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. IPR2023-00608
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, Evans, claimed compositions comprising about $1x10^{7}$-$1x10^{13}$vp/ml purified virus, a buffer acceptable for human parenteral use at a pH of about 7.5-8.5, sodium chloride at about 25mM-250mM, a divalent cation selected from $MgCl_2$ and $CaCl_2$ at about 0.1mM-5mM, and a non-ionic detergent. Another reference, Frei, exemplified a composition comprising $1.6x10^{13}$vp/ml purified virus in 20mM NaPi buffer having pH8 at 2-10°C, 100mM NaCl, 2mM $MgCl_2$, 2% sucrose, and 10% glycerol. Evans and Frei each taught that such compositions (also called "formulations") provide enhanced long-term storage stability for purified virus particles, and demonstrated successful storage stability for several exemplary adenovirus compositions. And both references taught their compositions could be used with adeno-associated virus ("AAV").

The challenged claims are obvious variants of and read directly on Evans's and Frei's compositions. Challenged claim 1 is drawn to compositions comprising a

[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.

known buffer (*i.e.*, having a pH "between 7.5 and 8.0," excipients comprising "multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate," and an "ionic strength…greater than 200mM") for storing a 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 difference between the claims and the compositions in Evans or Frei, it could only be the recited virus concentration measured in vg/ml or the natural result, *i.e.*, the absence of "significant aggregation." But the prior art, Patent Owner's admissions, and expert testimony indicate those arguments should fail. Several years before the '542 patent's priority date, the prior art (Mingozzi and Huang) had produced purified AAV compositions having concentrations of $>10^{13}$ and 5-$10x10^{13}$vg/ml, and Mingozzi had successfully used such preparations to deliver transgenes in mice. Thus, the claimed vg/ml concentrations were known and successfully used. Regarding any alleged absence of "significant aggregation," that claim element is not inventive and, instead, is the recognition of a natural event flowing from the compositions of Evans and Frei, which contain all the claimed structural features. Because a POSA would have been motivated to incorporate AAV into Evans's and Frei's compositions at high

concentrations useful for gene therapy, and would have reasonably expected success in achieving the composition recited in challenged claim 1, that claim 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). Challenged claims 2, 5, and 6 are also unpatentable.

Petitioners 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

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, 5, and 6	§103	Evans in view of Huang and Mingozzi
2	2	§103	Evans and Wright in view of Huang and Mingozzi
3	1, 2, 5, and 6	§103	Frei in view of Huang and Mingozzi

III. THE '542 PATENT

The '542 patent purports to have developed isotonic compositions with high ionic strength to solve the "problem" of concentration-induced virus 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's 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 prior art 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 "without significant 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. 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 valencies…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 significant 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 known in the art. As further explained in §XII *infra*, the challenged claims were allowed because the Examiner (1) overlooked critical teachings in the cited art; (2) was not aware of the relevant art asserted herein; 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, 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 final virus compositions 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, 1:41-53. 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 2000's 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 Evans, Frei, and other prior art. *Id.* Indeed, Wright taught that "purification conditions that may affect aggregation include buffer ionic strength and pH, shear and vector concentration." Ex.1007, 175, 176 (explaining that initial aggregation "could be reversed by adjusting buffer pH"). 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 (500mM NaCl) buffer (Ex.1011, 417-419).

Building on these developments, Evans taught that viral compositions with enhanced viral stability contain a salt, such as NaCl, "at an ionic strength which is physiologically acceptable to the host," that NaCl can be "added at concentration within a range of upwards of 250 mM," and reported "optimum" long-term stability at pH 7.5 when stored at 15°C, between pH 7.0-7.5 when stored at 25°C, and between 8.0-8.5 when stored at 2-8°C. Ex.1003, 9:16-22, 11:13-21, 27:26-32. Similarly, Frei taught that pharmaceutically acceptable divalent and monovalent metal salts such as magnesium and sodium can be used as stabilizers for virus preparations, that suitable concentrations include 1mg/ml and 10mg/ml, respectively, and that preferred pH ranges are about 7.7-8.3 for storage at refrigeration temperatures, and about 7.3-8.2 for room temperatures. Ex.1004, 5:31-6:11, 6:12-30.

Thus, skilled artisans already knew of and 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 reads on 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 co-pending litigation may raise controversies that require resolution 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 another 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. Evans

Evans is a PCT application published in 2001, and qualifies as prior art to the '542 patent under 35 U.S.C. §102(b). Ex,1003, (21), (43); Ex.1025, ¶91.

Evans discloses viral compositions for use in gene therapy. Ex.1003, Abstract, 1:15-19. Like the '542 patent, Evans teaches buffer conditions to maintain its compositions for potential human parenteral administration. Ex.1003, 1:15-19 Evans explains that "[a]n ongoing challenge in the field of gene therapy and vaccine research is to generate liquid virus formulations which are stable for longer periods of time within a useful temperature range," and solves the problem by developing compositions that show improved storage stability. *Id.*, 1:16-19, 28-30; Ex.1025, ¶92. Evans discloses that its compositions comprise a buffer, a salt, a divalent cation, and a non-ionic detergent. Ex.1003,, 1:19-21; Ex.1025, ¶93.[3] Evans further discloses the identity of and concentration ranges for those components. *See* Ex.1003, 8:22-11:4; Ex.1025, ¶94. Evans also discloses that the compositions support virus concentrations of about $1x10^{7}$-$1x10^{13}$vp/ml. Ex.1003, 8:5-11; Ex.1025, ¶95.

[3] Although Evans also discusses using an inhibitor of free radical oxidation, it did not deem such components critical. *Compare* Ex.1003, claim 1 *with* claim 10.

Evans claims a virus composition comprising a purified virus with a concentration of about $1x10^7$-$1x10^{13}$vp/ml, a buffer acceptable for human parenteral use at a pH of about 7.5-8.5, sodium chloride at about 25mM-250mM, a divalent cation selected from $MgCl_2$ and $CaCl_2$ at about 0.1mM-5mM, and a non-ionic detergent. Ex.1003, 36 (claim 5); Ex.1025, ¶95. Although Evans's working examples utilized adenovirus compositions, Evans teaches that its compositions may be used with AAV. Ex.1003, 3:12-14; 7:16-18; Ex.1025, ¶96.

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. *Id.* 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; Ex.1025, ¶111. Huang describes concentrating an AAV vector preparation and observing that when the concentration reached 5-$10x10^{13}$vg/ml, gene transfer efficiency was 10-100-fold lower compared to the same vector administered at the same dose but having a concentration of 1-$5x10^{12}$vg/ml. Ex. 1005, S286. Huang conducted a series of formulation studies to prevent and dissolve AAV

aggregates, and reported a 30-50% reduction in aggregate size 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, 10497; 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. *Id.* Mingozzi describes the purification of both vectors by repeated CsCl gradient centrifugation, and reports final concentrations of $>10^{13}$vg/ml. Ex.1006, 10497; Ex.1025, ¶115. Both preparations led to productive hepatic gene transfer. Ex.1006, 10498, FIG. 1; Ex.1025, ¶115.

D. Wright

Wright is a review article listing the named inventors of the '542 patent as co-authors, and qualifies as prior art under 35 U.S.C. §102(b). Ex.1007, 174; Ex.1025, ¶116.

Wright teaches that AAV "is a promising vector for human gene transfer" and has "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, ¶117. Wright discusses the development of compositions for AAV and teaches 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. Wright discusses aggregation of AAV particles, noting that "loss of rAAV following a 0.2-μm filtration step correlates with the extent of vector aggregation." *Id.*, 175-76; Ex.1025, ¶120. Wright notes that buffer ionic strength, pH, and vector concentration affect aggregation. *Id.*, 175; Ex.1025, ¶¶118, 121. Wright teaches that empty capsids have "size and surface characteristics [that] are similar to that of genome containing particles, [and] contribute to particle aggregation." *Id.* (citation omitted). Wright therefore "[a]ssum[es] that full vector particles and empty capsids aggregate by a similar mechanism." *Id.* Wright teaches that "AAV vectors are typically prepared at final purified concentrations in the range of 10^{11} to 10^{13}vg/ml," and reports that "highly purified vector preparations at concentrations of 5 x 10^{13}cp/ml are stable in a non-aggregated, monomeric state when stored at 2 to 8°C" without freeze-thaw cycles. Ex.1007, 175-176; Ex.1025, ¶119.

E. Frei

Frei is a PCT published in 1999, and qualifies as prior art under 35 U.S.C. §102(b). Ex.1004, (21), (43); Ex.1025, ¶97.

Frei discloses viral compositions for use in gene therapy. Ex.1004, Abstract, 1:15-20. Like the '542 patent, Frei developed stable virus-containing compositions that can be stored and transported while retaining safety and efficacy. *Id.*, 1:23-26. Frei identifies "a critical need to develop formulations that stabilize relatively high concentrations of virus," and provides a novel buffered formulation that stabilizes high concentrations of recombinant virus for use in gene therapy and maintains viability after storage. *Id.*, 4:26-36, 7:7-11, 8:27-29, 8:34-36; Ex.1025, ¶98.

Frei discloses that its compositions comprise a buffer system that maintains a pH of about 7.0-8.5 despite storage between -80°C and 27°C. Ex.1004, 6:21-24. Frei's compositions include pharmaceutically acceptable divalent metal salt stabilizers, and Frei teaches that magnesium salts are particularly preferred in an amount of about 0.1mg/ml-1mg/ml. *Id.*, 5:31-36. Pharmaceutically acceptable monovalent salt stabilizers are also included, and Frei discloses that sodium chloride in an amount of 0.6mg/ml-10.0mg/ml is preferred. *Id.*, 5:37-6:6; Ex.1025, ¶99. Frei further teaches that "the formulation of the present invention can maintain stability of the virus at concentrations ranging up to 1 x 10^{13} particles/mL." Ex.1004, 7:9-11.

Frei exemplifies a virus composition ("Example D-1") comprising purified adenovirus at a concentration of $1.6x10^{13}$vp/ml, in 20mM NaPi buffer, 100mM NaCl, 2mM $MgCl_2$, 2% sucrose, and 10% glycerol, having pH 8 at 2-10°C.[4] *Id.*, 22:17-31. Based on Frei's dynamic light scattering data, its D-1 composition prevented adenovirus aggregation. *Id.*, 22:30 (reporting A320/A260=0.22); Ex.1015, 6:62-63 ("free virus particles display a light scattering ratio of about 0.22-0.30:1"); Ex.1025, ¶100. Frei also teaches that its compositions may be used with other recombinant viruses, including AAV. Ex.1004, 8:18-26.

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

Each element of claims 1, 5, and 6 of the '542 patent is present in the compositions disclosed in Evans, 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-

[4] Although Frei's D-1 composition includes polyhydroxy hydrocarbons (*see, e.g.*, Ex.1004, 4:37-5:30), the challenged claims do not preclude such components. Ex.1001, 14:15-16 (reciting the open-ended transition phrase "comprising").

induced viral vector aggregation. Ex.1001, Abstract, 1:41-66, 3:11-15. Evans, Huang, and Mingozzi likewise relate to high-concentration viral compositions, including AAV compositions, for use in gene therapy. Ex.1003, Abstract, 3:12-14; Ex.1005, S286; Ex.1006, 10497. Evans teaches that its compositions show improved storage stability (Ex.1003, Abstract), 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 Evans, Huang, and Mingozzi, 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, Gatlin, Croyle, and Liu), Patent Owner's admissions in the '542 patent and during prosecution, and the opinions of Petitioners' expert, Dr. Amiji. Ex. 1025, ¶¶18-19, 140-209. Claims 1, 5, and 6 are unpatentable as obvious.

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

Evans's claim 5 describes a composition that meets all but the concentration exceeding $1x10^{13}$ "vg/ml" limitation of challenged claim 1. Ex.1025, ¶141. But Huang and Mingozzi describe AAV compositions with the recited vg/ml concentrations.

Claim Limitations	Teachings in Evans/Huang/Mingozzi
A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising: purified, recombinant AAV vector particles	**Evans claim 5**: "A virus formulation comprising: a) a purified virus" (Ex.1003, 36:3-4). **Evans**: "The recombinant viruses of the present invention which show enhanced storage stability include but are not limited to adenovirus, adeno-associated virus…." *Id.*, 3:12-14. **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	**Evans claim 5**: "a virus concentration in the range from about $1x10^{7}$ vp/mL to about $1x10^{13}$ vp/mL" (Ex.1003, 36:15-16). **Huang**: "it is desirable to deliver high doses of vector in small volumes." Ex.1005, S286. **Mingozzi**: describes 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	**Evans claim 5**: "b) a buffer…selected from a group of buffers acceptable for human parenteral use, preferably a Tris buffer, at a pH from about 7.5 to about 8.5." Ex.1003, 36:5, 16-18.
excipients comprising one or more multivalent ions selected from the	**Evans claim 5**: "e) a divalent cation…selected from the group consisting of $MgCl_2$" (*id.*, 36:8, 25-26).

group consisting of citrate, sulfate, magnesium, and phosphate	
wherein the ionic strength of the composition is greater than 200mM	**Evans claim 5**: "d) a salt; e) a divalent cation"; "wherein the salt is sodium chloride from about 25 mM to about 250 mM"; "$MgCl_2$…in an amount from about 0.1 mM to about 5 mM." *Id.*, 36:7-8, 21-22, 26-27. A POSA would understand that a composition comprising 250mM NaCl and 5mM $MgCl_2$ has an ionic strength of 265mM. Ex.1025, ¶174.
and wherein the purified AAV vector particles are stored in the composition without significant aggregation.	**Evans**: "The enhanced long-term stability up through the 2-8°C range results in an extended shelf life of the virus formulations disclosed herein, allowing for storage and eventual host administration of these liquid formulations over about a 1-2 year period with acceptable losses in virus infectivity." Ex.1003, 4:21-25.

The composition of challenged claim 1 is obvious over the combined teachings of Evans, Huang, and Mingozzi, when taken with the general knowledge in the field, as evidenced by Wright, Clark, Gatlin, Croyle, Liu, and Patent Owner's admissions. Ex.1025, ¶¶141-193.

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

Evans is directed to "stabilized virus formulations and related pharmaceutical products for use in gene therapy and/or vaccine applications." Ex.1003, 3:2-3. Evans'

claims include compositions comprising purified virus particles, which include AAV particles. *Id.*, 36:3-27 (claims 1, 3-5); 3:12-14.

To the extent the preamble of claim 1 is limiting, Evans discloses its compositions are for storing purified virus particles. *See, e.g.*, *id.*, 2:29-32 ("The present invention addresses and meets these needs by disclosing improved recombinant virus liquid formulations which show enhanced stability for longer periods of time at temperatures in the range of 2-8°C"); *see also* 3:10-12; Ex.1025, ¶¶142-143. Evans also reports results from experiments that involved storing several exemplary adenovirus compositions. *See, e.g.*, Ex.1003, Examples 3, 4, 7-11, 13, 14; Ex.1025, ¶144.

To the extent Patent Owner argues that the claims of Evans do not relate to AAV particles, a POSA would have been motivated to apply Evans's teachings to AAV because Evans expressly discloses that its methods and compositions could be used with AAV. Ex.1003, 3:12-14; 7:16-18 (similar); Ex.1025, ¶145. 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, S9 (touting AAV's ability "to mediate long-term, robust in vivo gene expression in numerous cell types"). Thus, a POSA

would have been motivated to use purified, recombinant AAV vector particles in Evans's claim 5 composition. Ex.1025, ¶¶145-147; *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 alleged that adenovirus is distinct from and "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 the '542 patent's admissions 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, 149. 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 Evans's teachings regarding storage stability as being limited to adenovirus, she would have reasonably expected Evans's compositions to provide similar, if not better stability for storing AAV particles. Ex.1025, ¶¶148-150.

Accordingly, Evans 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"

Evans's claim 5 composition comprises "a virus concentration in the range from about $1x10^{7}$ vp/mL to about $1x10^{13}$ vp/mL." Ex.1003, claim 3 (from which claim 5 depends). A POSA would understand that "about" $1x10^{13}$vp/ml encompasses variation that would result in values that are above and below $1x10^{13}$vp/ml. *In re Woodruff*, 919 F.2d 1575, 1577 (Fed. Cir. 1990) (holding prior art concentrations of "about 1-5%" allow for concentrations slightly above 5% and read on claim limitation of "more than 5%"); Ex.1014 (defining "about" as "a little more or less than the stated number or amount"); Ex.1025, ¶151. Assuming that 100% of the particles contain vector genomes, Evans's claim 5 composition therefore comprises viral particles at a concentration exceeding $1x10^{13}$vg/ml, as recited in challenged claim 1. Ex.1025, ¶152.

Even if Evans's claim 5 composition contained a portion of empty capsids (i.e., viral particles lacking genomes), a POSA would have been motivated to remove them while maintaining Evans's purified virus concentration, because high concentrations of vector-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."); Ex.1025, ¶¶153-156. Patent Owner admitted as much in the '542 patent.

See, e.g., Ex.1001, 2:11-14 ("in vivo administration of AAV2 vectors to certain sites, such as the central nervous system, may require small volumes of highly concentrated vector"). For example, Mingozzi reported that AAV vector doses of 10^{12}vg/kg resulted in sustained transgene expression in a large-animal (canine) model, which corresponds to doses of $3.2x10^{13}$vg for a 60kg human. Ex.1006, 10497; *see also* Ex.1012, S-9 ("a clinical dose in humans will require 10^{12} to 10^{14} rAAV vector particles"). Moreover, it was known that most parenteral compositions have an injection volume limit of only a few milliliters. 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 vector genome concentrations exceeding 10^{13}vg/ml. Ex.1025, ¶156.

A POSA would have reasonably expected success in achieving such concentrations because Evans itself taught that "[t]he formulations of the present invention provide stability to adenovirus at varying degrees of virus concentration" for pharmaceutical administration. Ex.1003, 7:31-33; Ex.1025, ¶157. And a POSA would have reasonably expected a composition having a concentration of "about $1x10^{13}$vp/mL," as in Evans's claim 5 composition, and a composition having a concentration "exceeding $1x10^{13}$vg/ml," as recited in challenged claim 1, to exhibit similar stability. *Ante*, §VIII.A.6 (discussing role of virus particles in concentration-dependent aggregation).

Moreover, by June 2004, methods of generating high yields of AAV were well-known, as were methods for removing empty capsids and concentrating genome-containing vectors. Ex.1012, S12 (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 remove empty capsids while maintaining Evans's claim 5 purified virus concentration. Ex.1025, ¶¶38, 158.

Indeed, by June 2004, the prior art had already achieved AAV compositions exceeding $1x10^{13}$vg/ml. For example, Huang described AAV compositions having concentrations of 5-$10x10^{13}$vg/ml. Ex.1005, S286. Although Huang observed lower gene transfer efficiency with such compositions compared to compositions having concentrations of 1-$5x10^{12}$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." *Id.* Thus, based on Huang, a POSA would have reasonably expected that high-concentration AAV compositions (e.g., 5-$10x10^{13}$vg/ml) could be achieved and utilized for successful gene transfer. Ex.1025, ¶¶159-161. 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.

Accordingly, Evans renders obvious "at a concentration exceeding $1x10^{13}$vg/ml up to $6.4x10^{13}$vg/ml," as recited in challenged claim 1. *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.").

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

Evans's claim 5 composition contains a buffer "acceptable for human parenteral use, preferably a Tris buffer, at a pH from about 7.5 to about 8.5." Ex.1003, claim 3 (from which claim 5 depends). Because the pH range recited in challenged claim 1 ("between 7.5 and 8.0") is within the range disclosed in Evans's claim 5 composition ("about 7.5 to about 8.5"), the pH limitation of challenged claim 1 is *prima facie* obvious. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) ("a prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness."); Ex.1025, ¶162.

A POSA would have been motivated to select and reasonably expected success in using a pH within the lower end of Evans's claimed range, since Evans itself exemplified several adenovirus compositions, all but two of which had pH values of between pH 7.5 and 8.0. Ex.1003, 21:27-24:16; Ex.1025 ¶¶163-168.

Furthermore, Evans reported that its pH 7.5 compositions achieved optimum long-term stability when stored at 15°C, while pH 7.0-7.5 was optimum for long-term storage at 25°C, and pH 8.0-8.5 was optimum for long-term storage at 2-8°C. Ex.1003, 27:26-32. A POSA would have reasonably expected similar stability for AAV compositions, since Croyle reported that AAV "was not as sensitive to pH changes upon freezing as the adenovirus at the concentrations studied." Ex.1013, 1282. As Dr. Amiji explains, selection of an appropriate pH for therapeutic compositions is a matter of routine optimization. Ex.1025, ¶¶72-77, 167. *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."); *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.").

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

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

Evans's claim 5 composition contains a divalent cation "selected from the group consisting of $MgCl_2$ and $CaCl_2$ in an amount from about 0.1mM to about 5mM." Ex.1003, claim 5. A POSA would have been motivated to select $MgCl_2$ with

a reasonable expectation of success based on the dozens of "particular" and "specific" embodiments taught in Evans containing $MgCl_2$, as opposed to only two embodiments containing $CaCl_2$. *Id.*, 11:9-17:15, Example 1 (*contra* 17:16-22, 22:23-24); Ex.1025, ¶¶169-172. Thus, Evans renders obvious "excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate," as recited in challenged claim 1.

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

Evans's claim 5 composition contains "sodium chloride from about 25 mM to about 250 mM" and either $MgCl_2$ or $CaCl_2$ "in an amount from about 0.1 mM to about 5 mM." Ex.1003, claim 4 (from which claim 5 depends), claim 5; *see also* 9:6-9 (teaching that a preferred divalent cation is $MgCl_2$ at a concentration ranging of about 0.1mM-5mM). Accepting the high end of both ranges, Evans's claim 5 composition comprising 250mM of NaCl and 5mM of $MgCl_2$ has an ionic strength of 265mM. Ex.1025, ¶¶173-174. Because the ionic strength range recited in challenged claim 1 ("greater than 200mM") encompasses the ionic strength achieved by an embodiment falling within the scope of Evans's claim 5 composition (265mM), the ionic strength limitation of 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.").

A POSA would have been motivated to select the high end of the concentration ranges for NaCl and $MgC1_2$ in Evans's claim 5 composition, because ionic strength was a known condition that likely affects vector aggregation. Ex.1007, 175; Ex.1025, ¶¶175-177. Evans itself teaches that "[a] purpose of inclusion of a salt in the formulation is to attain the desired ionic strength or osmolarity" and that including a salt in the composition can "enhance viral stability." Ex1003, 9:16-20. And the '542 patent admits that "AAV2 vectors require elevated concentrations of salt to prevent aggregation" and that it was "known that high salt concentrations increase AAV2 vector solubility." Ex.1001, 1:54-55; *see also* 4:67-5:2. As Dr. Amiji explains, selection of an appropriate ionic strength for a therapeutic composition is a matter of routine optimization. Ex.1025, ¶¶61-71, 181; *Aller,* 220 F.2d at 456 ("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."); *Senju*, 780 F.3d at 1353.

A POSA would have reasonably expected success in using the high end of the concentration ranges for NaCl and $MgC1_2$ in Evans's claim 5 composition, because Evans explicitly taught that NaCl can be "added at a concentration within a range of

upwards of 250 mM" and that $MgCl_2$ can be added "in a range from about 0.1 mM to about 10 mM." Ex.1003, 11:13-19; Ex.1025, ¶178. In addition, the prior art taught numerous instances of high ionic strength virus storage compositions. Ex.1025, ¶¶179-180. For instance, protocols for the large-scale production of rAAV had been described that involved eluting and storing the resulting rAAV stocks in high-ionic strength (500mM NaCl) buffer. Ex.1011, 417-419, 429. The prior art had also demonstrated that adenovirus can be stored at ~4°C for 7 days in a "storage buffer (25 mM Tris, 300 mM NaCl, 5 mM $MgCl_2$, 0.0025% polysorbate 80, 5% trehalose, pH 7.5)" having an ionic strength of ~315mM, with "no signs of settling or precipitation" and "no significant decrease in particle number." Ex.1009, [00366], [00369], Table 15. Patent Owner and the inventors also admitted that a POSA would have expected studies of adenoviral compositions to be reasonably predictive of success with AAV. Ex.1001, 1:65-2:8, 5:67-6:4, 9:7-18; Ex.1007, 174.

Accordingly, Evans renders obvious "wherein the ionic strength of the composition is greater than 200 mM," as recited in challenged claim 1. *Alcon Research*, 687 F.3d at 1368; Ex.1025, ¶182.

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

A POSA would have reasonably expected Evans's claim 5 composition to prevent aggregation.[5] Ex.1025, ¶¶183-187. Although that composition contains a virus concentration measured in particles/ml, rather than genomes/ml, the '542 patent admits empty capsids also contribute to virus aggregation. Ex.1001, 1:60-64 ("empty capsids…contribute to particle concentration."); *see also id.*, 1:46-48, 4:65-67, 7:13-17 (discussing aggregation in the context of concentrations measured in particles/ml). 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, given that the elements of the compositions are the same, a POSA would have reasonably expected an AAV composition having a concentration of "about $1x10^{13}$ vp/mL," as in Evans's claim 5

[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.

composition, to exhibit levels of aggregation similar to an AAV composition having a concentration "exceeding $1x10^{13}$ vg/ml," as recited in challenged claim 1. Ex.1025, ¶184.

A POSA also would have reasonably expected no aggregation in such compositions, since Evans teaches that its compositions "show enhanced stability for longer periods of time at temperatures in the range of 2-8°C," "allowing for storage and eventual host administration of these liquid formulations over about a 1-2 year period." Ex.1003, 2:29-32, 4:21-25. And a POSA would have reasonably expected an AAV composition having a concentration of "about $1x10^{13}$vp/mL," as in Evans's claim 5, to exhibit even greater stability than the adenovirus compositions tested in Evans's examples, since Croyle taught that AAV "is significantly more stable than the adenovirus." Ex.1013, 1283. Indeed, 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, ¶191. 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 Evans's claim 5 does not teach compositions "without significant aggregation," a POSA would have been motivated to develop such compositions. Ex.1025, ¶¶188-189. 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* 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.").

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 from such compositions as being "without significant aggregation." As discussed above, the structural components of the challenged claims were obvious based on the teachings of Evans, 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."); Ex.1025, ¶¶190-193.

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

B. Claim 5 is Obvious Over Evans 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, ¶¶194-195. If true, and because the Evans compositions prevent aggregation (*infra* §VIII.A.6), then this claim element should provide 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). Because Evans's claim 5 composition prevented aggregation, a POSA would have reasonably expected AAV particles stored therein would have an Rh of <~20 nm 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. *Id.*, 9:25-27 ("Rh values >20 nm are deemed to indicate the occurrence of some level of aggregation.").

To the extent claim 5 requires less aggregation than claim 1, a POSA would have been motivated to minimize any potential aggregation in Evans's claim 5

[6] Patent Owner merely made legally erroneous arguments that inherency is inappropriate in obviousness rejections. Ex.1002, 131, 133, 170, 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).

formulation. 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 in Evans's claim 5 composition. Ex.1025, ¶196; *KSR*, 550 U.S. at 421; *Senju*, 780 F.3d at 1353. 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 particle size in view of Huang's teaching that its optimized compositions "could lead to a 30-50% reduction in the size of aggregates at high vector concentrations." Ex.1005, S286. Indeed, "no signs of settling or precipitation" were observed for prior art 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" used in Liu (Ex.1013, 1283); Ex.1025, ¶¶197-198. Thus, only routine optimization would be required to obtain an average AAV Rh of <20nm in Evans's claim 5 composition. Ex.1025, ¶¶199-201. *Senju*, 780 F.3d at 1353.

Accordingly, the compositions of challenged claim 5 are obvious.

C. Claim 6 is Obvious Over Evans 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 0.22 μm filter." Ex.1001, 14:38-41. Patent Owner admits that claim 6 merely "provide[s] [a] method[] of ensuring that there is no substantial aggregation." Ex.1023, 72; *see also* Ex.1025, ¶¶202-204. If true, and because Evans 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), and since Evans's claim 5 composition prevented virus aggregation, a POSA would have reasonably expected that at least 90% of the AAV particles stored in Evans's claim 5 composition would be recovered following filtration through a 0.22μm filter. Ex.1025, ¶204.

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; Ex.1025, ¶204. 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 Evans's claim 5 formulation, 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 the known stabilization factors in Evans's claim 5 composition. Ex.1025, ¶205. *KSR*, 550 U.S. at 421; *Senju*, 780 F.3d at 1353. Patent Owner admitted as much in the '542 patent. *See, e.g.*, 2:9-47.

A POSA also would have reasonably expected success in maximizing particle recovery after filtration because POSA knew that Huang taught its optimized compositions "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 Evans's claim 5 formulation through a 0.22μm filter. Ex.1025, ¶¶206-209; *Senju*, 780 F.3d at 1353.

Accordingly, the composition of challenged claim 6 was obvious.

IX. GROUND 2: CLAIM 2 IS OBVIOUS OVER EVANS AND WRIGHT 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. Evans's claim 5 composition contains "a non-ionic detergent." Ex.1003, claim 1 (from which claim 5 depends). Evans further teaches using "the Pluronic series of non-ionic surfactants (e.g., Pluronic 121)." *Id.*, 9:4-5. A POSA would have known that Pluronic® F68, a commercially-available product, belongs to the Pluronic series of non-ionic surfactants. Ex.1025, ¶210.

A POSA would have been motivated and reasonably expected success from selecting Pluronic® F68 as the non-ionic detergent in Evans's claim 5 composition 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." Ex.1007, 175, 176; Ex.1025, ¶ 211. A POSA would have further expected success in using Pluronic® F68 in Evans's claim 5 composition based on Croyle's disclosure that AAV compositions comprising this detergent have an expiration date of 240 days when stored at 4°C.

Ex.1013, 1284 (Table 3, composition comprising "0.01% Pluronic"), 1288 (identifying detergent as "Pluronic block copolymer F68"); Ex.1025, ¶¶212-213.

Accordingly, the composition of challenged claim 2 was obvious.

X. GROUND 3: CLAIMS 1, 2, 5, AND 6 ARE OBVIOUS OVER FREI IN VIEW OF HUANG AND MINGOZZI

Each element of claims 1, 2, 5, and 6 of the '542 patent is also present in the compositions disclosed in Frei, Huang, and Mingozzi, 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. Frei teaches that its compositions have the ability to stabilize high concentrations of virus during storage (Ex.1004, 1:15-20, 7:7-9, 8:18-22), and Huang and Mingozzi both relate to high-concentration viral compositions, including AAV compositions, for use in gene therapy (Ex.1005, S286; Ex.1006, 10497). A POSA would have combined the teachings of Frei, 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, Croyle, and Liu), Patent Owner's admissions in the '542 patent and during prosecution, and the opinions of Dr. Amiji. Ex. 1025, ¶¶20-22, 214-273. Claims 1, 2, 5, and 6 are unpatentable as obvious.

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

Frei's Example D-1 describes a composition that meets all but three of the limitations of challenged claim 1. But Frei teaches its compositions may comprise two of the absent limitations ("adeno-associated virus (AAV) vector particles" and preferred salt concentrations that yield an "ionic strength of the composition [] greater than 200mM"), and Huang and Mingozzi describe AAV compositions having the final feature (a concentration exceeding $1x10^{13}$ "vg/ml"); Ex.1025, ¶215.

Claim Limitations	Teachings in Frei/Huang/Mingozzi
A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising: purified, recombinant AAV vector particles	**Frei's D-1**: "In the following three examples [including D-1], stable concentrations of adenovirus were prepared…. The preparations were then subjected to further purification by Superdex-200 gel filtration chromatography to obtain the final formulation" (Ex.1004, 22:17-21). **Frei**: "A wide range of viruses can be used in the compositions of the present invention, including but not limited to…adeno-associated viruses" (*id.*, 8:18-21). "The viruses are preferably recombinant viruses" (*id.*, 8:22-23). "The compositions of the present invention are useful in maintaining the stability of viruses during storage" (*id.*, 1:16-17). **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	**Frei's D-1**: "Conc. = 1.6 x 10^{13} particles/ml" (Ex.1004, 22:31). **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	**Frei's D-1**: "20 mM NaPi [buffer]…pH 8 at 2-10°C" (Ex.1004, 22:26-27); Ex.1025, ¶232.
excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate	**Frei's D-1**: "2 mM $MgCl_2$" (Ex.1004, 22:26).
wherein the ionic strength of the composition is greater than 200 mM	**Frei's D-1**: "20 mM NaPi, 100 mM NaCl, 2 mM $MgCl_2$" (*id.*, 22:26) yields an ionic strength of ~160mM (Ex.1025, ¶239). **Frei**: "Preferably, the salt is sodium chloride present in the amount of 0.6 to 10.0 mg/ml" (*id.*, 5:39-6:5). Increasing the NaCl in D-1 to 10mg/mL (171.94mM) yields an ionic strength of ~231mM (Ex.1025, ¶240).
and wherein the purified AAV vector particles are stored in the composition without significant aggregation.	**Frei's D-1**: "Light Scattering (A320/A260) = 0.22" (Ex.1004, 22:30), indicating no aggregation (Ex.1025, ¶249) (non-aggregated virus particles display DLS scores of 0.22-0.30).

	Frei: Tables 1-5 report light scattering data indicative of storage without aggregation for five exemplary adenovirus formulations (Ex.1004, 12-14; Ex.1025, ¶249).

The composition of challenged claim 1 is obvious over Frei, Huang, and Mingozzi, when taken with the general knowledge in the field, as evidenced by Wright, Clark, Gatlin, Croyle, Liu, and Patent Owner's admissions. Ex.1025, ¶¶215-252.

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

Frei is directed to "compositions comprising viruses, especially viral vectors" that "are useful in maintaining the stability of the virus during storage." Ex.1004, 1:15-17. Frei demonstrates a formulation (Example D-1) comprising "stable concentrations of adenovirus [] prepared by concentrating DEAE pools in 30% glycerol" followed by "further purification by Superdex-200 gel filtration chromatography to obtain the final formulation." *Id.*, 22:17-31. Thus, Frei discloses a composition comprising purified virus particles.

To the extent the preamble of claim 1 is limiting, Frei discloses its compositions are for the storage of purified recombinant virus particles. *See, e.g.*, *id.*, 1:16-20 ("The compositions of the present invention are useful in maintaining the stability of viruses during storage, and virus-containing compositions of the

present invention are particularly useful for therapeutic uses such as gene therapy. New methods for concentrating and purifying virus preparations are also provided."); 8:22-23 ("The viruses are preferably recombinant viruses"); Ex.1025, ¶¶216-218. Frei also reports results from experiments that involved storing several exemplary adenovirus compositions. *See, e.g.*, Ex.1004, Tables 1-5.

A POSA would have been motivated to apply Frei's teachings to AAV because Frei disclosed that its methods and compositions could be used with AAV. *Id.*, 8:18-21. Additional motivation comes from the teachings in Mingozzi, Wright, and Clark touting AAV's advantages. *See* §VIII.A.1 *supra*; Ex.1025, ¶¶219-220.

As discussed in §VIII.A.1, even if a POSA would have viewed Frei's teachings regarding storage stability as being limited to adenovirus, she would have reasonably expected Frei's compositions to provide similar, if not better stability for storing AAV particles based on Croyle's report that AAV "is significantly more stable than the adenovirus." Ex.1013, 1283; Ex.1025, ¶¶221-222. Thus, despite Patent Owner's prosecution arguments to the contrary discussed in §VIII.A.1, Frei 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; *see also PGS*, 891 F.3d at 1365; *Urbanski*, 809 F.3d at 1244.

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

Frei's D-1 composition has a virus concentration of "1.6 x 10^{13} particles/ml." Ex.1004, 22:31. Provided that >62.5% of the particles contain vector genomes, Frei's D-1 composition comprises viral vector particles exceeding $1x10^{13}$vg/ml, as recited in challenged claim 1. Ex.1025, ¶¶223-224.

Even if Frei's D-1 composition contained >38.5% empty capsids, a POSA would have been motivated to remove those empty capsids while maintaining Frei's purified virus concentration to prepare therapeutically useful amounts of AAV particles via parenteral administration. *Supra* §VIII.A.2 (citing Huang, Mingozzi, Clark, Gatlin); Ex.1025, ¶¶225-226. Patent Owner admitted as much in the '542 patent. *See, e.g.*, Ex.1001, 2:11-14. Thus, a POSA would have been motivated to develop compositions having vector genome concentrations exceeding 10^{13}vg/ml.

A POSA would have reasonably expected success in achieving such concentrations because Frei itself taught that "[t]he formulation of the present invention has the additional advantage of having the ability to stabilize high concentrations of virus." Ex.1004, 7:7-8. As explained above, a POSA would have reasonably expected a composition having a concentration exceeding $1x10^{13}$vp/mL, as in Frei's D-1 composition, to exhibit similar stability as a composition having the

claimed concentration of "exceeding $1x10^{13}$vg/ml." *Supra*, §VIII.A.6; Ex.1025, ¶227.

Moreover, by June 2004, methods of generating high yields of AAV were well-known, as were methods for removing empty capsids and concentrating genome-containing vectors. *Supra*, §VIII.A.2 (citing Clark, Wright, Huang). Frei itself provides "[n]ew methods for concentrating and purifying virus preparations." Ex.1004, 1:19-20, 19:25-21:35. A POSA would have understood that such methods could be used to successfully remove empty capsids while maintaining or even increasing Frei's D-1 purified virus concentration. Ex.1025, ¶228.

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). Thus, a POSA would have reasonably expected success in preparing high-concentration AAV compositions (*e.g.*, exceeding $1x10^{13}$vg/ml) for use in gene transfer therapies. Ex.1025, ¶229.

Accordingly, Frei 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"

Frei's D-1 composition comprises a sodium phosphate buffer ("20 mM NaPi") and has "pH 8 at 2-10°C" (Ex.1004, 22:26-27), which falls within the pH of "between 7.5 and 8.0" recited in challenged claim 1. *See* Ex.1001, claim 1. Thus, the pH limitation of challenged claim 1 is anticipated. *Connell*, 722 F.2d at 1548; *Wertheim*, 541 F.2d at 267; Ex.1025, ¶¶231-233.

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

Frei's D-1 composition contains "2mM $MgCl_2$." Ex.1004, 22:26. Thus, D-1 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, ¶¶234-235.

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

Frei's D-1 composition contains "20mM NaPi, 100mM NaCl, 2mM $MgCl_2$," yielding an ionic strength of ~160mM. Ex.1004, 22:26; Ex.1025, ¶¶236-239. However, Frei taught that "[p]referably, the salt is sodium chloride present in the amount of 0.6 to 10.0 mg/ml." Ex.1004, 5:39-6:5. Increasing the NaCl concentration in Frei's D-1 composition to the high-end of that range yields an ionic strength of

~231mM, which satisfies the "greater than 200mM" recited in challenged claim 1. Ex.1025, ¶240.[7]

A POSA would have been motivated to select the high end of Frei's concentration ranges, since Wright identified ionic strength as a condition that may affect vector aggregation. Ex.1007, 175; Ex.1025, ¶¶241-243. Frei itself teaches that "[i]n addition to stabilizing the composition, sodium chloride may suppress the rate and extent of the appearance of by-products of fermentation, resulting in a more pharmaceutically elegant presentation that may have reduced antigenicity potential due to protein aggregates" and "[t]he addition of sodium chloride does not affect the pH of the formulation." Ex.1004, 6:7-11. Moreover, the '542 patent admits "AAV2 vectors require elevated concentrations of salt to prevent aggregation." Ex.1001, 1:54-55; *see also id.*, 4:67-5:2. And selection of an appropriate ionic strength for a therapeutic composition is a matter of routine optimization. Ex.1025, ¶246; *Aller,* 220 F.2d at 456; *Senju*, 780 F.3d at 1353.

[7] Frei likewise taught "[p]referably, the salt (*e.g.*, the magnesium salt) is present in an amount of from about 0.1 to 1 mg/mL." Ex.1004, 5:34-36. Modifying Frei's D-1 composition to comprise the high-end of that range would further increase the ionic strength by 24mM. Ex.1025, ¶240, n.7.

A POSA would have reasonably expected success in using the high ends of Frei's concentration ranges based on the teachings of Potter, Liu, Wright, and the admissions in the '542 patent. *Supra*, §VIII.A.5; Ex.1025, ¶¶243-245. Accordingly, Frei renders obvious "wherein the ionic strength of the composition is greater than 200 mM." *Alcon*, 687 F.3d at 1368.

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

A POSA would have been motivated to develop compositions capable of storing AAV vector particles "without significant aggregation" based on the teachings of Huang, Wright, and the admissions in the '542 patent. *Supra*, §VIII.A.6; Ex.1025, ¶¶188-189.

A POSA also would have reasonably expected Frei's D-1 composition to prevent "significant aggregation." Frei's light scattering data confirms its D-1 composition prevented aggregation. Ex.1025, ¶¶248-250. Although Frei reported its virus concentration in vp/ml, the inventors admitted in both the '542 patent and in Wright that empty capsids contribute to virus aggregation and that "full vector particles and empty capsids [presumably] aggregate by a similar mechanism," so there is really no difference as it relates to aggregation. Ex.1001, 1:60-64; *see also id.*, 1:46-48, 4:65-67, 7:13-17; Ex.1007, 175; Ex.1025, ¶250. Thus, a POSA would have expected an AAV composition having a concentration exceeding $1x10^{13}$vp/mL,

as in Frei's D-1 composition, to exhibit levels of aggregation similar to an AAV composition having a concentration "exceeding $1x10^{13}$vg/ml," as recited in challenged claim 1. Ex.1025, ¶250.

A POSA also would have reasonably expected no aggregation after storage, since Frei teaches its compositions "are useful in maintaining the stability of viruses during storage," and "are stable at typical refrigeration temperatures of *e.g.*, 2° to 8°C, or higher, for substantial periods of time, preferably for several months or more." Ex.1004, 1:16-19, 4:32-34. Indeed, Frei taught that its salt-containing DEAE pool could be stored "for >10 days at 2-10°C (thus allowing for subsequent steps of virus concentration and/or gel filtration to be performed on separate days with substantial flexibility across a 10 day period." Ex.1004, 22:10-12. Frei also demonstrated stability after short- and long-term storage (1 week to 12 months) for multiple adenoviral compositions, albeit at lower virus concentrations. *See, e.g.*, *id.*, Tables 1-5.[8] Ex.1025, ¶249.

[8] Liu likewise reported "no signs of settling or precipitation" and "no significant decrease in particle number" after storing its high ionic strength adenovirus compositions for 7 days at ~4°C, although at lower concentrations than Frei's D-1 composition. Ex.1009, [00366]-[00369], Table 15.

A POSA would have reasonably expected an AAV composition having a concentration of $1.6x10^{13}$vp/mL, as in Frei's D-1 composition, to exhibit even greater stability than the adenovirus compositions tested in Frei's Tables 1-5, since Croyle taught that AAV "is significantly more stable than the adenovirus." Ex.1013, 1283. And Wright already described compositions capable of storing purified AAV vector particles at the claimed concentrations "without significant aggregation," and therefore, this claim element cannot form the basis of patentability. Ex.1007, 175; *supra*, §VIII.A.6; Ex.1025, ¶251.

Since the structural components recited in challenged claim 1 were obvious based on the teachings of Frei, Huang, and Mingozzi, the lack of "significant aggregation" recited in challenged claim 1 is also obvious. *Atlas Powder*, 190 F.3d at 1347; Ex.1025, ¶252. For at least these reasons, challenged claim 1 is unpatentable.

B. Claim 2 is Obvious Over Frei 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. Frei motivated the use of Pluronic® F68 in its D-1 composition with a reasonable expectation of success by teaching that "[a] surfactant, preferably a nonionic detergent such as a polyethylene fatty acid ester…can optionally be included" and that "[e]xemplary detergents include but are not limited to…PLURONIC®-F68 detergent." Ex.1004, 7:22-26, 7:38-8:10; Ex.1025, ¶¶253-254.

A POSA would have been further motivated and expected success from including Pluronic® F68 in Frei's D-1 composition based on the inventors' teachings in Wright that adding "Pluronic® F68…effectively prevent[s] 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, 1288; Ex.1025, ¶¶255-257.

Accordingly, the composition of challenged claim 2 was obvious.

C. Claim 5 is Obvious Over Frei 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 Owner admitted that the recited radius is exemplary of no "significant aggregation." *Id.*, 9:25-27; *supra*, §VIII.B. And Frei's light scattering data shows that its D-1 composition contained monomeric particles. Ex.1025, ¶¶258-259. As explained above, Patent Owner never disputed and, thereby, admitted the inherency of this recited feature. *Supra* §VIII.B.

To the extent claim 5 requires less aggregation than what Frei measured, a POSA would have been motivated to minimize any potential aggregation in Frei's D-1 composition based on Huang, Wright, and admissions in the '542 patent. *Supra*,

§VIII.B; Ex.1025, ¶260; *KSR*, 550 U.S. at 421. A POSA would have reasonably expected success in minimizing particle size in view of Huang and Liu. *Supra*, §VIII.B. Indeed, Frei teaches its compositions "are useful in maintaining the stability of viruses during storage," and "are stable at typical refrigeration temperatures of *e.g.*, 2° to 8°C, or higher, for substantial periods of time, preferably for several months or more." Ex.1004, 1:16-19, 4:32-34. And a POSA would have understood that AAV "is significantly more stable than the adenovirus." Ex.1013, 1283. Thus, only routine optimization of the known stabilization factors in Frei's D-1 composition would be required to obtain an average AAV Rh <20 nm. Ex.1025, ¶¶261-266; *Senju*, 780 F.3d at 1353.

Accordingly, the composition of challenged claim 5 was obvious.

D. Claim 6 is Obvious Over Frei 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. As explained above, Patent Owner never disputed and, thereby, admitted the inherency of this recited feature. *Supra* §VIII.C; Ex.1025, ¶¶267-268.

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.C; Ex.1025, ¶269.

A POSA also would have reasonably expected success in minimizing vector aggregation, and thereby maximizing particle recovery after filtration, in view of Frei, Huang, Liu, and Croyle. *Supra* §VIII.C. Thus, to the extent Frei's D-1 formulation requires 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, ¶¶270-273; *Senju*, 780 F.3d at 1353.

Accordingly, the composition of challenged claim 6 was obvious.

XI. SECONDARY CONSIDERATIONS

Petitioners are unaware of any secondary considerations that would outweigh the compelling conclusion of obviousness set forth above, and reserves the right to address any such evidence submitted in this proceeding.

XII. 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).

1. *Advanced Bionics* Part One

During prosecution, Evans, Frei, and Mingozzi were not cited, and Huang and Wright were only discussed in the Background of the '542 patent.[9] Ex.1002, 51-54. The art asserted in Grounds 1-3 and Petitioners' associated arguments are not cumulative with those substantively considered during prosecution because, unlike the references cited herein, none of the references applied during prosecution teaches achieving high-titer recombinant virus particles stored in stable formulations without aggregation. *Supra* §§VIII-X.

The Examiner's prior art rejections instead relied on Zolotukhin's (Ex.1026) use of high ionic strength *elution buffers* during AAV purification, and secondary references teaching formulations for hepatitis and non-virus proteins. Ex.1002, 315.

[9] During prosecution, the Examiner cited U.S. Publication No. 2004/0166122 ("Evans 2" (Ex.1027)), which is essentially identical to Evans. As explained *infra*, Evans 2 was never applied by the Examiner as prior art despite it being prior art to the '542 patent under 35 U.S.C. §102(e), and Evans was never identified or applied at all.

In contrast, Evans and Frei each teach *storing* high titer virus compositions with improved stability, directly matching the challenged claim language. *Supra* §§VIII.A.1. and X.A.1. Indeed, Frei specifically teaches its D-1 formulation exhibited no aggregation, and Mingozzi achieved successful gene delivery *in vivo* with its high-titer AAV compositions. *Supra* §§VIII.A.6. and X.A.6. Neither of these teachings can be found in the references cited during prosecution or discussed by the Examiner.

Huang reports successfully reducing aggregation in high-titer AAV compositions. *Supra* § VII.B. These teachings are not discussed in the Background of the ’542 patent and are non-cumulative with the art applied by the Examiner, which never mentioned reducing virus particle aggregation in recombinant AAV compositions, much less recombinant high-titer AAV compositions. *E.g.*, Ex.1002, 315. Wright’s teachings (1) listing known factors to control aggregation, and (2) linking (i) AAV and adenovirus formulation techniques, (ii) 0.2μm filtration recovery rates to aggregation levels, and (iii) empty capsids to aggregation, provided motivation and reasonable expectation of arriving at the challenged claims. *Supra*, §VII.D. None of these teachings can be found in the references applied by the Examiner, and it was material error for the Examiner to ignore these highly relevant and non-cumulative teachings in Huang and Wright.

Furthermore, because the Examiner never applied Evans, Frei, and Mingozzi as prior art and also failed to substantively evaluate the relevant teachings in Huang and Wright, he did not have the opportunity to consider the combinations of references asserted in Grounds 1-3 or Petitioners' 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.

2. *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 15 (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 16 (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 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, and Wright's teachings that render the challenged claims obvious. *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]").

Second, despite the Examiner's mention of Evans 2 as "pertinent art," he failed to realize Evans 2 is 35 U.S.C. §102(e) *prior* art, and mistakenly excluded that reference from his obviousness rejections. Ex.1002, 191, 224, 321. Specifically, although Evans 2 was published after the '542 patent's priority date, it was filed nearly three months *before* the '542 patent's priority date as a continuation of a parent application filed nearly *three years before* the '542 patent's priority date. Ex.1027, (60). The Examiner also missed two earlier-published versions of Evans 2 (Evans and U.S. Publication No. 2002/0041884), neither of which was cited during prosecution, and both of which are 35 U.S.C. §102(b) prior art. Ex.1004; Ex.1028.

The Examiner's discussions of Evans 2 in sections at the end of his Office Actions titled "pertinent art" notably contrast with his discussions of "pertinent *prior*

art" in Office Actions issued in the parent patent, further indicating that he misunderstood Evans 2 as non-prior art. *Compare* Ex.1002, 191, 224, 321 (emphasis added) *with* Ex.1029, 137-38, 178-79, 278; *contra id.*, 94. The Examiner's failure to raise any rejections based on Huang, Wright, Evans, or Evans 2 constitutes material error. *See 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" and "was not the basis for a rejection.").

Third, 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, 41-64, 2:9-47, 1:54-55, 4:67-5:2. 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).

XIII. 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, IPR2023-00609.

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

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XIV. 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 13,945 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 1001-1029** 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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