions. Ex.1025, ¶¶331-371.

1. "A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising: purified, recombinant AAV vector particles"

Lochrie provides "efficient and commercially viable methods for producing stocks of rAAV virions with reduced amounts of empty capsids." Ex.1010, 5:2-4. Lochrie's Example 2 describes the production and purification of rAAV virions at a concentration of $4x10^{12}$vg/mL formulated in 20mM NaH_2PO_4, 150mM NaCl,

5% sorbitol, and 0.1% Tween-80, at pH7.4. *Id.*, 28:22-29:14. Thus, Lochrie discloses a composition comprising purified rAAV vector particles. Ex. 1025, ¶¶332-334.

To the extent the preamble of claim 1 is limiting, Lochrie describes the rAAV purified in Example 2 as "stocks" (*id.*, 29:13-14), which a POSA would understand are compositions for storage. Ex.1025, ¶332. The '542 patent admits as much. Ex.1001, Abstract (describing its "stock solutions" as "[f]ormulations for AAV preparation and storage").

Accordingly, Lochrie renders obvious "[a] composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising: purified, recombinant AAV vector particles," as recited in challenged claim 1. *See O'Farrell*, 853 F.2d at 903.

2. "at a concentration exceeding $1x10^{13}$vg/ml up to $6.4x10^{13}$vg/ml"

Lochrie's Example 2 composition comprises "a concentration of 4 x 10^{12} vector genomes/milliliter (vg/mL)." Ex.1010, 29:7-9. As discussed above, a POSA would have been motivated to raise the concentration of Lochrie's composition to >$1x10^{13}$vg/mL to deliver increased amounts of AAV particles via parenteral administration based on the successes described in Mingozzi. *Supra* §VIII.A.2 (also

citing Huang, Clark, Gatlin); Ex.1025, ¶¶336-340. Patent Owner admitted as much in the '542 patent. *See, e.g.*, Ex.1001, 2:11-14.

A POSA would have reasonably expected success in achieving such concentrations, since Lochrie itself provides methods for generating high yields of AAV, removing empty capsids, and concentrating genome-containing vectors. Ex.1010, 15:15-17:15, 24:5-26:12, Examples; *see also* Ex.1012, S-12 (reporting that stable cell lines can yield > $1x10^{14}$ AAV particles per large-scale preparation); Ex.1007, 175 (discussing cesium chloride and iodixanol gradient ultracentrifugation for separating "genome-containing[] vector particles from the lighter empty capsids"); Ex.1005, S286 (reporting that "the same vector prep was concentrated to different concentrations"). A POSA would have understood that such methods could be used to successfully increase Lochrie's AAV genome concentration. Ex.1025, ¶¶341-342.

Indeed, by June 2004, the prior art had already achieved AAV compositions exceeding $1x10^{13}$vg/ml. *Supra*, §VIII.A.2 (discussing Huang's disclosure of AAV compositions having concentrations of 5-$10x10^{13}$vg/ml and Mingozzi's successful use of purified AAV-2 and AAV-5 having concentrations >10^{13}vg/ml for gene transfer in mice); Ex.1025, ¶¶343-345. Thus, a POSA would have reasonably expected success in preparing high-concentration AAV compositions (*e.g.*, >$1x10^{13}$ vg/ml) for use in gene transfer therapies.

Accordingly, Lochrie renders obvious "at a concentration exceeding $1x10^{13}$ vg/ml up to $6.4x10^{13}$ vg/ml," as recited in challenged claim 1. *Alcon*, 687 F.3d at 1368.

3. "a pH buffer, wherein the pH of the composition is between 7.5 and 8.0"

Lochrie's Example 2 composition "was formulated in 20 mM NaH_2PO_4…at pH 7.4." Ex.1010, 29:7-9. As discussed in §IX.A.2, a POSA would have been motivated to increase Lochrie's virus concentration to $>10^{13}$vg/ml to prepare therapeutically useful amounts of AAV particles via parenteral administration. Since Patent Owner admitted it was well-known that "significant aggregation occurs at concentrations of 10^{13} particles/mL,"[7] a POSA would have been motivated to modify Lochrie's concentrated composition to prevent such aggregation. Ex.1001, 1:46-49; *see also id.*, 1:55-58; Ex.1007, 175 (reporting aggregation "at concentrations $\geq 10^{14}$ capsid particles (cp)/ml"); Ex.1025, ¶¶346-347. And, as the inventors acknowledged in Wright, pH was a recognized variable to modify. Ex.1007, 175 (listing buffer pH among the known "conditions that may affect aggregation"); Ex.1025, ¶¶72-77, 348.

[7] *See* §VIII.A.6, *supra*, for role of virus particles in concentration-dependent aggregation.

A POSA would have targeted the claimed pH of 7.5 based on Johnson, which examined the effect of pH on aggregation of AAV particles and observed "AAV particles to associate into increasingly large aggregates as the environmental pH is lowered" to below pH 7.5. Ex.1019, 585. Specifically, Johnson reported "aggregates of virus were present at pH 7.2 and below, but at pH 7.5 no aggregates were seen." *Id.*, 589. Thus, a POSA would have been motivated to prevent any concentration-induced aggregation by increasing the pH of Lochrie's composition to 7.5. Ex.1025, ¶¶349-350.

A POSA would have reasonably expected success in raising the pH of Lochrie's composition, since Johnson demonstrated that "[a]t pH 7.5, the virus particles occurred singly and were evenly distributed." *Id.* And selection of an appropriate pH for therapeutic compositions is a matter of routine optimization. Ex.1025, ¶¶351-353; *In re Aller,* 220 F.2d 454, 456 (CCPA 1955) ("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.").

Accordingly, "a pH buffer, wherein the pH of the composition is between 7.5 and 8.0," as recited in challenged claim 1, would have been obvious.

4. "excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate"

Lochrie's Example 2 composition contains 20mM NaH_2PO_4, which contains a multivalent phosphate ion. Ex.1010, 29:6-9; Ex.1025, ¶354. The '542 patent establishes that sodium phosphate can act as a buffer and an excipient. Ex.1001, 12:1-2 (Test Formulation 1), Tables 1-3. Thus, Lochrie discloses "excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate," as recited in challenged claim 1. Ex.1025, ¶355.

5. "wherein the ionic strength of the composition is greater than 200mM"

Lochrie's Example 2 composition containing "20 mM NaH_2PO4, 150 mM NaCl…at pH 7.4" (Ex.1010, 28:22-29:9) has an ionic strength of ~194mM. Ex.1025, ¶¶356-358. And when the pH is increased to 7.5 (*see* §IX.A.3), the ionic strength becomes ~196mM. *Id.*, ¶¶359-361. As discussed above, a POSA would have expected virus aggregation could occur after increasing Lochrie's virus concentration to $>10^{13}$vg/ml, and would have been motivated to modify Lochrie's concentrated composition to prevent such aggregation. *Supra* §IX.A.3. And, as the inventors acknowledged in Wright, ionic strength was a recognized variable to modify. Ex.1007, 175 (listing buffer ionic strength among the known "conditions that may affect aggregation"); Ex.1025, ¶¶61-71.

A POSA would have been motivated to increase the ionic strength of Lochrie's composition to prevent aggregation because, as the '542 patent admits, it was known that "AAV2 vectors require elevated concentrations of salt to prevent aggregation." Ex.1001, 1:54-55; *see also* 4:67-5:2 ("It is known that high salt concentrations increase AAV2 vector solubility"). And a POSA would have understood that high salt concentrations yield high ionic strengths. Ex.1025, ¶¶362-364.

A POSA would have further been motivated to target the claimed ionic strength of "greater than 200 mM" based on Liu, which reported "no signs of settling or precipitation over the 7 day [storage] period" and "[n]o significant change in the number of viral particles or infectious viral particles" after storing virus compositions having an ionic strength of ~315mM. Ex.1009, [00369], [00371]; Ex.1025, ¶¶362-364. Liu concludes "viral vector compositions can be stably stored in the [high ionic strength] buffers of the invention for extended periods of time." Ex.1009, [00371]. And a POSA would have reasonably expected AAV particles to exhibit even greater stability in such buffers than the adenovirus tested in Liu, since Croyle taught that AAV "is significantly more stable than the adenovirus." Ex.1013, 1283. Ex.1025, ¶¶365-367.

Accordingly, "wherein the ionic strength of the composition is greater than 200 mM" recited in challenged claim 1 was obvious. *Alcon*, 687 F.3d at 1368.

6. "wherein the purified AAV vector particles are stored in the composition without significant aggregation"

As discussed above, the structural components of the challenged claims were obvious based on the teachings of Lochrie, Huang, Mingozzi, Johnson, and Liu, and so the lack of "significant aggregation" recited in challenged claim 1 is also obvious. Moreover, compositions capable of storing purified AAV vector particles at the claimed concentrations without observable aggregation were described in Wright and, therefore, cannot form the basis for patentability. *Slayter*, 276 F.2d at 411.

To the extent modifications to Lochrie's composition, beyond those described above, would be required to achieve storage "without significant aggregation," a POSA would have been motivated to make such modifications based on the teachings of Huang, Wright, and the admissions in the '542 patent. *Supra*, §VIII.A.6. As explained above, Huang linked virus aggregation to reduced gene transfer efficiency (Ex.1005, S286), and the inventors taught "potentially deleterious consequence of vector aggregation" in Wright (Ex.1007, 176). Thus, a POSA would have been motivated to reduce AAV aggregation through routine optimization of known stabilization factors. Ex.1025, ¶¶368-369; *KSR*, 550 U.S. at 421. Patent Owner admitted as much in the '542 patent. *See, e.g.*, Ex.1001, 2:9-47 (discussing known drawbacks to aggregation).

A POSA would have reasonably expected success in minimizing vector aggregation based on Huang's observation that optimized compositions "could lead to a 30-50% reduction in the size of aggregates at high vector concentrations" (Ex.1005, S286) and Liu's "demonstrat[ion] that viral vector compositions can be stably stored in the temporary storage buffers of the invention for extended periods of time" (Ex.1009, [00371]). And a POSA would have understood that AAV "is significantly more stable than the adenovirus." Ex.1013, 1283. Thus, only routine optimization would be required to store Lochrie's composition, as modified by Huang, Mingozzi, Johnson, and Liu, "without significant aggregation." Ex.1025, ¶¶370-371.

For at least these reasons, challenged claim 1 is unpatentable.

B. Claim 2 is Obvious over Lochrie in view of Huang, Mingozzi, Johnson, and Liu

Claim 2 recites a composition of claim 1 "further comprising ethylene propylene oxide block copolymer Pluronic® F68." Ex.1001, 14:27-28. A POSA would have been motivated and expected success from adding Pluronic® F68 to the obvious variants of Lochrie's Example 2 composition discussed above based on Liu's teaching that "[i]n another preferred embodiment, the temporary storage composition further comprises a nonionic surfactant," including "Pluronic F68." Ex.1009, [00189].

A POSA would have been further motivated and expected success from including Pluronic® F68 in the obvious variants of Lochrie's Example 2 composition discussed above based on the inventors' teachings in Wright that "addition of the surfactants Polysorbate 80 or Pluronic® F68…effectively prevent losses due to non-specific binding during [virus] vector sampling and transfer," and Croyle's disclosure that AAV compositions comprising this detergent have an expiration date of 240 days when stored at 4°C. Ex.1007, 175, 176; Ex.1013, 1284 (Table 3, composition comprising "0.01% Pluronic"), 1288 (identifying detergent as "Pluronic block copolymer F68"); Ex.1025, ¶¶371-375.

Accordingly, the composition of challenged claim 2 was obvious.

C. Claim 5 is Obvious Over Lochrie in View of Huang, Mingozzi, Johnson, and Liu

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]." Ex.1001, 14:34-37. Patent Owner admitted that the recited radius is exemplary of no "significant aggregation." *Id.*, 9:25-27; *supra*, §VIII.B. And since the inventors acknowledged in Wright that AAV particles have a diameter of ~26nm (Ex.1007, 174), a POSA would have reasonably expected that AAV particles stored without observable aggregation in the obvious variants of Lochrie's Example 2 composition described above also have

an Rh of less than about 20nm measured by DLS. Ex.1025, ¶376. Indeed, the '542 patent does not identify anything critical about the recited radius of less than about 20nm other than it being exemplary of no "significant aggregation." Ex.1001, 9:25-27.

To the extent modifications to Lochrie's composition, beyond those described above, would be required to achieve the features of claim 5, a POSA would have been motivated to make such changes to minimize any potential aggregation for the reasons explained *supra* in §VIII.C (citing Huang, Wright, and Patent Owner's admission). Ex.1025, ¶377. A POSA also would have reasonably expected success in minimizing particle size for the reasons explained *supra* in §VIII.C (citing Huang). Indeed, "no signs of settling or precipitation" were observed for adenovirus compositions stored in a high ionic strength buffer over a 7-day period (Ex.1009, [00369]) and a POSA 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 of <20nm using the obvious variants of Lochrie's Example 2 composition discussed above. Ex.1025, ¶¶378-380; *Senju*, 780 F.3d at 1353.

Accordingly, the composition of challenged claim 5 was obvious.

D. Claim 6 is Obvious Over Lochrie in View of Huang, Mingozzi, Johnson, and Liu

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." Ex.1001, 14:38-41. As explained above, Patent Owner never disputed and, thereby, admitted the inherency of this recited feature. *Supra* §VIII.D; Ex.1025, ¶¶381-382.

Even if the additional limitation is not inherent, a POSA would have been motivated to develop AAV compositions that are sufficiently stable to allow recovery of high levels of virus particles following filtration through a 0.22μm filter based on Wright, Huang, and Patent Owner's admissions. *Supra*, §VIII.D; Ex.1025, ¶383.

A POSA also would have reasonably expected success in maximizing particle recovery after filtration in view of Huang, Liu, and Croyle. *Supra* §VIII.C. Thus, to the extent the obvious variants of Lochrie's Example 2 composition described above require further modification to improve recovery following filtration through a 0.22μm filter, only routine optimization of the known stabilization factors already contained therein would be needed to reduce any residual aggregation. Ex.1025, ¶¶384-387; *Senju*, 780 F.3d at 1353.

Accordingly, the composition of challenged claim 6 was obvious.

X. SECONDARY CONSIDERATIONS

Petitioners are unaware of any secondary considerations that would outweigh the compelling conclusion of obviousness set forth above, and reserve the right to address any such evidence submitted in this proceeding. *In re Rinehart*, 531 F.2d 1048, 1052 (CCPA 1976) (discussing process for evaluating rebuttal evidence when *prima facie* obviousness is established).

XI. DISCRETIONARY DENIAL IS NOT WARRANTED

Institution should not be denied under 35 U.S.C. §325(d) because the arguments and evidence presented here were not previously and/or properly considered by the Office. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020); *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential).

A. Advanced *Bionics* Part One

During prosecution, Liu, Lochrie, Mingozzi, and Johnson, were not cited, and Huang was only discussed in the Background of the ’542 patent. Ex.1002, 51-54, 193, 235. The Examiner’s prior art rejections relied on Zolotukhin’s (Ex.1026) use

of intermediate high ionic strength elution buffers during AAV purification,[8] and secondary references teaching formulations for hepatitis and non-virus proteins. Ex.1002, 315.

The asserted prior art references in Grounds 1 and 2 are distinct from those applied during prosecution in that they are all directed to improving stability of viral formulations, including AAV formulations, and achieving high-titer recombinant virus particles stored for an extended period of time without virus particle self-aggregation. *Supra* §§VIII-IX. Importantly, unlike Zolotukhin, which never mentioned *storing* AAV in a high ionic strength buffer, Liu expressly teaches that the composition tested in its Example 17 is a "*storage composition[]* of the invention," which was demonstrated "to effectively *maintain a stable population of adenoviral vector particles*" over 7 days. Ex.1009, [00365] (emphasis added). Also distinct from Zolotukhin, Liu specifically tested potential *self-aggregation of the recombinant virus particles* in its storage composition and reported that using the Example 17 storage composition, no virus aggregation and "[n]o significant change in the number of viral particles or infectious viral particles was observed" "during

[8] The Examiner considered, and properly rejected, Patent Owner's arguments that the claims require storage compositions used after all purification steps. *E.g.*, Ex. 1002, 147.

the tested "extended periods of time." *Id.*, [0371]. These teachings and the Petition's related arguments were never considered by the Examiner.

Lochrie is also distinct from Zolotukhin by teaching *formulating* purified rAAV virions in *stock* compositions from eluents. Ex.1010, 29:7-9. In addition, Johnson eliminated rAAV vector particle aggregation by adjusting the pH of purified rAAV compositions, and Mingozzi achieved successful gene delivery *in vivo* with its high-titer AAV compositions. Ex.1019, 589; Ex.1006, 10497-98. None of these teachings can be found in the references cited during prosecution or applied by the Examiner.

In addition, the Examiner did not appreciate Huang's teachings of successfully reducing aggregation in high-titer AAV compositions. These teachings are not discussed in the Background of the '542 patent and are non-cumulative with the art applied by the Examiner. *E.g.*, Ex.1002, 315-317.

Furthermore, because the Examiner never considered Liu, Lochrie, Mingozzi, and Johnson as prior art and also failed to substantively evaluate the relevant teachings in Huang, he did not have the opportunity to consider the combinations of references asserted in Grounds 1 and 2 or the Petition's rationales for motivation to combine and reasonable expectation of success based on the asserted art. *St. Jude Medical, LLC v. Snyders Heart Valve LLC*, Case No. IPR2018-00105, Paper 15 at 12 (PTAB May 3, 2018) (instituting where "evidence of record does not demonstrate

that the Examiner considered the references in the combinations relied upon by Petitioner or addressed arguments similar to those Petitioner now presents"). Thus, *Becton Dickenson* Factors (a), (b), and (d) support institution.

B. Advanced *Bionics* Part Two

The Board need not reach Part Two of the *Advanced Bionics* framework. But if it does, the *Becton Dickenson* Factors also favor institution.

As explained above, the Examiner did not substantively evaluate any of Petitioners' asserted art. Thus, factor (c) favors institution. *Microsoft Corporation v. SurfCast, Inc*., IPR2022-00590, Paper 9 at 16 (PTAB Oct. 7, 2022) (finding factor (c) favors institution because the cited art "was not extensively evaluated during examination and was not the basis for a rejection"); *Amazon.com, Inc. v. M2M Sols. LLC*, IPR2019-01205, Paper 14 at 15 (PTAB Jan. 27, 2020) ("a reference that 'was neither applied against the claims nor discussed by the Examiner' does not weigh in favor of exercising the Board's discretion under § 325(d) to deny a petition").

Factor (e) also supports institution in view of the Examiner's mistakes. First, the Examiner erroneously ignored Huang's highly-relevant teachings that common formulation techniques can be used to reduce aggregation in high-titer rAAV compositions. *Guardant Health, Inc. v. Univ. of Washington*, IPR2022-00817, Paper 14 at 8 (PTAB Oct. 13, 2022) (instituting when "examiner misapprehended or overlooked the teachings of [cited art]"); *see also Apple Inc. v. Telefonaktiebolaget*

LM Ericsson, IPR2022-00457, Paper 7 at 8 (PTAB Sep. 21, 2022) (Examiner erred in overlooking disclosures in relevant cited art because it "was not discussed in any Office Action or Response" or "was [] the basis for a rejection.").

Second, in allowing the claims, the Examiner was led astray by Patent Owner's allegation that "causes of aggregation of recombinant AAV particles" were unknown before the '524 patent. Ex. 1002, 242. But whether specific causes of rAAV aggregation were known is irrelevant because rAAV aggregation was a well-known problem, and recognized ways of addressing it were reported. Indeed, as Petitioners explained, the '524 patent itself acknowledged that rAAV aggregation was a known problem and that prior approaches had been taken to reduce it. Ex.1001, 1:41-64, 2:9-47, 1:54-55 (recognizing prior knowledge that "AAV2 vectors require elevated concentrations of salt to prevent aggregation"); *see also* 4:67-5:2 ("It is known that high salt concentrations increase AAV2 vector solubility"). Other variables to reduce rAAV aggregation, including pH, addition of surfactants and other known stabilizing agents, were also well known and already used to minimize rAAV aggregation. *Supra* § IV.C. The Examiner's failure to consider any "other material prior art available to a person of ordinary skill in the art" constitutes material error that favors institution under factor (e). *Matsing, Inc. v. All.Space Networks Limited f/k/a Isotropic Systems, Ltd*., IPR2022-01108, Paper 9 at 28 (PTAB Dec. 14, 2022) (Examiner erred by failing to consider whether a newly amended limitation

would have been obvious over "other material prior art available to a person of ordinary skill in the art").

In addition to presenting art and arguments that were not considered by the Examiner, Petitioners also provide Dr. Amiji's declaration, which further explains a POSA's understanding of the art as of June 1, 2004. Thus, *Becton Dickenson* Factor (f) likewise favors institution. *Celltrion, Inc. v. Genentech, Inc.*, No. IPR2017-01140, Paper 31 at 13-14 (PTAB Jan. 25, 2018) (instituting when, "taking the expert declaration…into account, Petitioner's testimonial evidence presents the prior art in a new light.").

Accordingly, institution should not be denied under 35 U.S.C. §325(d).

XII. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

A. Real Parties-in-Interest (37 C.F.R. §42.8(b)(1))

Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation are the real parties-in-interest.

B. Related Matters (37 C.F.R. §42.8(b)(2))

The '542 patent has been asserted against Petitioners in an action for infringement: *Genzyme Corporation v. Novartis Gene Therapies, Inc.*, 1:21-cv-01736-RGA (D. Del. Feb. 23, 2022). Additionally, Petitioners are concurrently filing a separate IPR petition against the '542 patent, IPR2023-00608.

C. Lead and Backup Counsel and Service Information (37 C.F.R. §§42.8(b)(3) and (b)(4))

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XIII. CERTIFICATION UNDER 37 C.F.R §42.24(D)

Pursuant to 37 C.F.R. §42.24(a)(1)(i), the foregoing PETITION FOR *INTER PARTES* REVIEW contains 13,038 words, excluding parts of this Petition exempted under §42.24(a), as measured by the word-processing system used to prepare this paper.

Respectfully Submitted

Date: February 22, 2023

By: / John D. Livingstone /
John D. Livingstone
Reg. No. 59,613

Lead Counsel for Petitioners Novartis Gene Therapies, Inc., and Novartis Pharmaceuticals Corporation

CERTIFICATE OF SERVICE

The undersigned certifies that, in accordance with 37 C.F.R. § 42.6(e) and 37 C.F.R. § 42.105(a), **Petition for *Inter Partes* Review, Petitioners' Power of Attorney, Petitioners' Exhibit List, and the associated Exhibits 1001-1026** were served via FedEx on February 22, 2023, on the correspondence address of record below indicated in the Patent Office's public PAIR system for U.S. Patent No. 9,051,542.

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Dated: February 22, 2023

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