

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KELONIA THERAPEUTICS, INC.
Petitioner

v.

INTERIUS BIOTHERAPEUTICS, INC.
Patent Owner

U.S. Patent No. 11,767,366

**PETITION FOR POST-GRANT REVIEW
OF U.S. PATENT NO. 11,767,366**

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I. INTRODUCTION

U.S. Patent No. 11,767,366 (“the ’366 patent”) is generally directed to mutants of vesicular stomatitis virus glycoprotein (“VSV-G”). The ’366 patent’s purported innovation lies in allegedly novel amino acid mutations to VSV-G that inhibit the binding of VSV-G to its native receptor without altering its normal role of mediating fusion with cellular targets and protect against serum inactivation. These claimed mutations either alone or in combination, however, were well-known and obvious in the art.

While unnoticed by the Examiner, the prior art plainly disclosed mutations at the primary amino acid position of VSV-G claimed by the ’366 patent. These mutations were therefore both anticipated and obvious in view of the prior art, including state-of-the-art crystal structures of VSV-G that would have guided a person of ordinary skill directly to the specific mutations that the ’366 patent alleges to be novel. Additional mutations alleged to evade serum inactivation of VSV-G had also been reported years before the priority date of the ’366 patent.

Therefore, as demonstrated below and in the supporting declaration submitted by Professor John K. Rose, Ph.D., claims 1-30 of the ’366 patent (“the challenged claims”) are rendered anticipated and obvious in view of the prior art. Petitioner therefore requests that this Petition be granted and that the challenged claims be found unpatentable and canceled.

II. MANDATORY NOTICES

Real Parties-in-Interest: Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner identifies the following as the real parties-in-interest: Kelonia Therapeutics, Inc.

Related Matters: There are no related matters.

The '366 patent issued on September 26, 2023 from Application No. 18/066,420 (“the '420 application”). The '420 application was filed on December 15, 2022, and claims priority to U.S. Provisional Application No. 63/289,888, filed on December 15, 2021, U.S. Provisional Application No. 63/289,977, filed on December 15, 2021, U.S. Provisional Application No. 63/266,044, filed on December 27, 2021, and U.S. Provisional Application No. 63/267,039, which was filed on January 21, 2022.

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III. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15 AND 42.103

The PTO is authorized to charge any fees due during this proceeding to Deposit Account No. 50-2613.

IV. GROUNDS FOR STANDING

Petitioner certifies under 37 C.F.R. § 42.204(a) that the '366 patent is available for post-grant review and that Petitioner is not barred or estopped from requesting post-grant review on the grounds identified herein.

V. PRECISE RELIEF REQUESTED AND GROUNDS RAISED

Petitioner respectfully requests review of claims 1-30 of the '366 patent and cancellation of these claims as unpatentable. The challenged claims should be found unpatentable based on the following grounds:

Ground 1: Claims 1-3 and 10-25 are unpatentable under 35 U.S.C. § 102 as anticipated by International Application Pub. No. WO 2022/183072 ("*Perkins*") (Ex. 1005).

Ground 2: Claims 3-9 and 26-30 are unpatentable under 35 U.S.C. § 103 as obvious based on *Perkins* (Ex. 1005) and B. Hwang and D. Schaffer, *Engineering a serum-resistant and thermostable vesicular virus G glycoprotein for pseudotyping retroviral and lentiviral vectors*, 20(8) GENE THER. 807-815 (2013) ("*Hwang*") (Ex. 1007).

Ground 3: Claims 1-3 and 10-25 are unpatentable under 35 U.S.C. § 103 as obvious based on *Perkins* (Ex. 1005) in view of the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Databank (PDB) ("*RCSB PDB*").

Ground 4: Claims 3-9 and 26-30 are unpatentable under 35 U.S.C. § 103 as obvious based on *Perkins* (Ex. 1005) in view of the *RCSB PDB* and *Hwang* (Ex. 1007).

The *RCSB PDB* does not appear in the '366 patent's "References Cited" Section. Although *Perkins* and *Hwang* appear in the "References Cited" section, there is no indication that the Patent Office substantively considered *Perkins* or *Hwang*. Moreover, the Patent Office did not consider *Perkins* in combination with the *RCSB PDB* and *Hwang*.

The earliest application to which the '366 patent purports to claim priority has a filing date of December 15, 2021. Even if claims 1-30 of the '366 patent are entitled to a priority date of December 15, 2021—which Petitioner does not concede—*Perkins* qualifies as prior art under 35 U.S.C. §102(a)(2) based on its earlier effective filing date of February 26, 2021. *RCSB PDB* and *Hwang* qualify as prior art under 35 U.S.C. §102(a)(1) based on the publication date identified in Section VIII for these references.

VI. BACKGROUND

A. Overview of the Technology

1. Gene Therapy with Lentiviral Vectors

By the 1990s, gene therapies involving the insertion of a DNA molecule ("a retroviral vector") carrying a gene of interest into a cell had become appealing for

the treatment of patients with immunodeficiencies or cancer. (*See, e.g.*, Ex. 1008 at 1; Ex. 1002 at ¶ 22.)¹ In particular, the use of lentiviral vectors (*i.e.*, retroviral vectors that come from lentiviruses, a type of virus that includes HIV), was known as early as 1996 to provide stable and effective delivery of genes into cells. (*See, e.g.*, Ex. 1009 at 263; Ex. 1008 at 1; Ex. 1002 at ¶ 22.)

By the 2020s, lentiviral vectors were known to be “among the most promising vectors” for cellular therapies and, for certain cells, “the tools of choice.” (*See, e.g.*, Ex. 1010 at 1; Ex. 1008 at 1; Ex. 1002 at ¶ 23.) This stems not only from their stable and effective delivery of genes into cells, also known as cell “transduction,” but also a lower probability of inducing an innate immune response during cell transduction. (*See, e.g.*, Ex. 1010 at 2; Ex. 1002 at ¶ 23.) Lentiviral vectors were known to be able to carry an envelope protein that mediates cell transduction. (*See, e.g.*, Ex. 1010 at 1-2; Ex. 1002 at ¶ 23.) The nature of the envelope protein carried by a lentivirus vector “is the major determinant for the specificity of transduction.” (*See, e.g.*, Ex. 1010 at 1; Ex. 1002 at ¶ 23.)

To expand the use of lentiviral vectors, researchers have commonly replaced the envelope protein of a lentivirus with those of other viruses, a process called

¹ Unless otherwise noted, this Petition cites the original page numbering of any non-patent exhibits.

“pseudotyping.” (*See, e.g.*, Ex. 1010 at 2; Ex. 1012 at 130; Ex. 1002 at ¶ 24.)

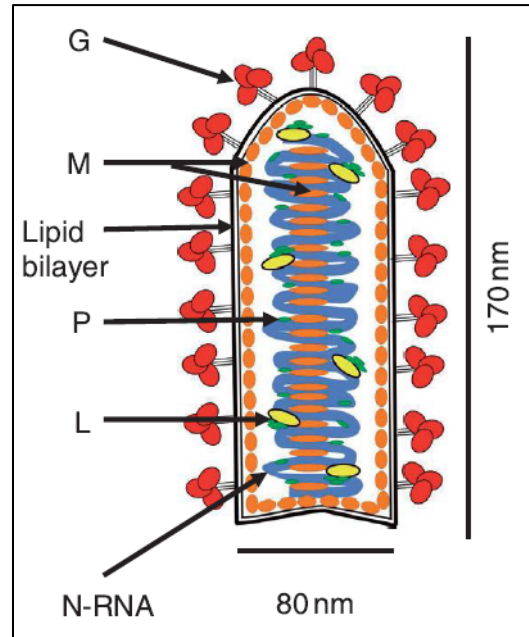
Pseudotyping lentiviral vectors with envelope proteins of different viruses allows for the properties of lentiviruses to be combined with the viral entry properties of other viruses. (*See, e.g.*, Ex. 1010 at 7; Ex. 1002 at ¶ 24.) For instance, some envelope proteins possess a broad tropism, also called “pantropism,” which means they have the ability to infect a wide gamut of cell types. (*See, e.g.*, Ex. 1010 at 1; Ex. 1002 at ¶ 24.) This property, however, also makes their use more challenging for *in vivo* treatments, where “a high specificity for the target cells is required to avoid off-target transduction.” (*See, e.g.*, Ex. 1010 at 1; Ex. 1002 at ¶ 24.)

By the 2020s, it was known that pseudotyping lentiviral vectors by the vesicular stomatitis virus envelope glycoprotein (G) was the most common approach for pseudotyping lentiviral vectors. (*See, e.g.*, Ex. 1010 at 9; Ex. 1002 at ¶ 25.) For instance, it was reported in 2013 that “VSV-G-pseudotyped lentiviruses exhibit the same broad tropism as VSV, excellent stability, and high transduction efficiency, rendering them the gold standard for experimental gene transfer procedures.” (*See, e.g.*, Ex. 1016 at 7307; Ex. 1002 at ¶ 25.)

2. Vesicular Stomatitis Virus Glycoprotein

VSV-G is a transmembrane glycoprotein (G) that is incorporated into the lipid bilayer in VSV viral particles and mediates attachment of VSV to host cells through VSV-G-host cell receptor binding, and catalyzes fusion of viral and cellular

membranes to initiate infection. (*See, e.g.*, Ex. 1011 at 291-292, 296; Ex. 1002 at ¶ 26.) A schematic illustration of a VSV viral particle is reproduced below for illustration:



The interior of VSV viral particles were known to include an “N-RNA” ribonucleoprotein core associated with two viral components: the large polymerase protein (“L”), and the accessory phosphoprotein (“P”), which form the replication machinery of the virus, and a matrix (“M”) protein that mediates particle assembly and is efficiently incorporated into virions during the process of viral assembly. (*See, e.g.*, Ex. 1011 at 291-292, 295-96, FIG. 1; Ex. 1002 at ¶ 27.) The exterior of a VSV viral particle was known to contain a lipid envelope (“lipid bilayer”) decorated with trimeric spikes of the VSV-G (G) protein. (*See, e.g., id.*)

VSV-G was known to have “a critical role during the initial steps of virus infection,” including both recognition and binding of the receptor at the cell surface, and subsequently in mediating “the fusion between the viral and endosomal membranes.” (*See, e.g.*, Ex. 1012 at 118; Ex. 1002 at ¶ 28.) In particular, after receptor binding, VSV was understood to enter a cell by the endocytic pathway. (*See, e.g.*, Ex. 1012 at 120-121; Ex. 1015 at 1717; Ex. 1002 at ¶ 28.) Subsequently, “the viral envelope fuses with a cellular membrane within the acidic environment of the endosome.” (*See, e.g.*, Ex. 1015 at 1717; Ex. 1002 at ¶ 28.) Fusion was known to be triggered by the low pH of the endosome and mediated by the VSV-G glycoprotein, with optimal fusion occurring at pH 6. (*See, e.g.*, Ex. 1015 at 1717; Ex. 1012 at 120; Ex. 1002 at ¶ 28.)

By the mid to late 2000s, crystal structures of the pre-fusion and post-fusion states of VSV-G had been published. (*See, e.g.*, Ex. 1013 at 843; Ex. 1014 at 187.) Armed with this structural characterization of VSV-G, researchers investigated the regions of VSV-G’s structure that were responsible for the fusion characteristics of VSV-G, including identifying which mutations potentially impacted the fusion properties of VSV-G. (*See, e.g.*, Ex. 1015 at 1722 (Table 1); Ex. 1002 at ¶ 29.)

In 2013, the native receptor for VSV-G binding—which had until then remained elusive—was determined to be the low-density lipoprotein receptor (“LDL-R”). (*See* Ex. 1016 at 7306, 7310; Ex. 1002 at ¶ 30.) This helped to explain

the broad tropism of VSV-G, as the LDL-R is a highly ubiquitous receptor found in many cell types. (*See* Ex. 1016 at 7306; Ex. 1002 at ¶ 30.) It also explained why VSV-G pseudotyped lentiviral vectors did not provide efficient transfer of genetic materials in certain desirable gene-therapy targets, such as quiescent T cells, as these cells had low expression of the LDL-R. (*See, e.g.*, Ex. 1017 at 1422-23; Ex. 1002 at ¶ 30.)

3. Making “Mutations” to Prepare Mutants of VSV-G

A POSA would have understood that nucleotides (or “nucleic acids”)—the building blocks of genetic information—can be joined together to form polymers of nucleic acids, also known as “polynucleotides.” (*See, e.g.*, Ex. 1022 at 39-44; Ex. 1002 at ¶ 31.) Polynucleotides are nucleic acid molecules that include both deoxyribonucleic acid (“DNA”) and ribonucleic acid (“RNA”). (*See, e.g.* Ex. 1022 at 39-44; Ex. 1002 at ¶ 31.)

DNA contains genes that encode for the production of amino acid polymers, or “polypeptides,” which includes proteins. (*See, e.g.*, Ex. 1022 at 49, 78; Ex. 1002 at ¶ 32.) A POSA would have understood that changes to the DNA sequence, also known as “mutations,” could result in proteins with altered amino acids, structures, functions, and expression levels. (*See, e.g. id.*) This can occur, for instance, when one or more altered DNA nucleotides results in an altered amino acid sequence for the encoded protein. (*See, e.g., id.*)

Proteins are composed of 20 “standard” amino acids. (*See, e.g.*, Ex. 1022 at 74-77; Ex. 1002 at ¶ 33.) A POSA was also well aware of the abbreviated one-letter symbols for amino acids. (*See, e.g.*, Ex. 1022 at 76-77, 81-82; Ex. 1002 at ¶ 33.) For example, the amino acid “isoleucine” using its one-letter symbol is referred to as “I.” (*See, e.g.*, Ex. 1022 at 76; Ex. 1002 at ¶ 33.)

Wild-type VSV-G includes a 16 amino acid signal peptide (also referred to as a “signal sequence”). (*See, e.g.*, Ex. 1001 at 1:36-39, 17:32-39, 17:31-19:23; Ex. 1005 at 12:16-29, 20:15-18, 74 (SEQ ID NO: 88); Ex. 1006 at 9-10, 17, 50 (SEQ ID NO: 72), 51 (SEQ ID NO: 78); Ex. 1002 at ¶ 34.) In the wild-type amino acid sequence of VSV-G absent its signal peptide, the amino acid at position 182 is isoleucine, which in one-letter code is represented by “I182.” (*See, e.g.*, 1005 at 74-75 (SEQ ID NO: 90); Ex. 1002 at ¶ 34.) In the amino acid sequence of VSV-G with its signal sequence still present, the same isoleucine would be represented by I198, which is shifted forward 16 positions to account for the signal peptide. (*See, e.g.*, Ex. 1002 at ¶ 34.)

A POSA would have understood that mutations at a single amino acid residue can be easily represented by the one-letter amino acid symbol. (*See* Ex. 1002 at ¶ 35.) For instance, if the native isoleucine (I) at position 182 of VSV-G is to be mutated to glutamic acid (E), this would be represented by a “I182E” mutation. (*See, e.g.*, Ex. 1022 at 77; Ex. 1002 at ¶ 35.) In order for a DNA molecule to encode the

VSV-G protein including a “I182E” mutation, its nucleic acid sequence would need to be altered to reflect the corresponding change in amino acid from isoleucine to glutamic acid in the encoded protein. (*See* Ex. 1002 at ¶ 35.)

4. Engineering of VSV-G Pseudotyped Lentiviral Vectors

To best utilize the VSV-G pseudotyped lentiviral vectors, which had become the gold standard for experimental gene transfer procedures, researchers sought to modify the tropism of VSV-G and tailor it to certain high-impact gene therapy applications. (*See, e.g.*, Ex. 1005 at 4:1-23, 90:25-91:11, 110:24-116:23; Ex. 1002 at ¶ 37.) These applications included, for instance, the efficient engineering of T-cells, both *ex vivo* and *in vivo*, for potential anti-cancer treatments. (*See, e.g.*, Ex. 1005 at 96:11-98:6; Ex. 1002 at ¶ 37.)

Importantly, Nikolic *et al.* reported in 2018 the crystal structure of VSV-G bound to the LDL-R. (*See* Ex. 1018 at 1.)² This study established that VSV-G binds to either one of two specific cysteine-rich domains of the LDL-R, known as “CR3” and “CR2.” (*See, e.g.*, Ex. 1018 at 1, 4-5; Ex. 1002 at ¶ 38.) This study also demonstrated that “receptor-blind” mutants of VSV-G could be prepared that ablated the interaction with the LDL-R, and at the same time retained the membrane fusion

² The crystal structures of VSV-G bound to the LDL-R was submitted to the *RCSB PDB* and made publicly available in 2018. (*See, e.g.*, Exs. 1024, 1025, 1026.)

activity of VSV-G, thereby suggesting a pathway for “develop[ing] recombinant VSVs with modified tropism.” (*See, e.g.*, Ex. 1018 at 10; *see also id.* at 8-9 (“it is possible to uncouple G fusion protein activity and receptor protein recognition”); Ex. 1002 at ¶ 37.)

The Nikolic *et al.* study had important ramifications for anti-cancer therapies, such as replacing the wide tropism of VSV-G with specific targeting to a tumor cell, which “should allow for the design of fully retargeted oncolytic VSVs” that “should be able to eliminate cancerous cells while sparing normal ones.” (*See, e.g.*, Ex. 1018 at 10; Ex. 1002 at ¶ 38.) Specific mutations in VSV-G were subsequently discovered and disclosed in the prior art that modified the tropism of VSV-G to better suit cellular therapy applications, including mutations at “I182” of VSV-G, among other positions. (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27; Ex. 1006 at 17-18; Ex. 1019 at ¶¶ [0015]-[0016]; Ex. 1002 at ¶ 38.)

It was also well-known that serum inactivation of VSV-G pseudotyped vectors posed a significant challenge for *in vivo* gene delivery. (*See, e.g.* Ex. 1020 at 218; Ex. 1007 at 807; 1002 at ¶ 39.) To overcome this challenge, researchers discovered and disclosed specific mutations that provided protection against serum inactivation of VSV-G, including “T214N” and “T352A.” (*See, e.g.*, Ex. 1007 at 807, 809, 811; *see also* Ex. 1021 at ¶¶ [0005], [0030]; 1002 at ¶ 39.) They further proposed that “incorporating a VSV variant encoding a human serum-resistant and

thermostable VSV-G may enhance the therapeutic potential of VSV for treating human cancer.” (*See, e.g.*, Ex. 1007 at 813; Ex. 1002 at ¶ 39.)

B. Overview of the '366 Patent

The '366 patent issued on September 26, 2023 from Application No. 18/066,420 (“the '420 application”), filed on December 15, 2022. The '366 patent claims priority to four U.S. provisional applications, two filed on December 15, 2021, one filed on December 27, 2021, and one filed on January 21, 2022.

The '366 patent claims a combination of disclosed technologies relating to the mutation of VSV-G and related viral applications. The first challenged independent claim, claim 1, reads as follows:

A polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2 and a I182E mutation as compared to SEQ ID NO. 2.

The second challenged independent claim, claim 2, is the same as claim 1, but recites a I182D mutation instead of a I182E mutation.

The challenged dependent claims of independent claim 1 (including claims 3-5 and 9-21) and the challenged dependent claims of independent claim 2 (including claims 6-8 and 22-30) do not add anything of significance and instead recite basic features, such as known components of a lentiviral vector application of VSV-G (Ex. 1001 at 145:47-146:16), percent identity between sequence ID Nos. (*id.* at 146:17-

40), and additional known mutations to provide protection against serum inactivation of VSV-G in a lentiviral vector (*id.* at 145:19-40).

C. Overview of the '366 Patent Prosecution History

During prosecution of the '420 application, which ultimately issued as the '366 patent, the Examiner issued a June 23, 2023 Non-Final Rejection that objected to claim language and raised a provisional double patenting rejection, but did not otherwise raise any novelty or obviousness rejections based on prior art. (*See* Ex. 1004 at 1484-89.) In response to this Non-Final Rejection, on June 28, 2023, the Applicant filed a response with claim amendments. (*Id.* at 1522-28.) On July 26, 2023, the Examiner issued a Notice of Allowance. (*Id.* at 1616-27.) The Examiner's reasons for allowance indicated:

The prior art does not teach or suggest VSV-G envelope proteins (SEQ ID NO: 2) comprising the recited I182E or I182D substitution mutations. The closest relevant art is represented by Kim et al (US 20210106632), which teaches the VSV-G envelope protein comprising substitutions at residue 162.

(*Id.* at 1621.)

The Examiner's indication in the Notice of Allowance that "VSV-G envelope protein comprising substitutions at *residue 162*" is the "closest relevant art" makes clear that the Examiner did not consider prior art of record that expressly disclosed

substitutions at *residue 182*, such as *Perkins*. Indeed, of the three prior art references at issue here, *Perkins* and *Hwang* both were of record during prosecution of the '366 patent, but neither were cited or discussed by the Examiner. (Ex. 1001, Title Page.) The *RCSB PDB* was not of record during prosecution of the '366 patent.

VII. LEVEL OF ORDINARY SKILL

A person of ordinary skill in the art (“a POSA”) at the time of the alleged invention would have had an advanced degree in molecular biology, biochemistry, or an equivalent field, as well as one to three years of experience in retroviruses and the modification of envelope proteins associated with retroviruses.³ (Ex. 1002 at ¶ 21.) The challenged claims would have been unpatentable even if the definition for a POSA was altered to some extent to account for a slightly greater or lesser level of skill in the art, at least because the prior art discloses the claim limitations in a straightforward manner. (*Id.*)

³ Petitioner submits the declaration of Professor John K. Rose, Ph.D. (Ex. 1002), an expert in the field of the '366 patent. In 1981, Dr. Rose's laboratory reported the first sequence of VSV-G mRNA and protein determined from a cDNA clone (Ex. 1028), and then, in 1984, showed that cells expressing VSV-G protein in the absence of other VSV proteins would fuse at low pH. (Ex. 1029; Ex. 1002 at ¶ 7.)

VIII. OVERVIEW OF THE PRIOR ART

A. Overview of *Perkins*

International Application Pub. No. WO 2022/183072 (“*Perkins*”), titled “Lymphocyte Targeted Lentiviral Vectors,” was filed on February 25, 2022, and published on September 1, 2022. (Ex. 1005 at Cover Page.) *Perkins* claims priority to U.S. Provisional Application No. 63/154,639 (“the ’639 application”), which was filed on February 26, 2021. (Ex. 1006 at Filing Receipt). *Perkins* is prior art under 35 U.S.C. §102(a)(2) based on its earliest effective filing date of February 26, 2021.

Perkins described lentiviral vectors that are targeted to lymphocytes, *e.g.*, T-cells, in order to modify these cells and enable the treatment of diseases such as cancer. (See, *e.g.*, Ex. 1005 at Title, 96:1-17; Ex. 1006 at 1,⁴ 56; Ex. 1002 at ¶ 46.) In particular, *Perkins* disclosed “[e]ngineered lentiviral vectors” which include (1) “a mutated, heterologous *envelope protein*,” (2) “a *targeting protein*,” and (3) “at least one *transgene* for delivery to and expression by a cell characterized by the targeting protein.” (See, *e.g.*, Ex. 1005 at 4:2-4 (emphasis added); Ex. 1006 at 1; Ex. 1002 at ¶ 46.)

⁴ Citations to Ex. 1006 are to the internal page numbers of the specification of the ’639 application.

Perkins disclosed that the mutated heterologous envelope protein includes “at least one mutation that inhibits the envelope protein’s ability to bind its native target, while preserving the envelope protein’s fusogenic properties.” (*See, e.g.*, Ex. 1005 at 19:26-29; Ex. 1006 at 16; Ex. 1002 at ¶ 47.) For example, “the heterologous envelope protein is a vesicular stomatitis virus G protein . . . that includes one or more mutations that inhibit binding of VSV-G to the low-density lipid receptor (“LDL-R”) while preserving the VSV-G protein’s fusogenic function.” (*See, e.g.*, Ex. 1005 at 19:29-20:2; Ex. 1006 at 16; Ex. 1002 at ¶ 47.) *Perkins* specifically disclosed that the mutated VSV-G envelope protein includes a mutation at “I182,” among other amino acid positions. (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 47.)

Perkins disclosed that the targeting protein in some embodiments is selected to target an immune cell, for example a lymphocyte or T cell. (*See* Ex. 1005 at 4:5-6; Ex. 1006 at 1, 16, 18; Ex. 1002 at ¶ 48.) *Perkins* disclosed that the LVV is “capable of specifically binding to the target immune cell and transducing the target immune cell such that the transgene is expressed by the immune cell.” (Ex. 1005 at 19:16-21; Ex. 1006 at 16; Ex. 1002 at ¶ 48.) *Perkins* also disclosed that, “in further specific embodiments, the transgene encodes a chimeric antigen receptor (CAR).” (*Id.*)

B. *Perkins* Properly Claims Priority to the '639 Application

Perkins properly claims the benefit of its earlier '639 provisional application, which was filed on February 26, 2021, pursuant to 35 U.S.C. § 102(d). (Ex. 1006 at Filing Receipt; *see also* Ex. 1002 at ¶¶ 49-51.) The PCT international application published as *Perkins* was properly filed within a year of the '639 application on February 25, 2002. (Ex. 1005 at Cover Page.) *Perkins* further names at least one inventor in common, includes a specific reference to the '639 application, and claims the benefit of its earlier filing. (Ex. 1005 at Cover Page; Ex. 1006 at Filing Receipt.) Finally, as explained below, the subject matter in *Perkins* relied upon by Petitioner for its analysis finds support in the '639 application.

Specifically, *Perkins* meets the test laid out in *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375 (Fed. Cir. 2015), detailing when a non-provisional application can claim the benefit of its earlier provisional filing for purposes of serving as prior art in the instant proceeding.⁵ Specifically, the '639

⁵ Petitioner notes that, because the '366 patent is a post-AIA patent, the *Dynamic Drinkware* analysis is not necessary for *Perkins* to be entitled to the effective filing date of the '639 application. (Ex. 1006 at Filing Receipt.) This is because the prior art date for a published patent application, where such patent claims the benefit of a provisional application, is determined based on § 102(d)(2). *See* 35 U.S.C.

provisional application provides support for at least one claim of *Perkins*. *Ex parte Mann*, 2016 WL 7487271, at *6 (P.T.A.B. Dec. 21, 2016). The following chart demonstrates the support in the '639 application for claim 1 in the anticipatory *Perkins* reference:

<i>Perkins</i> at Claim 1 (Ex. 1005 at 117:1-10)	Support in the '639 Application (Ex. 1006)
A lentiviral vector, comprising:	<i>See, e.g.</i> , Ex. 1006 at 75 (claim 1); <i>see also id.</i> at 16
(a) a viral envelope comprising:	<i>See, e.g.</i> , Ex. 1006 at 75 (claim 1); <i>see also id.</i> at 16-18
a heterologous lymphocyte targeting protein, the lymphocyte targeting protein comprising:	<i>See, e.g.</i> , Ex. 1006 at 75 (claim 1); <i>see also id.</i> at 16, 18-19
an extracellular domain comprising a lymphocyte targeting domain; and	<i>See, e.g.</i> , Ex. 1006 at 75 (claim 1); <i>see also id.</i> at 16, 18-19
a transmembrane domain; and	<i>See, e.g.</i> , Ex. 1006 at 75 (claim 1); <i>see also id.</i> at 16, 18-19, 29-32

§ 102(d)(2). And § 102(d)(2) specifies that the published patent application is prior art as of the provisional application filing date if such provisional application “describes the subject matter” at issue in the published patent application. *Id.* Petitioner, however, provides an analysis under *Dynamic Drinkware* only out of abundance of caution.

(b) a mutated VSV-G envelope protein that exhibits inhibited binding to an LDL-R but mediates membrane fusion; and	<i>See, e.g.</i> , Ex. 1006 at 75 (claim 1); <i>see also id.</i> at 16-18
(c) an expression cassette that comprises a heterologous transgene.	<i>See, e.g.</i> , Ex. 1006 at 75 (claim 1); <i>see also id.</i> at 16, 26, 29-32, 41-42, 52

Consistent with the Board’s precedent, Petitioner further demonstrates that the ’639 application provides sufficient support for the subject matter relied upon in the reference patent. *See Forescout Techs., Inc. v. Fortinet, Inc.*, IPR2021-01328, Paper No. 12 at 9-10 (P.T.A.B. Jan. 27, 2022). Petitioner’s citations to *Perkins* throughout this Petition include additional citations to the ’639 application (Ex. 1006) that support the disclosures relied upon in *Perkins* for prior art purposes.

Perkins is thus prior art as of February 26, 2021.

C. Overview of the *RCSB PDB*

The *RCSB PDB* was “established in 1971” and known to be “the first open access digital resource in biology for sharing three-dimensional (3D) protein structures.” (*See, e.g.*, Ex. 1024 at 569; Ex. 1002 at ¶ 52.) The *RCSB PDB* was known to be “one of the most heavily used biological data resources worldwide,” and provided annotated information about 3D protein structures to the public. (*Id.*)

Crystal structures of VSV-G bound to the CR3 and CR2 domains of LDL-R were deposited to the *RCSB PDB* on September 8, 2017, and released to the public on March 21, 2018. (*See, e.g.*, Ex. 1025 at 1; Ex. 1026 at 1; Ex. 1002 at ¶ 53.) This

included entry “5OY9” for VSV-G bound to the CR3 domain (Ex. 1025), and entry “5OYL” for VSV-G bound to the CR2 domain (Ex. 1026). (Ex. 1002 at ¶ 53.)

An electronic publication, such as an online database or internet publication, is considered to be a “printed publication” within the meaning of 35 U.S.C. § 102(a)(1) “provided the publication was accessible to persons concerned with the art to which the document relates.” *See* MPEP 2128. Furthermore, “[p]rior art disclosures on the Internet or on an on-line database are considered to be publicly available as of the date the item was publicly posted.” *Id.* Accordingly, the *RCSB PDB* and its contents, including the 5OY9 and 5OYL crystal structures are prior art printed publications under 35 U.S.C. § 102(a)(1). *See Pfizer, Inc. v. Genentech, Inc.*, IPR2017-01489, Paper No. 84 at 5-6, 13-14, 55-56 (P.T.A.B. Nov. 29, 2018) (determining claims unpatentable based on the Protein Data Bank (PDB).)

The *RCSB PDB* was also “disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it and recognize and comprehend therefrom the essentials of the claimed invention without need of further research or experimentation.” *In re Wyer*, 655 F.2d 221, 226 (C.C.P.A. 1981). Indeed, the *RCSB PDB* was known to offer “free access to a broad range of primary research data and educational materials for all users. Structural entries in the PDB are

extensively annotated and validated according to current community standards, providing a rich resource for chemical exploration.” (*See, e.g.*, Ex. 1024 a 573.)

As explained in his accompanying declaration, Dr. Rose navigated to the *RCSB PDB* and downloaded the crystal structures associated with accession codes 5OY9 and 5OYL, which are in a *.pdb file format. (Ex. 1002 at ¶ 54.) The front page of the website for each of the structures under accession codes 5OY9 and 5OYL on the *RCSB PDB* is shown by Exs. 1025 and 1026, respectively. (Ex. 1002 at ¶ 54.)

It was also known that many “free resources and tools utilize PDB data to serve their users,” including UCSF’s “Chimera.” (*See, e.g.*, Ex. 1024 at 569; Ex. 1027 at 1605; Ex. 1002 at ¶ 55.) As of 2021, free navigation tools were commonly used to view and analyze structural data on the *RCSB PDB*. (Ex. 1002 at ¶ 55.) As explained by Dr. Rose, he accessed each of the *.pdb structure files associated with accession codes 5OY9 and 5OYL and visualized the 3D structures using the UCSF Chimera software, as a POSA would have done at the relevant time. (Ex. 1002 at ¶ 55.)

D. Overview of *Hwang*

Hwang, titled “Engineering a serum-resistant and thermostable vesicular virus G glycoprotein for pseudotyping retroviral and lentiviral vectors,” was published in *GENE THERAPY* by at least August 2013. (*See* Ex. 1007). *Hwang* was publicly accessible as evident from the cover page of *GENE THERAPY* volume 20, issue 8,

which was retrieved from the National Library of Medicine. (*Id.* at 1.) The '366 patent incorporates by reference *Hwang* to teach mutations at T214N and T352A and therefore, confirms that *Hwang* was publicly accessible as of the filing date of the '366 patent. (*See, e.g.*, Ex. 1001 at 28:1-12.) *Hwang* qualifies as prior art under 35 U.S.C. §102(a)(1) based on its publication date.

Hwang disclosed that “VSV-G” is “the most widely used envelope protein for retroviral and lentiviral pseudotyping; however, serum inactivation of VSV-G pseudotyped vectors is a significant challenge for *in vivo* gene delivery. To address this problem, we conducted directed evolution of VSV-G to increase its resistance to human serum inactivation.” (*See, e.g.*, Ex. 1007 at 807; Ex. 1002 at ¶ 56.)

Hwang disclosed that “[v]ector pseudotyped with several mutant VSV-G showed a greater resistance to human serum compared with wild-type VSV-G pseudotyped lentiviral vector Importantly mutants T230N + T368A or K66T + S162T + T230N + T368A had higher combined thermostability and serum resistance than wild-type VSV-G.”⁶ (*See, e.g.*, Ex. 1007 at 809; Ex. 1002 at ¶ 57.)

⁶ A POSA would have understood that the positions of the amino acid mutations discussed throughout *Hwang* are in reference to the VSV-G envelope protein inclusive of its 16 amino acid signal sequence. (*See* Ex. 1002 at ¶ 57.) Thus,

Hwang disclosed that its study “successfully created variants with higher resistance to human, rabbit, and mouse sera *in vitro* and human serum *in vivo*, and that “these results may enhance the utility of retroviral and lentiviral vectors to treat human disease.” (*See, e.g.*, Ex. 1007 at 812-13; Ex. 1002 at ¶ 58.) *Hwang* goes on to state that “VSV itself has emerged as a promising candidate in the field of oncolytic virus therapy. Therefore, incorporating a VSV variant encoding a human serum-resistant and thermostable VSV-G may enhance the therapeutic potential of VSV for treating human cancer.” (*See, e.g.*, Ex. 1007 at 813; Ex. 1002 at ¶ 58.)

IX. CLAIM CONSTRUCTION

For PGR proceedings, the Board applies the claim construction standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). *See* 83 Fed. Reg. 51,340-59 (Oct. 11, 2018). Under *Phillips*, claim terms are typically given their ordinary and customary meanings, as would have been understood by a POSA, at the time of the invention, having taken into consideration the language of the claims, the specification, and the prosecution history of record. *Phillips*, 415 F.3d at 1313; *see also id.* at 1312-16.

Hwang’s disclosure of “T230N + T368A” is equivalent to “T214N + T352A” in a VSV-G envelope protein without its signal sequence. (*See id.*)

The Board, however, only construes the claims when necessary to resolve the underlying controversy. *Toyota Motor Corp. v. Cellport Systems, Inc.*, IPR2015-00633, Paper No. 11 at 16 (P.T.A.B. Aug. 14, 2015). Here, given the correlation between the prior art and the challenged claim of the '366 patent, the Board need not construe any terms of the challenged claim to resolve the underlying controversy, as any reasonable construction reads on the prior art.

X. DETAILED EXPLANATION OF GROUNDS

Each challenged claim is unpatentable. *Perkins* disclosed lentiviral vectors containing mutant VSV-G envelope proteins comprising a I182 mutation. Thus, the mutant VSV-G proteins comprising I182E and I182D in independent claims 1 and 2 of the '366 patent were both anticipated by *Perkins*, as well as their dependent claims 3 and 10-25. (Ground 1.) Mutant VSV-G proteins further comprising T214 and T352 mutations were disclosed by *Hwang*, and dependent claims 3-9 and 26-30 would have been obvious over *Perkins* in view of *Hwang*. (Ground 2). To the extent the Board deems claims 1-3 and 10-25 not anticipated by *Perkins*, they would have at least been obvious over *Perkins* in view of crystal structures in the *RCSB PDB*. (Ground 3). Claims 3-9 and 26-30 would have been obvious over *Perkins* in view of the *RCSB PDB* and *Hwang*. (Ground 4). Petitioner does not concede that claim 1 is not invalid under other sections of the Patent Act.

A. Ground 1: *Perkins* Anticipates Claims 1-3 and 10-25

1. Claim 1

i) [1.a] “A polypeptide”

Perkins disclosed this limitation. (Ex. 1002 at ¶ 61.) *Perkins* disclosed the “amino acid sequence of a reference VSV-G envelope protein” without its signal peptide at SEQ ID NO: 90. (See, e.g., Ex. 1005 at 20:11-21, 74-75 (SEQ ID NO: 90).) SEQ ID NO: 90 from *Perkins* is reproduced below:

KFTIVFPHNQKGNWKNVPSNYHYC
PSSSDLNWHNDLIGTALQVKMPKS
HKAIQADGWMCHASKWVTTCDFR
WYGPKYITHSIRSFTPSVEQCKESIE
QTKQGTWLNPGFPPQSCGYATVTD
AEAVIVQVTPHHVLVDEYTGEWVD
SQFINGKCSNYICPTVHNSTTWHS
YKVKGLCDSNLISMDITFFSEDGEL

SSLGKEGTGFRSNYFAYETGGKAC
KMQYCKHWGVRLPSGVWFEMAD
KDLFAAARFPECPEGSSISAPSQTSV
DVSLIQDVERILDYSLCQETWSKIR
AGLPISPVDLSYLAPKNPGTGPAFTI
INGTLKYFETRYIRVDIAAPILSRMV
GMISGTTTERELWDDWAPYEDVEI
GPNGVLRTSSGYKFPLYMIGHGML
DSDLHLSSKAQVFEHPHIQDAASQL
PDDESLFFGDTGLSKNPIELVEGWF
SSWKSSIASFFFIIGLIIGLFLVLRVGI
HLCIKLKHTKKRQIYTDIEMNRLGK
(SEQ ID NO: 90)

(Ex. 1005 at 74-75 (SEQ ID NO: 90).)

The '639 application describes SEQ ID NO: 90 in *Perkins*. (Ex. 1002, ¶ 64.) Specifically, the '639 application disclosed that “SEQ ID NO: 78 is an amino acid sequence of a reference VSV-G envelope protein.” (Ex. 1006, 17.) SEQ ID NO: 78 is reproduced below:

MKCLLYLAFLFIGVNCKFTIVFPHNQKGNWKNV
PSNYHYCPSSSDLNWHNDLIGTALQVKMPKSH
KAIQADGWMCHASKWVTTCDFRWYGPKYITHS
IRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSC
GYATVTDAEAVIVQVTPHHVLVDEYTGEWVDSQ
FINGKCSNYICPTVHNSTTWHSDYKVKGLCDSN
LISMDITFFSEDGELSSLGKEGTGFRSNYFAYET
GGKACKMQYCKHWGVRLPSGVWFEMADKDLF
AAARFPECPEGSSISAPSQTSVDVSLIQDVERIL
DYS LCQETWSKIRAGLPISPVDLSYLAPKNPGT
GPAFTIINGTLKYFETRYIRVDIAAPILSRMVGMIS
GTTTERELWDDWAPYEDVEIGPNGVLRTSSGY
KFPLYMIGHGMLDSDLHLSSKAQVFEHPHIQDA
ASQLPDDES LFFGDTGLSKNPIELVEGW FSSWK
SSIASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQI
YTDIEMNRLGK (SEQ ID NO: 78)

(Ex. 1006 at 51 (underlining added).)

SEQ ID NO: 78 in the '639 application differs from SEQ ID NO: 90 in *Perkins* only in the initial 16 amino acids (“MKCLLYLAFLFIGVNC”). This 16-amino-acid sequence is a “signal sequence” for the reference VSV-G envelope protein and is illustrated as SEQ ID NO: 72, reproduced below:

VSV-G signal sequence	
Nucleotide	Amino acid
ATGAAGTGTCTGCTGTACCTGGCGTTCCTGTT TATCGGGGTGAACTGC (SEQ ID NO: 71)	MKCLLYLAFLFIGVNC (SEQ ID NO: 72)

(Ex. 1006 at 50 (highlighting added).) The '639 application expressly contemplates an amino acid sequence without the “signal sequence.” (*Id.*, 9-10 (“For polypeptide sequences disclosures herein, where a signal sequence is noted, the polypeptide sequence absent the signal sequence or having a partial sequence is also contemplated”); Ex. 1002 at ¶ 66.) As such, SEQ ID NO: 78 without the signal sequence (SEQ ID NO: 72) results in SEQ ID NO: 90 in *Perkins*. (Ex. 1002, ¶ 66.)

In fact, SEQ ID NO: 78 in the '639 application is identical to SEQ ID NO: 78 in *Perkins*. (Ex. 1006, 51 (SEQ ID NO: 78); Ex. 1005, 73 (SEQ ID NO: 78).) And the '639 application's signal sequence (SEQ ID NO: 72) is further identical to the signal sequence (SEQ ID NO: 88) in *Perkins*. (Ex. 1006, 50; Ex 1005, 74.) *Perkins* teaches that SEQ ID NO: 90 is SEQ ID NO: 78 without the signal sequence (SEQ ID NO: 88). (Ex. 1005, 74-75 (SEQ ID NO: 90 is described as “WT VSV-G without signal sequence”), 20:13-21.) Thus, while the '639 application does not reproduce SEQ ID NO: 90 like *Perkins* does, it disclosed the same amino acid sequence by expressly contemplating removal of the “signal sequence” from SEQ ID NO: 78, which is precisely how *Perkins* derives SEQ ID NO: 90 from SEQ ID NO: 78. (Ex. 1002, ¶ 67.) This is further confirmed by the mutations identified in the '639 application. Specifically, the '639 application discloses “a mutation at H8, N9, Q10

...” (Ex. 1006, 17.) But there is no “H” at position 8, no “N” at position 9, or “Q” at position 10 in SEQ ID NO: 78. (*Id.*, 51.) It is only when one removes the first 16 amino acids (*i.e.*, the signal sequence) from SEQ ID NO: 78 and begins counting with “K” at position 1 does one arrive at H8, N9, Q10. (Ex. 1002, ¶ 68.)⁷

Perkins states that the terms “polypeptide” and “protein” are “used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds.” (See Ex. 1005 at 11:27-29; Ex. 1006 at 9; 1002 at ¶ 69.) A POSA would have understood the *amino acid sequence* in SEQ ID NO: 90, as well as the reference to “VSV-G envelope *protein*” to represent “a polypeptide.” (Ex. 1002, at ¶ 69.)

ii) **[1.b] “comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2”**

Perkins disclosed this limitation. (Ex. 1002 at ¶ 71.) As explained in limitation [1.a] above, *Perkins* disclosed at SEQ ID NO: 90 the “*amino acid sequence* of a reference VSV-G envelope protein” without its signal sequence. (See,

⁷ Moreover, a POSA would have understood that full-length VSV-G is not expressed on the viral envelope, but rather the mature form of VSV-G that lacks its signal sequence. (Ex. 1002, ¶ 68.) SEQ ID NO: 78 is processed to its mature form, SEQ ID NO: 90, which is then expressed on the viral envelope. (*Id.*)

e.g., Ex. 1005 at 20:11-21, 74-75 (SEQ ID NO: 90) (emphasis added).) The same sequence is also disclosed in the '639 application, as discussed above in limitation

[1.a]. SEQ ID NO: 90 from *Perkins* is reproduced below:

```
KFTIVFPHNQKGNWKNVPSNYHYC  
PSSSDLNWHNDLIGTALQVKMPKS  
HKAIQADGWMCHASKWVTTCDFR  
WYGPKYITHSIRSFTPSVEQCKESIE  
QTKQGTWLNPGFPPQSCGYATVTD  
AEAVIVQVTPHHVLVDEYTGEWVD  
SQFINGKCSNYICPTVHNSTTWHS  
D  
YKVKGLCDSNLISMDITFFSEDGEL
```

```
SSLGKEGTGFRSNYFAYETGGKAC  
KMQYCKHWGVRLPSGVWFEMAD  
KDLFAAARFPECPEGSSISAPSQTSV  
DVSLIQDVERILDYSLCQETWSKIR  
AGLPISPVDLSYLA PKNPGTGPAFTI  
INGTLKYFETRYIRVDIAAPILSRMV  
GMISGTTTERELWDDWAPYEDVEI  
GPNGVLRTSSGYKFPLYMIGHGML  
DSDLHLSSKAQVFEHPHIQDAASQL  
PDDESLFFGDTGLSKNPIELVEGWF  
SSWKSSIASFFFIIGLIIGLFLVLRVGI  
HLCIKLKHTKKRQIYTDIEMNRLGK  
(SEQ ID NO: 90)
```

(Ex. 1005 at 74-75 (SEQ ID NO: 90).)

SEQ ID NO: 2 from the '366 patent is reproduced below:

SEQ ID NO: 2	moltype = AA length = 495					
FEATURE	Location/Qualifiers					
source	1..495					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 2						
KFTIVFPHNQ	KGWKNVPSN	YHYCPSSSDL	NWHNDLIGTA	LQVKMPKSHK	AIQADGWMCH	60
ASKWVTTCDF	RWYGPKYITH	SIRSFTPSVE	QCKESIEQTK	QGTWLNPGFP	PQSCGYATVT	120
DAEAVIVQVT	PHHVLVDEYT	GEWVDSQFIN	GKCSNYICPT	VHNSTTWHS	YKVKGLCDSN	180
LISMDITFFS	EDGELSSLGK	EGTGFRSNYF	AYETGGKACK	MQYCKHWGVR	LPSGVWFEMA	240
DKDLFAAARF	PECPEGSSIS	APSQTSVDVS	LIQDVERILD	YSLCQETWSK	IRAGLPISPV	300
DLSYLAPKNP	GTGPAFTIIN	GTLKYFETRY	IRVDIAAPIL	SRMVGMISGT	TTERELWDDW	360
APYEDVEIGP	NGVLRRTSSGY	KFPLYMIGHG	MLDSDLHLSS	KAQVFEHPHI	QDAASQLPDD	420
ESLFFGDTGL	SKNPIELVEG	WFSSWKSSIA	SFFFIIGLII	GLFLVLRVGI	HLCIKLKHTK	480
KRQIYTDIEM	NRLGK					495

(Ex. 1001 at 121 (SEQ ID NO: 2).)

As apparent from a comparison of SEQ ID NO: 90 in *Perkins* and SEQ ID NO: 2 in the '366 patent, the two sequences have an identical amino acid sequence of 495 amino acids, both of which represent the wild-type VSV-G envelope protein without its signal sequence. (Ex. 1002, ¶ 75.) Based on this identical amino acid sequence, a POSA would have understood that SEQ ID NO: 90 in *Perkins* is “at least 95% identical to the amino acid sequence of SEQ ID NO. 2,” as claimed. (*Id.*)

iii) [1.c] “and a I182E mutation as compared to SEQ ID NO: 2.”

Perkins disclosed this limitation. (Ex. 1002, ¶ 76.) As an initial matter, “I182E mutation” simply means that position 182 has an amino acid referenced by the letter “I” and that amino acid is substituted (*i.e.*, mutated) with an amino acid referenced by the letter “E.” (*Id.*) Like SEQ ID NO: 2 in the '366 patent, SEQ ID NO: 90 in *Perkins* has amino acid “I” at position 182, which is reproduced below:

KFTIVFPHNQKGNWKNVPSNYHYC
PSSSDLNWHNDLIGTALQVKMPKS
HKAIQADGWMCHASKWVTTCDFR
WYGPKYITHSIRSFTPSVEQCKESIE
QTKQGTWLNPGFPPQSCGYATVTD
AEAVIVQVTPHHVLVDEYTGEWVD
SQFINGKCSNYICPTVHNSTTWHS
YKVKGLCDSNLISMDITFFSEDGEL

SSLGKEGTGFRSNYFAYETGGKAC
KMQYCKHWGVRLPSGVWFEMAD
KDLFAAARFPECPEGSSISAPSQTSV
DVSLIQDVERILDYSLCQETWSKIR
AGLPISPVDLSYLAPKNPGTGPAFTI
INGTLKYFETRYIRVDIAAPILSRMV
GMISGTTTERELWDDWAPYEDVEI
GPNGVLRTSSGYKFPLYMIGHGML
DSDLHLSSKAQVFEHPHIQDAASQL
PDDESLFFGDTGLSKNPIELVEGWF
SSWKSSIASFFFIIIGLIIGLFLVLRVGI
HLCIKLKHTKKRQIYTDIEMNRLGK
(SEQ ID NO: 90)

(Ex. 1005 at 74-75 (SEQ ID NO: 90) (annotated to show “I” at position 182).⁸)

Perkins specifically disclosed “a mutation at amino acid position . . . I182,” among other positions. (See, e.g., Ex. 1005 at 20:29-21:14, Ex. 1006 at 17-18; Ex.

⁸ “I” is at position 182 starting from “K” as position 1.

1002 at ¶ 79.⁹) *Perkins* disclosed a VSV-G envelope protein where I182 was among 13 amino acid positions for making one, two, or more mutations. (See, e.g., Ex. 1005 at 21:16-27, Ex. 1006 at 17-18; Ex. 1002 at ¶ 79.) *Perkins* in fact disclosed a mutated VSV-envelope protein comprising a mutation at four amino acid positions, including “a I182 mutation.” (Ex. 1005 at 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 79.)

Perkins’ disclosure of a mutation at amino acid position I182 means a substitution of a single amino acid (“I”) at position 182 of SEQ ID NO. 90 with another amino acid. (Ex. 1002, ¶ 83.) But “I182” does not specify what “I” is replaced with. (*Id.*) A POSA would therefore understand that *Perkins* allows substituting amino acid “I” with any of the other 19 natural amino acids besides isoleucine (“I”). (Ex. 1002 at ¶ 83.) Indeed, a POSA would have understood that there are 20 natural amino acids with a one-letter code, including 19 natural amino acids besides the isoleucine already present at “I182,” of which glutamic acid (“E”)

⁹ It is apparent from *Perkins* that the mutations (such as H8, N9, Q10, I182, etc.) refer to mutations for SEQ ID NO: 90 because there is an “H” at position 8, “N” at position 9, “Q” at position 10, and “I” at position 182 in SEQ ID NO: 90. (Ex. 1005 at 74-75; Ex. 1002, ¶ 82.)

was one option. (*See* Ex. 1022 at 74-77; Ex. 1002 at ¶ 83.) Stated differently, an “I182” mutation includes “I182E” mutation as one of 19 options. (*Id.*)

Therefore, based on *Perkins* disclosure of a mutation at amino acid position I182 of SEQ ID NO: 90 and a genus of 19 possible amino acids, a POSA would have understood that *Perkins* disclosed “a I182E mutation as compared to SEQ ID NO: 2.” (Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; 1002 at ¶ 84.) *See In re Petering*, 301 F.2d 676, 681-82 (CCPA 1962) (holding that claims requiring a specific compound were anticipated by the prior art disclosure of a genus of 20 compounds that included the claimed compound.); *Rayvio Corp. v. Nitride Semiconductors Co., Ltd.*, IPR2018-01139, Paper 40 at 37-38 (finding that a POSA would have “at once envisaged each member of” a genus comprising 45-47 combinations).

Any argument from Patent Owner that *Perkins*’ disclosure of a mutation at amino acid position I182 does not anticipate a I182E mutation is legally insufficient. The Federal Circuit has long “reject[ed] the notion that one of [a number of alternatives] cannot anticipate because it appears without special emphasis in a longer list.” *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005). Equally, “anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art.” *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246

F.3d 1368, 1379 (Fed. Cir. 2001); *see also Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023).

Indeed, the Federal Circuit has repeatedly analyzed each genus in a list separately from the other genera in the list. In *Perricone v. Medicis Pharm. Corp.*, the prior art disclosed a list of fourteen genera of ingredients, with each genera comprising at least twenty members, if not 2000 members. 432 F.3d 1368, 1376 (Fed. Cir. 2005). There, the Federal Circuit held that the prior art anticipated claims that required subgenera of one specific ingredient in that list. 432 F.3d 1368, 1376-77 (Fed. Cir. 2005). Moreover, the Federal Circuit in *In re Gleave* held that the prior art, which comprised a list of more than 1400 members of fifteen-base-long oligodeoxynucleotides that coded for parts of a protein, anticipated specific 18-22 base-pair-long nucleotides that were complementary to the nucleotides that coded for parts of the protein. 560 F.3d 1331, 1333-34, 1337-38 (Fed. Cir. 2009). The Federal Circuit relied on the prior art's disclosure that "[the complementary] oligonucleotides are preferably between fifteen and twenty-five bases in length," to show anticipation in view of the list of more than 1400 members. *Id.* at 1333. In other words, the Federal Circuit treated each member of the list of nucleotides that coded for parts of a protein as a separate genus comprising 15-25-base-long oligodeoxynucleotides.

Similarly, here, *Perkins* disclosed a list of possible amino acid positions for mutating the VSV-G envelope protein, including a mutation at amino acid position number 182. (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶¶ 79-82.) As discussed above, amino acid position number 182 is a small genus that comprises 19 amino acids besides isoleucine (referenced by “I”). (Ex. 1022 at 74-77; Ex. 1002 at ¶ 83.) Because each listed genera is treated separately, a POSA would “at once envisage each member of this limited class.” *See Petering*, 301 F.2d at 681-82; *Rayvio Corp. v. Nitride Semiconductors Co., Ltd.*, IPR2018-01139, Paper 40 at 37-38; Ex. 1002 at ¶ 84.) *Perkins*’ disclosures would have enabled a POSA to arrive at a I182E mutation. (Ex. 1002 at ¶ 84.)

Furthermore, a POSA would have understood that a mutant VSV-G envelope protein including one, two, three, or more mutations, including a mutation at I182, consistent with *Perkins*’ disclosure, was “at least 95% identical to the amino acid sequence of SEQ ID NO. 2” as claimed in the ’366 patent. (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 85.) The ’366 patent states that “the identity between two amino acid or two nucleic acid sequences is a direct function of the number of matching or identical positions.” (*See* Ex. 1001 at 13:31-33.) A POSA would have understood that both SEQ ID NO: 2 of the ’366 patent and SEQ ID NO: 90 of *Perkins* contained 495 amino acids, and with mutations at up to four positions, would still be at least 99% identical to the amino acid

sequence of SEQ ID NO: 2. (*See, e.g.*, Ex. 1001 at 121 (SEQ ID NO: 2.); Ex. 1002 at ¶ 85.) Indeed, *Perkins*' VSV-G envelope protein could be mutated at up to 24 positions and still be "at least 95% identical to the amino acid sequence of SEQ ID NO. 2," as claimed in the '366 patent. (*See* Ex. 1001 at 13:31-33; Ex. 1002 at ¶ 86.)

2. Claim 2

i) [1.a] "A polypeptide"

Perkins disclosed this limitation. (Ex. 1002, ¶ 88.) As discussed in Section X.A.1.i, *Perkins* disclosed a polypeptide at SEQ ID NO: 90.

ii) [1.b] "comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO. 2"

Perkins disclosed this limitation. (Ex. 1002, ¶ 89.) As discussed in Section X.A.1.ii, *Perkins* disclosed at SEQ ID NO: 90 a polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO. 2."

iii) [1.c] "and a I182D mutation as compared to SEQ ID NO: 2."

Perkins disclosed this limitation. (Ex. 1002, ¶ 90.) As discussed in Section X.A.1.iii, *Perkins* specifically disclosed that the mutated VSV-G envelope protein includes a mutation at amino acid position I182, among other positions. (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 92.) A POSA would have understood that there are 20 natural amino acids with a one-letter

code, including 19 natural amino acids besides the isoleucine already present at “I182,” of which aspartic acid (“D”) was one option. (*See* Ex. 1022 at 74-77; Ex. 1002 at ¶ 93.)

Based on *Perkins* disclosure of a mutation at amino acid position I182 of SEQ ID NO: 90 and a genus of 19 possible amino acids, a POSA would have understood that *Perkins* disclosed “a I182D mutation as compared to SEQ ID NO: 2” for the same reasons discussed above in Section X.A.1.iii. (Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 93.)

Furthermore, for the same reasons discussed above in Section X.A.1.iii, a POSA would have understood that a mutant VSV-G envelope protein including one, two, or three mutations, including a mutation at I182, consistent with *Perkins*’ disclosure, was “at least 95% identical to the amino acid sequence of SEQ ID NO. 2,” as claimed in the ’366 patent. (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶¶ 94-95.)

3. Claim 3: “The polypeptide of claim 1, wherein the polypeptide further comprises a mutation at position 214, a

mutation at position 352, or a mutation at both position 214 and position 352 as compared to SEQ ID NO: 2.¹⁰

Perkins disclosed this limitation. (Ex. 1002, ¶ 97.) *Perkins* disclosed that the mutated VSV-G envelope protein includes “a mutation at amino acid position . . . I182 . . . T352,” among other positions. (See, e.g., Ex. 1005 at 20:29-21:14; Ex. 1006 at 17-18; Ex. 1002 at ¶ 99.) *Perkins* disclosed a VSV-G envelope protein where I182 and T352 were among 13 amino acid positions for making one, two, or more mutations. (See, e.g., Ex. 1005 at 21:16-27, Ex. 1006 at 17-18; Ex. 1002 at ¶ 99.) *Perkins* in fact disclosed a mutated VSV-envelope protein comprising a mutation at four amino acid positions, including “a I182 mutation” and “a T352 mutation.” (Ex. 1005 at 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 99.)

As described above in Section X.A.1, a POSA would have understood that the I182 and T352 mutations were in reference to SEQ ID NO: 90 in *Perkins*, which matches SEQ ID NO: 2 in the '366 patent, and that up to 24 positions could be mutated and still be “at least 95% identical to the amino acid sequence of SEQ ID NO. 2” as claimed in the '366 patent. (Ex. 1002 at ¶ 100.)

¹⁰ Claim 3 recites a list including three options separated by an “or.” Thus, the prior art only needs to teach one of the options and *Perkins* disclosed a mutation at amino acid position T352.

4. Claim 10: “A nucleic acid molecule encoding the polypeptide of claim 1.”

Perkins disclosed this limitation. (Ex. 1002, ¶ 101.) *Perkins* discloses a nucleic acid molecule (SEQ ID NO: 89) encoding SEQ ID NO: 90 (“polypeptide”). (Ex. 1005, 20:18-20.) *Perkins* disclosed that its mutations to SEQ ID NO: 90 also pertain to the SEQ ID NO: 89. (See, e.g., Ex. 1005 at 20:21-25 (“[t]he position and nature of VSV-G mutations ***disclosed herein*** are in reference to the nucleic acid sequence and the amino acid sequence provided by SEQ ID NO: 77 ***absent the N-terminal signal sequence of SEQ ID NO: 87*** and SEQ ID NO: 78 ***absent the N-terminal signal sequence of SEQ ID NO: 88***, respectively.” (emphasis added); Ex. 1002 at ¶ 103.) “SEQ ID NO: 77 ***absent the N-terminal signal sequence of SEQ ID NO: 87***” is SEQ ID NO: 89; similarly, “SEQ ID NO: 78 ***absent the N-terminal signal sequence of SEQ ID NO: 88***” is SEQ ID NO: 90. (*Id.* at 20:13-20, 73-76 (SEQ ID NOs. 77, 87, 89); Ex. 1002 at ¶ 103.)

Perkins disclosed that SEQ ID NO: 89 is the nucleic acid reference sequence for wild-type VSV-G envelope protein without its signal sequence, which a POSA would have understood is modified based on *Perkins*’ discussion of mutated VSV-G envelope proteins. (See, e.g., Ex. 1005 at 20:29-21:14, 21:16-27; 73-76 (SEQ ID NO: 89); Ex. 1002, ¶ 104.) Thus, for the reasons explained as to claim 1 (Section X.A.1), a POSA would have understood that the I182E mutation also applied to the nucleic acid sequence at SEQ ID NO: 89, and thus disclosed, as claimed in the ’366

patent, “[a] nucleic acid molecule encoding the polypeptide of claim 1.” (Ex. 1002, ¶ 104.)

The ’639 application includes the same disclosure as *Perkins*. For example, the ’639 application discloses that the VSV-G mutations are “described in reference to” the amino acid sequence and the nucleic acid sequence encoding the amino acid sequence. (Ex. 1006 at 17.) And the nucleic acid sequence in the ’639 application is the same as the nucleic acid sequence (SEQ ID NO: 89) in *Perkins*. Specifically, SEQ ID NO: 77 is the reference nucleic acid sequence encoding SEQ ID NO: 78 (the amino acid sequence). (*Id.*) It further includes a signal sequence (SEQ ID NO. 71) corresponding to the signal sequence (SEQ ID NO: 72) in SEQ ID NO. 78. (*Id.* at 17, 46, 50.) Just like SEQ ID NO: 78 in the ’639 application without its signal sequence results in SEQ ID NO: 90 in *Perkins*, SEQ ID NO: 77 in the ’639 application without its signal sequence results in SEQ ID NO: 89 in *Perkins*. (Ex. 1002, ¶ 105.)

5. Claim 11: “A vector comprising the nucleic acid molecule of claim 10.”

Perkins disclosed this limitation. (Ex. 1002, ¶ 107.) *Perkins* disclosed that “[t]he present disclosure provides self-inactivating lentiviral **vectors** (‘LVV’) that include a viral envelope comprising a mutated, heterologous envelope protein.” (See, e.g., Ex. 1005 at 19:14-15 (emphasis added); Ex. 1006 at 16; Ex. 1002 at ¶ 62.) The “mutated, heterologous envelope protein” is the mutated VSV-G envelope

protein (*e.g.*, VSV-G with an I182 mutation). However, a POSA would have understood that LVV first needs to be produced, for instance through the use of a vector which carries a nucleic acid molecule that encodes the mutated VSV-G envelope protein, and would have included SEQ ID NO: 89 with the mutations necessary for SEQ ID NO: 89 to encode a mutated VSV-G protein with SEQ ID NO: 90 modified at I182E. (Ex. 1002 at ¶ 109.) *Perkins* defines “a ‘vector’ as a nucleic acid molecule that is capable of transporting ***another nucleic acid***. Vectors may be, for example, ***plasmids***, cosmids, viruses, or phage.” (*See, e.g.*, Ex. 1005 at 14:13-14 (emphasis added); 1006 at 11.) The disclosure in *Perkins* further supports this understanding. (Ex. 1002 at ¶ 109.)

The disclosure of *Perkins*’ LVVs that “include a viral envelope comprising a mutated, heterologous envelope protein” is followed by a discussion of the nucleic acid and amino acid reference sequences for wild type VSV-G envelope protein and examples of mutated VSV-G envelope proteins “according to the present disclosure.” (*See, e.g.*, Ex. 1005 at 19:23-20:13; Ex. 1006 at 16-17; Ex. 1002 at ¶ 110.) *Perkins* disclosed at SEQ ID NO: 89 the nucleic acid reference sequence for wild-type VSV-G envelope protein without its signal sequence, which a POSA would have understood is modified based on *Perkins*’ disclosure of mutated VSV-G envelope proteins, and is incorporated into the LVV of *Perkins*’ disclosure.

(*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; 73-76 (SEQ ID NO. 89); Ex. 1006 at 9-10, 16-18; 50 (SEQ ID NO: 72), 51 (SEQ ID NO: 78); Ex. 1002 at ¶ 110.)

Perkins further disclosed that “[m]ethods for producing the **LVV disclosed** are provided herein.” (*See, e.g.*, Ex. 1005 at 54:8-11(emphasis added); Ex. 1006 at 41.) *Perkins* goes on to explain that the VSV-G envelope protein is one component of *Perkins*’ disclosed LVVs, which originates as VSV-G “**envelope plasmid**” that a POSA would understand to contain a nucleic acid sequence which encodes the mutant VSV-G envelope protein (*i.e.*, the nucleic acid molecule of claim 10), which is combined with other LVV component plasmids, transfected into producer cells, and harvested as LVV particles. (Ex. 1005 at 54:14-56:14 (emphasis added); Ex. 1006 at 41; Ex. 1002 at ¶ 111.)

Indeed, *Perkins* at FIG. 1 shows a schematic representation of “helper plasmids” for LVV production which includes a nucleic acid with “VSV-G.” (*See, e.g.*, Ex. 1005 at 56:14-15, FIG. 1; Ex. 1006 at 41, FIG. 1; Ex. 1002 at ¶ 112.) *Perkins* further disclosed that in “a four plasmid LVV system the VSV-G plasmid includes a tandem expression cassette that encodes a **mutated VSV-G envelope protein** and a targeting protein **as disclosed herein**.” (*See, e.g.*, Ex. 1005 at 56:25-27 (emphasis added); Ex. 1006 at 42; Ex. 1002 at ¶ 112.) A POSA would again read this disclosure as describing a vector comprising a nucleic acid molecule which encodes the mutated VSV-G envelope proteins according to *Perkins*’ disclosure, *i.e.*,

the mutant VSV-G described in *Perkins* at 19:23-22:26, which described a nucleic acid molecule encoding the polypeptide of claim 1. (Ex. 1002 at ¶ 112.)

A POSA would have understood that *Perkins* disclosed, as claimed in the '366 patent, “a vector comprising the nucleic acid molecule of claim 10.” (See Ex. 1002 at ¶ 113.)

6. Claim 12: “A cell comprising the nucleic acid molecule of claim 10.”

Perkins disclosed this limitation. (Ex. 1002 at ¶ 114.) *Perkins* disclosed that “[m]odified lentiviral genomes are useful as viral vectors for the delivery of a nucleic acids to a host cell.” (See, e.g., Ex. 1005 at 19:11-13; Ex. 1006 at 16; Ex. 1002 at ¶ 116.) *Perkins* further disclosed that its LVV “include a viral envelope comprising a mutated, heterologous envelope protein” and a “targeting protein,” and further includes “a transgene, with the LVV being capable of specifically binding to a target immune cell and transducing the target immune cell such that the transgene is expressed by the immune cell.” (See, e.g., Ex. 1005 at 19:16-19; Ex. 1006 at 16; Ex. 1002 at ¶ 116.) A POSA would have understood that while this disclosure is talking about the “target” immune cell for delivery of a transgene, claim 12 is directed to an earlier step, wherein LVV particles are produced by introducing component vectors (*i.e.*, an envelope plasmid) into a producer cell. Claim 10 is directed to the “cell” in this process of LVV production. (Ex. 1002 at ¶ 116.) Claim 10 is directed to the “cell” in this process of LVV production.

Additionally, as described in Section X.A.5, the vector carrying the nucleic acid of claim 10 (*i.e.*, the vector of claim 11) is specifically described by *Perkins* as being ***transfected into producer cells*** to transfer genes required for lentiviral particle production. (*See, e.g.*, Ex. 1005 at 54:14-56:14 (emphasis added); Ex. 1006 at 41; Ex. 1002 at ¶ 117.) The envelope plasmid (a vector) discussed above in Section X.A.5, which comprises the nucleic acid molecule of claim 10 used in the production of LVV particles, would necessarily need to be within a producer cell in order to produce productive LVV particles according to *Perkins*' disclosure. (*Id.*)

Claim 1 of *Perkins* also shows another example of LVV production wherein “a producer cell” is transfected with plasmids, including a “VSV-G env plasmid.” (*See* Ex. 1005 at 123:27-124:16; Ex. 1006 at 81-82.) The VSV-G env plasmid “comprises a polynucleotide encoding a mutated VSV-G envelope protein” and “is capable of expressing the mutated VSV-G envelope protein . . . within the producer cell line.” (*See id.*) A POSA would have understood that this method would similarly apply for envelope plasmids encoding the polypeptide of claim 1 (*i.e.*, where a producer cell is transfected by the vector of claim 11.) (Ex. 1002 at ¶ 118.)

A POSA would have thus understood that *Perkins* disclosed “[a] cell comprising the nucleic acid molecule of claim 10.” (*See* Ex. 1002 at ¶ 119.)

7. **Claim 13: “A viral particle comprising the polypeptide of claim 1.”**

Perkins disclosed this limitation. (Ex. 1002, ¶ 120.) *Perkins* at Example 1 disclosed methods for producing “[s]elf-inactivating lentiviral vectors (LVV) **as described herein**” which included the harvesting of “[p]roductive viral particles.” (See Ex. 1005 at 110:24-29 (emphasis added); Ex. 1006 at 71; Ex. 1002 at ¶ 122.) A POSA would have understood that *Perkins*’ method of producing viral particles at Example 1 is a general purpose method intended for the LVVs “**as described herein**,” and this would have applied to other parts of *Perkins*’ disclosure discussing exemplary LVVs. (See Ex. 1002 at ¶ 122.) *Perkins* also disclosed, as discussed above, that “[t]he LVV vector includes a mutated VSV-G envelope protein, where the mutated VSV-G includes mutations that abolish the binding of the mutated VSV-G to its native receptor such that viral entry occurs via the non-viral, tropism defining targeting protein.” (See Ex. 1005 at 111:2-4; Ex. 1006 at 71; Ex. 1002 at ¶ 122.) A POSA would have thus made a viral particle, as in Example 1, using the polypeptide of claim 1, as discussed above. (See Ex. 1002 at ¶ 122.)

Additionally, as discussed above in Section X.A.5, *Perkins* disclosed “[m]ethods for producing the **LVV disclosed** are provided herein,” which included VSV-G packing plasmid component which is transfected into a producer cell and harvested as LVV particles. (Ex. 1005 at 54:8-56:14 (emphasis added); Ex. 1006 at 41; Ex. 1002 at ¶ 123.) As described in Section X.A.5, *Perkins*’ LVVs are

described in the context of a carrying a mutated VSV-G envelope protein which includes a mutation at I182 (*i.e.*, the polypeptide of claim 1 as described in Section X.A.1). (Ex. 1002 at ¶ 123.)

Perkins also disclosed that in “a four plasmid LVV system, the VSV-G plasmid includes a tandem expression cassette that encodes a ***mutated VSV-G envelope protein*** and a targeting protein ***as disclosed herein.***” (*See, e.g.*, Ex. 1005 at 56:25-27 (emphasis added); Ex. 1006 at 42; Ex. 1002 at ¶ 124.) This plasmid would be transfected into cells to produce viral particles, using *Perkins*’ above described methods of producing LVVs. (Ex. 1002 at ¶ 124.)

A POSA would have understood *Perkins*’ disclosure of “viral particles,” as claimed in the ’366 patent, to comprise “the polypeptide of claim 1.” (*See* Ex. 1002 at ¶ 125.)

8. Claim 14: “The viral particle of claim 13, wherein the viral particle is a lentivirus comprising the polypeptide.”

Perkins disclosed this limitation. (Ex. 1002, ¶ 126.) As discussed in Section X.A.7, *Perkins* disclosed at Example 1 a method of producing LVVs which included the harvesting of “[p]roductive viral particles.” (*See, e.g.*, Ex. 1005 at 110:24-29; Ex. 1006 at 71; Ex. 1002 at ¶ 128.) *Perkins* further disclosed that “the LVV vector includes a mutated VSV-G is envelope protein, where the mutated VSV-G includes mutations that abolish the binding of the mutated VSV-G to its native receptor such

that viral entry occurs via the non-viral, tropism defining targeting protein.” (*See, e.g.,* Ex. 1005 at 111:2-4; Ex. 1006 at 71; Ex. 1002 at ¶ 128.)

As discussed in Section X.A.7, *Perkins* disclosed additional methods for the production of LVV particles that are specific to “lentivirus” as claimed and would have been understood by a POSA to include the production of mutant VSV-G in the form of the polypeptide of claim 1. (Ex. 1002 at ¶ 129.)

A POSA would have thus understood the “viral particles” disclosed in *Perkins* to comprise, as claimed in the ’366 patent, “the viral particle of claim 13, wherein the viral particle is a lentivirus comprising the polypeptide.” (*See* Ex. 1002 at ¶ 130.)

9. Claim 15: “The viral particle of claim 13, wherein the viral particle further comprises a heterologous nucleic acid molecule encoding a heterologous molecule of interest.”

Perkins disclosed this limitation. (Ex. 1002, ¶ 131.) As described above in Section X.A.7, *Perkins* disclosed that its LVVs as “described herein” were produced by harvesting “[p]roductive virus particles.” (*See, e.g.,* Ex. 1005 at 110:24-29; Ex. 1006 at 71; Ex. 1002 at ¶ 133.) Additionally, as described above in Sections X.A.5 and X.A.7, *Perkins* expressly disclosed the harvesting of LVV particles which include LVVs produced through the use of a multiple plasmid components, including the VSV-G envelope protein plasmid. (Ex. 1005 at 54:14-56:14; Ex. 1006 at 41; Ex. 1002 at ¶ 133.) In addition to the VSV-G envelope protein plasmid, *Perkins*’ LVVs are produced through the use of a “transfer plasmid” (or “transgene

plasmid”) for encoding a transgene molecule of interest. (*See, e.g.*, Ex. 1005 at 54:9-56:24; Ex. 1006 at 41-42; Ex. 1002 at ¶ 133.)

Perkins disclosed that “[t]he lentiviral vectors ***described herein*** include a transgene ***encoding*** one or more proteins that is delivered to and expressed by a lymphocyte . . . targeted by the vector. In particular embodiments, the transgene encodes a ***chimeric antigen receptor***.” (*See, e.g.*, Ex. 1005 at 41:5-8; Ex. 1006 at 29; Ex. 1002 at ¶ 134.) *Perkins* also disclosed that that the transgene plasmid “may ***encode*** a single ***heterologous protein*** (e.g., a single ***CAR*** as described herein.)” (Ex. 1005 at 56:21-22 (emphasis added); Ex. 1006 at 42; Ex. 1002 at ¶ 134.)

A POSA would have understood the word “heterologous” to refer to a non-native molecule (*i.e.*, protein) encoded by a non-endogenous nucleic acid introduced into a host cell. (*See, e.g.*, Ex. 1005 at 10:26-28; Ex. 1002 at ¶ 135.) Further, the ’366 patent states that “[f]or example, heterologous molecule of interest is meant to refer to any product that may be encoded by a nucleic acid” and includes “polypeptide[s],” including where the polypeptide “is a chimeric antigen receptor (‘CAR’).” (*See* Ex. 1001 at 59:30-37.) A POSA would have understood that *Perkins*’ “transfer plasmid” to be a heterologous nucleic acid molecule for encoding a heterologous molecule of interest, for instance, a CAR. (Ex. 1002 at ¶ 135.)

A POSA would have understood that *Perkins* disclosure of viral particles containing LVVs, including a transgene encoding a chimeric antigen receptor,

disclosed “[t]he viral particle of claim 14, wherein the viral particle further comprises a heterologous nucleic acid molecule encoding a heterologous molecule of interest.” (*See* Ex. 1002 at ¶ 136.)

10. Claim 16: “The viral particle of claim 15, wherein the heterologous molecule of interest is an siRNA, an shRNA, a non-coding RNA, a polypeptide, a viral payload, a viral genome, or a combination thereof.”

Perkins disclosed this limitation for the reasons described above in Section X.A.9, including that *Perkins* disclosed viral particles containing LVVs with a transgene encoding a “chimeric antigen receptor.” (*See* Ex. 1002 at ¶ 137.) A POSA would have understood a chimeric antigen receptor to be, as claimed in the ’366 patent, “a heterologous molecule of interest” which in this case is a “polypeptide.” (*See, e.g.*, Ex. 1005 at 7:10-21; Ex. 1006 at 4; Ex. 1002 at ¶ 139.)

11. Claim 17: “The viral particle of claim 15, wherein the heterologous molecule of interest is a chimeric antigen receptor (‘CAR’).”

Perkins disclosed this limitation for the reasons described above in Section X.A.9, including that *Perkins* disclosed viral particles containing LVVs, including a transgene encoding a “chimeric antigen receptor.” (Ex. 1002, ¶ 140.) Accordingly, a POSA would have understood that *Perkins* disclosed, as claimed in the ’366 patent, “[t]he viral particle of claim 15, wherein the heterologous molecule of interest is a chimeric antigen receptor (‘CAR’).” (*See* Ex. 1002 at ¶ 142.)

12. Claim 18: “The polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence that is at least 96% identical to the amino acid sequence of SEQ ID NO: 2.”

Perkins disclosed this limitation. (Ex. 1002, ¶ 143.) As described above in Section X.A.1.iii, *Perkins* disclosed a mutant VSV-G envelope protein including one, two, three, or more mutations, including a mutation at I182. (See, e.g., Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 144.) A POSA would have understood that both SEQ ID NO: 2 of the '366 patent and SEQ ID NO: 90 of *Perkins* contained 495 amino acids, and with three mutations, *Perkins*' SEQ ID NO: 90 as modified would still be at least 99% identical to the amino acid sequence of SEQ ID NO: 2. (See, e.g., Ex. 1001 at 121 (SEQ ID NO: 2.); Ex. 1002 at ¶ 144.)

13. Claim 19: “The polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence that is at least 97% identical to the amino acid sequence of SEQ ID NO: 2.”

Perkins disclosed this limitation for the reasons described in Section X.A.12 (Ex. 1002, ¶¶ 145-146.)

14. Claim 20: “The polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 2.”

Perkins disclosed this limitation for the reasons described in Section X.A.12 (Ex. 1002, ¶¶ 147-148.)

- 15. Claim 21: “The polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence that is at least 99% identical to the amino acid sequence of SEQ ID NO: 2.”**

Perkins disclosed this limitation for the reasons described in Section X.A.12 (Ex. 1002, ¶¶ 149-150.)

- 16. Claim 22: “The polypeptide of claim 2, wherein the polypeptide comprises an amino acid sequence that is at least 96% identical to the amino acid sequence of SEQ ID NO: 2.”**

Perkins disclosed this limitation. (Ex. 1002, ¶ 151.) As described above in Section X.A.2.iii, *Perkins* disclosed a mutant VSV-G envelope protein including one, two, three, or more mutations, including a mutation at I182. (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 152.) A POSA would have understood that both SEQ ID NO: 2 of the '366 patent and SEQ ID NO: 90 of *Perkins* contained 495 amino acids, and with three mutations, *Perkins*' SEQ ID NO: 90 as modified would still be at least 99% identical to the amino acid sequence of SEQ ID NO: 2. (*See, e.g.*, Ex. 1001 at 121 (SEQ ID NO: 2.); Ex. 1002 at ¶ 152.)

- 17. Claim 23: “The polypeptide of claim 2, wherein the polypeptide comprises an amino acid sequence that is at least 97% identical to the amino acid sequence of SEQ ID NO: 2.”**

Perkins disclosed this limitation for the reasons described in Section X.A.16 (Ex. 1002, ¶¶ 153-154.)

- 18. Claim 24: “The polypeptide of claim 2, wherein the polypeptide comprises an amino acid sequence that is at least 98% identical to the amino acid sequence of SEQ ID NO: 2.”**

Perkins disclosed this limitation for the reasons described in Section X.A.16 (Ex. 1002, ¶¶ 155-156.)

- 19. Claim 25: “The polypeptide of claim 2, wherein the polypeptide comprises an amino acid sequence that is at least 99% identical to the amino acid sequence of SEQ ID NO: 2.”**

Perkins disclosed this limitation for the reasons described in Section X.A.16 (Ex. 1002, ¶¶ 157-158.)

B. Ground 2: *Perkins* in View of *Hwang* Renders Claims 3-9 and 26-30 Obvious¹¹

- 1. Claim 3: “The polypeptide of claim 1, wherein the polypeptide further comprises a mutation at position 214, a mutation at position 352, or a mutation at both position 214 and position 352 as compared to SEQ ID NO: 2.”**

Perkins disclosed this limitation. (Ex. 1002, ¶ 160.) As described above in Section X.A.3, *Perkins* disclosed mutations at amino acid positions I182 and T352,

¹¹ As any evidence of objective indicia is considered after institution, Petitioner reserves the right to respond to any attempted showing by Patent Owner. *See, e.g., Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1378 (Fed. Cir. 2019); *Arctic Cat, Inc. v. Polaris Indus. Inc.*, IPR2017-00433, Paper 17 at 10 (P.T.A.B. July 5, 2017).

among other positions, which disclose the limitation of claim 3. (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 162.)

As yet another exemplary teaching, *Perkins* in view of *Hwang* disclosed or suggested this limitation. (Ex. 1002, ¶ 162.) *Hwang* disclosed a combined “T230N + T368A”¹² mutant VSV-G protein, which demonstrated “higher combined thermostability and serum resistance than wild-type VSV-G.” (*See, e.g.*, Ex. 1007 at 809.)

A POSA at the relevant time would have been aware that VSV-G pseudotyped vectors were vulnerable to inactivation in human serum, and at least one study had shown that “the level of susceptibility was always substantial.” (*See, e.g.*, Ex. 1020 at 218, 221; Ex. 1002 at ¶ 163.) A POSA would have been further aware that “serum inactivation of VSV-G pseudotyped viral vectors impedes their *in vivo* use.” (*See, e.g.*, Ex. 1007 at 807; Ex. 1002 at ¶ 163.)

To make use of the mutant VSV-G envelope proteins disclosed in *Perkins*, which in certain applications were intended for cellular therapy applications *in vivo*,

¹² As indicated at footnote 6, *supra*, *Hwang*’s disclosure of “T230N” and “T368A” mutations is in reference to the full length VSV-G envelope protein and is equivalent to T214N and T352A mutations, which are made with reference to the VSV-G envelope protein absent its 16 amino acid N-terminal signal sequence.

a POSA would have had a strong motivation to modify *Perkins*' mutant VSV-G protein with the additional T214N and T352A mutations disclosed in *Hwang* to achieve the intended objective of *Perkins*' disclosed invention. (See, e.g., Ex. 1005 at 41:24-30, 56:21-24, 91:25-92:16, 96:18-98:17, 115:18-116:9; Ex. 1006 at 54, 56-58, 73-74; Ex. 1002 at ¶ 164.) Indeed, *Hwang* expressly states that the results of its study "may enhance the utility of retroviral and lentiviral applications to treat human disease. . . . Therefore, incorporating a VSV variant encoding a human serum-resistant and thermostable VSV-G may enhance the therapeutic potential of VSV for treating human cancer." (See, e.g., Ex. 1007 at 813; Ex. 1002 at ¶ 164.) A POSA would have accordingly looked to *Hwang* to modify *Perkins*' disclosed mutant VSV-G protein. (See Ex. 1002 at ¶ 164.)

A POSA would also have had a reasonable expectation of success in adding *Hwang*'s T214N and T352A mutations to *Perkins*' mutant VSV-G protein as in claim 1 of the '366 patent. (See Ex. 1002 at ¶ 165.) *Perkins* disclosed that mutations at I182 and T352 could be combined in a mutant VSV-G protein. (See, e.g., Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 165.)

Additionally, while not required by claim 3, a POSA would not believe that *Hwang*'s T214N and T352A mutations would lead to a loss of fusogenic function of VSV-G protein. (See Ex. 1002 at ¶ 165.). A POSA would have appreciated that these residues were located in a different portion of the VSV-G crystal structure than

the domains that were known to be involved in fusion. (*See, e.g.*, Ex. 1018 at 4 (FIG. 3); Ex. 1002 at ¶ 165.) *Hwang* actually made VSV-G mutants with these mutations, and did not note any problems with fusogenic function. (*See, e.g.*, Ex. 1007 at 808; Ex. 1002 at ¶ 165.) Further, laboratories studying the amino acid residues which have an impact on the fusion characteristics of VSV-G did not indicate T214, T352, or any nearby residues. (*See, e.g.*, Ex. 1015 at 1722, Table 1, 1723, FIG. 6; Ex. 1002 at ¶ 166.) A POSA furthermore would have been aware of another instance where *Hwang*'s T214N and T352A mutations were taught for VSV-G mutants to overcome issues with serum inactivation. (*See, e.g.*, Ex. 1021 at ¶¶ [0005], [0030]; Ex. 1002 at ¶ 166.)

A POSA would have possessed ample motivation to further incorporate *Hwang*'s T214N and T352A mutations into *Perkin*'s disclosed VSV-G mutants, and would have had a reasonable expectation of success in making the mutations, as shown by the express disclosures in the prior art to make these mutations¹³ and

¹³ The '366 patent incorporates by reference the disclosures of *Hwang* to teach mutations at T214N and T352A. (*See, e.g.*, Ex. 1001 at 28:1-12.) The '366 patent further characterizes these mutations as "known serum stabilizing VSV-G mutations." (*See, e.g.*, Ex. 1001 at 105:25-39.)

crystal structure characterizations of the VSV-G protein showing compatibility. (Ex. 1002 at ¶ 167.)

2. **Claim 4: “The polypeptide of claim 1, wherein the polypeptide further comprises a T214N mutation, a T352A mutation, or a combination thereof, as compared to SEQ ID NO: 2.”**

Perkins in view of *Hwang* disclosed or suggested this limitation, as discussed in Section X.B.1. (Ex. 1002, ¶ 168.)

3. **Claim 5: “The polypeptide of claim 1, wherein the polypeptide further comprises a T214N mutation and a T352A mutation as compared to SEQ ID NO: 2.”**

Perkins in view of *Hwang* disclosed or suggested this limitation, as discussed in Section X.B.1. (Ex. 1002, ¶ 169.)

4. **Claim 6: “The polypeptide of claim 2, wherein the polypeptide further comprises a mutation at position 214, a mutation at position 352, or a mutation at both position 214 and position 352, as compared to SEQ ID NO: 2.”**

Perkins in view of *Hwang* disclosed or suggested this limitation, as discussed in Section X.B.1. (Ex. 1002, ¶ 170.) While the polypeptide of claim 2 incorporates a I182D mutation instead of the I1821E mutation in the polypeptide of claim 1, *Perkins* disclosed a I182D mutation as explained in Section X.A.2.iii, and *Perkins* in view of *Hwang* disclosed or suggested this limitation for the same reasons discussed in Section X.B.1. (Ex. 1022 at 76-77; Ex. 1002, ¶ 170.)

5. **Claim 7: “The polypeptide of claim 2, wherein the polypeptide further comprises a T214N mutation, a T352A mutation, or a combination thereof, as compared to SEQ ID NO: 2.”**

Perkins in view of *Hwang* disclosed or suggested this limitation, as discussed in Sections X.B.1 and X.B.4. (Ex. 1002, ¶ 171.)

6. **Claim 8: “The polypeptide of claim 2, wherein the polypeptide further comprises a T214N mutation and a T352A mutation as compared to SEQ ID NO: 2.”**

Perkins in view of *Hwang* disclosed or suggested this limitation, as discussed in Section X.B.1 and X.B.4. (Ex. 1002, ¶ 172.)

7. **Claim 9: “The polypeptide of claim 1, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 23.”**

Perkins in view of *Hwang* disclosed or suggested this limitation. (Ex. 1002, ¶ 173.) The '366 patent disclosed that “[i]n some embodiments, a VSV-G protein comprises an amino acid sequence of SEQ ID NO: 22 and SEQ ID NO: 23, which combines the I182D or I182E, respectively, with the T214N and T352A mutations.” (See, e.g., Ex. 1001 at 26:38-42.) SEQ ID NO: 23 of the '366 patent contains the amino acid sequence of a VSV-G envelope protein without its signal sequence, and includes three mutations: I182E, T214N, and T352A. (Ex. 1001, 5:58-61, 26:38-42, 129 (SEQ ID NO: 23); Ex. 1002 at ¶ 173.) SEQ ID NO: 23 is reproduced below:

SEQ ID NO: 23	moltype = AA length = 495	
FEATURE	Location/Qualifiers	
source	1..495	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 23		
KFTIVFPHNQ	KGNWKNVPSN	YHYCPSSSDL NWHNDLIGTA LQVKMPKSHK AIQADGWMCH 60
ASKWVTTCDF	RWYGPKYITH	SIRSFTPSVE QCKESIEQTK QGTWLNPGFP PQSCGYATVT 120
DAEAVIVQVT	PHHVLVDEYT	GEWVDSQFIN GKCSNYICPT VHNSTTWHSD YKVKGLCDSN 180
LESMDITFFS	EDGELSSLGK	EGTGFRSNYF AYENGKACK MQYCKHWGVR LPSGVWFEMA 240
DKDLFAAARF	PECPEGSSIS	APSQTSVDVS LIQDVERILD YSLCQETWSK IRAGLPISPV 300
DLSYLAPKNP	GTGPAFTIIN	GTLKYFETRY IRVDIAAPIL SRMVGMIISGT TAERELWDDW 360
APYEDVEIGP	NGVLRITSSGY	KFPLYMIGHG MLDSDLHLSS KAQVFEHPHI QDAASQLPDD 420
ESLFFGDTGL	SKNPIELVEG	WFSSWKSSIA SFFFIIGLII GLFLVLRVGI HLCIKLKHTK 480
KRQIYTDIEM	NRLGK	495

(Ex. 1001, 129 (SEQ ID NO: 23).)

As discussed in Sections X.A.3 and X.B.1, *Perkins* disclosed that the mutated VSV-G envelope protein includes “a mutation at amino acid position . . . I182 . . . T352,” among other positions. (See, e.g., Ex. 1005 at 20:29-21:14; Ex. 1006 at 17-18; Ex. 1002 at ¶ 174.) *Perkins* disclosed a VSV-G envelope protein where I182 and T352 were among 13 amino acid positions for making one, two, or more mutations. (See, e.g., Ex. 1005 at 21:16-27; Ex. 1006 at 17-18; Ex. 1002 at ¶ 174.) *Perkins* in fact disclosed a mutated VSV-envelope protein comprising a mutation at four amino acid positions, including “a I182 mutation” and “a T352 mutation.” (Ex. 1005 at 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 174.)

A POSA would have been motivated to further incorporate *Hwang*’s T214N and T352A mutations into *Perkins*’ mutant VSV-G protein as in claim 1 of the ’366 patent, and would have had a reasonable expectation of success in making the

additional mutations, for the reasons explained in Section X.B.1. (See Ex. 1002 at ¶ 175.) These mutations would result in “a polypeptide comprising the amino acid sequence of SEQ ID NO: 23” as claimed in the ’366 patent. (*Id.*)

8. Claim 26: “The polypeptide of claim 2, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 22.”

Perkins in view of *Hwang* disclosed or suggested this limitation. (Ex. 1002, ¶ 176.) SEQ ID NO: 22 of the ’366 patent differs from SEQ ID NO: 23 of the ’366 patent by a I182D mutation instead of a I182E. (Ex. 1001 at 129 (SEQ ID NOs: 22 and 23); Ex. 1002, ¶ 176.) SEQ ID NO: 22 is reproduced below:

SEQ ID NO: 22	moltype = AA length = 495				
FEATURE	Location/Qualifiers				
source	1..495				
	mol_type = protein				
	organism = synthetic construct				
SEQUENCE: 22					
KFTIVFPHNQ	KGNWKNVPSN	YHYCPSSSDL	NWHNDLIGTA	LQVKMPKSHK	AIQADGWMCH 60
ASKWVTTCDF	RWYGPKYITH	SIRSFTPSVE	QCKESIEQTK	QGTWLNPGFP	PQSCGYATVT 120
DAEAVIVQVT	PHHVLVDEYT	GEWVDSQFIN	GKCSNYICPT	VHNSTTWHS	YKVKGLCDSN 180
LDSMDITFFS	EDGELSSLGK	EGTGFRSNYF	AYENGKACK	MQYCKHWGVR	LPSGVWFEMA 240
DKDLFAAARF	PECPEGSSIS	APSQTSVDVS	LIQDVERILD	YSLCQETWSK	IRAGLPISPV 300
DLSYLAPKNP	GTGPAFTIIN	GTLKYFETRY	IRVDIAAPIL	SRMVGMISGT	TAERELWDDW 360
APYEDVEIGP	NGVLR	TSSGY	KFPLYMIGHG	MLDSDLHLSS	KAQVFEHPHI QDAASQLPDD 420
ESLFFGDTGL	SKNPIELVEG	WFSSWKSSIA	SFFFIIGLII	GLFLVLRVGI	HLCIKLKHTK 480
KRQIYTDIEM	NRLGK				495

(Ex. 1001, 129 (SEQ ID NO: 22).)

As explained in Section X.B.7, a POSA would have been motivated to further incorporate *Hwang*’s T214N and T352A mutations into *Perkins*’ mutant VSV-G protein as in claim 2 of the ’366 patent, and would have had a reasonable expectation

of success in making the additional mutations for the reasons explained in Sections X.B.1 and X.B.4. (See Ex. 1002 at ¶ 177.) These mutations would result in “a polypeptide comprising the amino acid sequence of SEQ ID NO: 22” as claimed in the ’366 patent. (See Ex. 1002 at ¶ 177.)

9. Claim 27: “A viral particle comprising the polypeptide of claim 9.”

Perkins in view of *Hwang* disclosed or suggested this limitation. (Ex. 1002, ¶ 178.) As discussed in Section X.A.7, *Perkins* disclosed viral particles comprising the polypeptide of claim 1. “[T]he polypeptide of claim 9” as claimed differs from the polypeptide of claim 1 by the addition of mutations at T214N and T352A. For the reasons explained in Sections X.A.5, X.A.7, and X.B.7, it also would have been obvious to a POSA to make a viral particle comprising the polypeptide of claim 9.

As discussed above in Section X.A.5, *Perkins* disclosed “[m]ethods for producing the *LVV disclosed* are provided herein,” which included VSV-G packing plasmid component which is transfected into a producer cell and harvested as LVV particles. (Ex. 1005 at 54:8-56:14 (emphasis added); Ex. 1006 at 41; Ex. 1002 at ¶ 179.) As described in Section X.A.5, *Perkins*’ LVVs are described in the context of a carrying a mutated VSV-G envelope protein (*i.e.*, the polypeptide of claim 9 as described in Section X.B.7).

As discussed above in Section X.A.7., *Perkins* also disclosed that in “a four plasmid LVV system, the VSV-G plasmid includes a tandem expression cassette that

encodes a *mutated VSV-G envelope protein* and a targeting protein *as disclosed herein.*” (See, e.g., Ex. 1005 at 56:25-27; Ex. 1006 at 42; Ex. 1002 at ¶ 180.) This plasmid would be transfected into cells to produce viral particles, using *Perkins*’ above described methods of producing LVVs. (Ex. 1002 at ¶ 180.)

10. Claim 28: “The viral particle of claim 27, wherein the viral particle further comprises a nucleic acid molecule encoding a chimeric antigen receptor.”

Perkins in view of *Hwang* disclosed or suggested this limitation, as discussed in Sections X.A.9 and X.A.11. (Ex. 1002, ¶ 181.) As described above in Sections X.A.9 and X.A.11, *Perkins* expressly disclosed the harvesting of LVV particles which include LVVs produced through the use of a multiple plasmid components, including a “transfer plasmid” for encoding a transgene molecule of interest. (See, e.g., Ex. 1005 at 54:9-56:24; Ex. 1006 at 41-42; Ex. 1002 at ¶ 181.) *Perkins* also disclosed that “[t]he lentiviral vectors *described herein* include a transgene *encoding* one or more proteins that is delivered to and expressed by a lymphocyte . . . targeted by the vector. In particular embodiments, the transgene encodes a *chimeric antigen receptor.*” (See, e.g., Ex. 1005 at 41:5-8 (emphasis added); Ex. 1006 at 29; Ex. 1002 at ¶ 181.) *Perkins* also disclosed that that the transgene plasmid “may *encode* a single *heterologous protein* (e.g., a single *CAR* as described herein.)” (Ex. 1005 at 56:21-22 (emphasis added); Ex. 1006 at 42; Ex. 1002 at ¶ 181.)

Based on these disclosures, it would have been obvious for a POSA to incorporate a transgene (*i.e.*, nucleic acid molecule) encoding the CAR into the viral particle of claim 27 for the same reasons discussed above. (Ex. 1002 at ¶ 182.)

11. Claim 29: “A viral particle comprising the polypeptide of claim 26.”

Perkins in view of *Hwang* disclosed or suggested this limitation, as discussed in Section X.B.9. (Ex. 1002, ¶ 183.) While the polypeptide of claim 26 incorporates a I182D mutation instead of I1821E mutation, it would not have changed the reasons as to why a POSA would have found claim 29 obvious. (Ex. 1022 at 76-77; Ex. 1002, ¶ 183.) As explained above in Section X.B.9, *Perkins*’ disclosed a method of producing “the *LVV disclosed*” as well as a plasmid system for producing LVV particles which include a VSV-G plasmid encoding “a mutated VSV-G envelope protein . . . as disclosed herein.” (*See, e.g.*, Ex. 1005 at 54:8-56:14 (emphasis added); Ex. 1006 at 41; Ex. 1002 at ¶ 183.) A POSA would have understood *Perkins*’ disclosures on the production of viral particles would be equally applicable to the polypeptide of claim 26. (Ex. 1002 at ¶ 183.)

12. Claim 30: “The viral particle of claim 29, wherein the viral particle further comprises a nucleic acid molecule encoding a chimeric antigen receptor.”

Perkins in view of *Hwang* disclosed or suggested this limitation, as discussed in Section X.B.10. (Ex. 1002, ¶ 184.) As discussed above in Sections X.B.10, *Perkins* disclosed LVVs “described herein” as including a transgene which encodes

the chimeric antigen receptor. (*See, e.g.*, Ex. 1005 at 41:5-8; Ex. 1006 at 29; Ex. 1002 at ¶ 184.) A POSA would have understood *Perkins*' disclosures on the use of transgenes encoding CAR to be equally applicable to the viral particle of claim 29. (Ex. 1002 at ¶ 184.)

C. Ground 3: *Perkins* in View of the *RCSB PDB* Renders Claims 1-3 and 10-25 Obvious

1. Claim 1

i) [1.a] "A polypeptide"

Perkins disclosed this limitation, as discussed in Section X.A.1.i. (Ex. 1002, ¶ 186.)

ii) [1.b] "comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO. 2"

Perkins disclosed this limitation, as discussed in Section X.A.1.ii. (Ex. 1002, ¶ 187.)

iii) [1.c] "and a I182E mutation as compared to SEQ ID NO: 2."

Perkins disclosed this limitation, as discussed in Section X.A.1.iii. Any argument that *Perkins*' disclosure of a mutant VSV-G envelope protein containing a mutation at amino acid position I182 does not disclose "a I182E mutation as compared to SEQ ID NO: 2" is incorrect. (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18.) But even if accepted, this limitation would at least been obvious over *Perkins* in view of the *RCSB PDB*. (Ex. 1002 at ¶ 188.)

A POSA at the relevant time would have viewed *Perkins* as disclosing novel methods of engineering lentiviral vectors for specific targeting of lymphocytes, which could be used, for instance, for *in vivo* cellular therapy including treatment of cancer. (See, e.g., Ex. 1005 at 41:24-30, 56:21-24, 91:25-92:16, 96:18-98:17, 115:18-116:9; Ex. 1006 at 54, 56-58, 73-74; Ex. 1002 at ¶ 190.) A POSA would have further appreciated that *Perkins* disclosed lentiviral vectors that are pseudotyped with a mutated viral envelope protein, which in specific embodiments is VSV-G. (See, e.g., Ex. 1005 at 19:9-20:13; Ex. 1006 at 16-17; Ex. 1002 at ¶ 190.)

With respect to the mutated VSV-G envelope protein, as described in Section V.A.1.iii, *Perkins* specifically disclosed a mutation at amino acid position I182 of SEQ ID NO: 90, among other positions. (See, e.g., Ex. 1005 at 20:29-21:14, Ex. 1006 at 17-18; Ex. 1002 at ¶ 191.) *Perkins*' I182 mutation is disclosed among 13 other amino acid positions for making one, two, or more mutations. (See, e.g., Ex. 1005 at 21:16-27, Ex. 1006 at 17-18; Ex. 1002 at ¶ 191.) *Perkins* also disclosed a mutated VSV-envelope protein comprising "a I182 mutation" out of four mutations. (Ex. 1005 at 22:2-3; Ex. 1006 at 17-18; Ex. 1002 at ¶ 191.)

Based on any of these disclosures in *Perkins* of mutation at I182 among a finite set, it would have been obvious for a POSA to make a I182 mutation to *Perkins*' VSV-G envelope protein. (Ex. 1002 at ¶ 192); *Valeant Pharms. Int'l, Inc.*

v. Mylan Pharms. Inc., 955 F.3d 25, 34 (Fed. Cir. 2020) (reversing summary judgment of validity where the set of compositions was finite and obvious to try).

As explained above in Section X.A.1.iii, a POSA would have understood *Perkins*' disclosure of a mutation at amino acid position I182 means a substitution of a single amino acid at position 182 of SEQ ID NO. 90 and that, by default, the genus of possible amino acids to be the other 19 natural amino acids besides isoleucine, if there were no other specified range, which was inclusive of I182E. (Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18; 1002 at ¶ 192.)

A POSA would have envisaged that an even smaller subset of amino acids, represented by mutations with different properties than isoleucine, were disclosed in this context where *Perkins* instructs that mutations inhibit the ability of VSV-G to bind its native target. (See Ex. 1005 at 19:26-29; Ex. 1006 at 16; 1002 at ¶ 193.) As discussed above, *Perkins* disclosed that one or more mutations "inhibit the envelope protein's ability to bind its native target, while preserving the envelope protein's fusogenic properties." (See, e.g., Ex. 1005 at 19:26-29; Ex. 1006 at 16; Ex. 1002 at ¶ 193.)

Perkins additionally disclosed that "a 'conservative substitution' is recognized in the art as a substitution of one amino acid for another amino acid that has similar properties. Exemplary conservative substitutions are well known in the art." (See, e.g., Ex. 1005 at 13:6-11 (citing *inter alia* WO 97/09433 (Ex. 1023) at

10); Ex. 1006 at 10.) *Perkins* cites to a particular table in Ex. 1023 which shows the most conservative mutations for isoleucine (I) were known to be leucine (L) and valine (V). (See Ex. 1023 at 9-10.) This table from Ex. 1023 is reproduced below:

ALIPHATIC	Non-polar	G A P
		I L V
	Polar - uncharged	C S T M
		N Q
	Polar - charged	D E
		K R
AROMATIC		H F W Y
OTHER		N Q D E

(See, e.g., Ex. 1023 at 10; see also Ex. 1005 at 13:6-11; Ex. 1002 at 194.)

A POSA reading *Perkins* disclosures, including how *Perkins* instructs making mutations to VSV-G and its definition of “conservative substitutions,” would have understood that 17 potential amino acids, *i.e.*, those other than I, L, and V, were potential candidates for a mutation at amino acid position I182 as disclosed in *Perkins*. (Ex. 1023 at 9-10; 1002 at ¶ 195.) Amino acids I, L, and V are similar and represent the most conservative mutations, which would not have been used by POSA if their intention was to alter VSV-G binding characteristics. (*Id.*) This

understanding is consistent with the exemplary mutations in *Perkins*, each of which involve substitutions to non-conservative amino acids. (*See, e.g.*, Ex. 1005 at 21:30-32; Ex. 1006 at 17; Ex. 1002 at ¶ 195.)

The potential amino acids that a POSA would have understood as disclosed in *Perkins* for a mutation at position I182—even without knowing the location of I182 in the VSV-G protein tertiary structure—would have also excluded proline (P), as that amino acid was well known to cause a bend in the protein chain. (*See, e.g.*, Ex. 1015 at 1723, FIG. 6; Ex. 1002 at ¶ 196.) It would have also excluded cysteine (C), which could potentially introduce a disulfide bond with another cysteine thereby disrupting correct VSV-G protein folding. (*See, e.g.*, Ex. 1014 at 187-191 (describing VSV-G crystal structure including 12 cysteine residues engaged in 6 disulfide bonds); Ex. 1002 at ¶ 196.) A POSA therefore would have considered I182P or I182C mutations to be less viable options in the context of *Perkins*' disclosure. (Ex. 1002 at ¶ 196.)

Considering the finite number of practical amino acid options for making a mutation at I182 in *Perkins*' VSV-G envelope protein—only 15 inclusive of “E”—and the finite set of amino acid positions in which to make a mutation, it would have at least been obvious for a POSA to make “a I182E mutation as compared to SEQ ID NO: 2.” (*See* Ex. 1002 at ¶ 197; *Valeant*, 955 F.3d at 34.)

But even if a I182E mutation was not obvious to a POSA from *Perkins*' express disclosure, it would have at least been obvious based on the guidance in *Perkins* to make a mutation at I182 to inhibit VSV-G's ability to bind its native target receptor, coupled with the location of I182 in the 3D crystal structure of VSV-G bound to its native target receptor, LDL-R, which was available to a POSA in the *RCSB PDB*. (See, e.g., Ex. 1005 at 19:26-29; Ex. 1006 at 16; Ex. 1025 at 1; 1026 at 1; 1002 at ¶ 198.)

A POSA would have looked to the structure of VSV-G in their ordinary course of research at the relevant time. (See Ex. 1002 at ¶ 199.) Furthermore, *Perkins* incorporates by reference Nikolic *et al.* (Ex. 1018), which is a state of the art publication underpinning the published crystal structures of VSV-G bound to its native LDL-R receptor.¹⁴ (See, e.g., Ex. 1005 at 22:16-19, 116:10-17; Ex. 1006 at 18; Ex. 1018 at 4, 11; Ex. 1025 at 1; Ex. 1026 at 1; *Paice LLC v. Ford Motor Co.*, 881 F.3d 894, 906-08 (Fed. Cir. 2018).)

The published crystal structures, known as “5OY9” and “5OYL” on the *RCSB PDB*, show VSV-G bound to two distinct cysteine-rich domains (CR3 and CR2) of

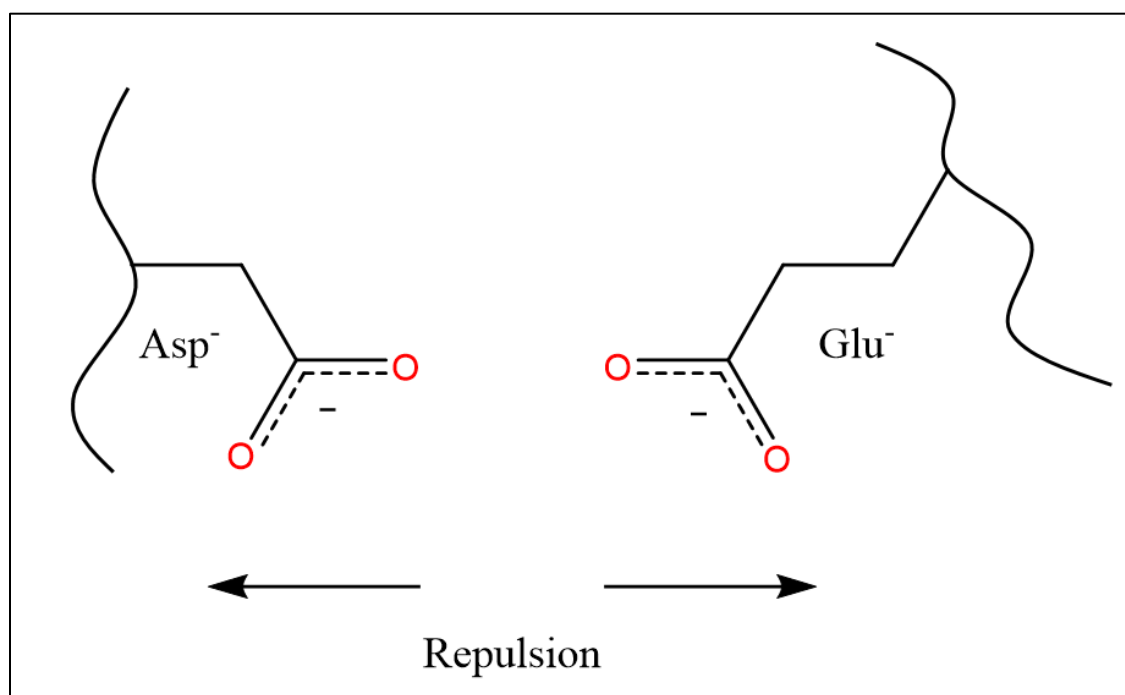
¹⁴ Nikolic *et al.* disclosed that “[t]he atomic coordinates and structure factors have been deposited in the Protein Data Bank (accession code 5OYL and 5OY9).” (Ex. 1018 at 11.)

the LDL-R, respectively. (Ex. 1025; Ex. 1026; Ex. 1002 at ¶ 200). As explained by Dr. Rose, a POSA at the relevant time would have routinely navigated these crystal structures using well-known visualization software, and would have immediately recognized that I182 is nearby aspartic acid residues on the LDL-R that may be negatively charged. (See, e.g., Ex. 1024 at 569; Ex. 1027 at 1605; Ex. 1002 at ¶¶ 201-204.)

A POSA would have been motivated to modify *Perkins* based on the VSV-G crystal structures in the *RCSB PDB*. (Ex. 1002 at ¶ 205.) *Perkins* taught that mutations to VSV-G “inhibit binding of VSV-G to the low-density lipoprotein receptor (‘LDL-R’), while preserving the VSV-G protein’s fusogenic function,” and expressly disclosed making a mutation at I182. (See, e.g., Ex. 1005 at 19:29-20:2, 20:29-21:14, 21:16-27; Ex. 1006 at 16; 1002 at ¶ 205.) The VSV-G crystal structures in the *RCSB PDB* taught that I182 is nearby negatively charged amino acids on the LDL-R. (Ex. 1002 at ¶ 205.) Thus, a POSA would have been motivated to incorporate a mutation which negated an interaction with the negatively charged residues in the LDL-R. (Ex. 1005 at 19:29-20:2; Ex. 1006 at 16; Ex. 1002 at ¶ 205.)

A POSA would have understood that aspartic acid is negatively charged at pH 6, which is the optimal pH condition for fusion of the VSV-G envelope protein to occur. (Ex. 1022 at 76-77; Ex. 1012 at 120; Ex. 1002 at ¶ 206.) Accordingly, it would have been immediately apparent to a POSA that mutation of isoleucine—

which is neither polar or charged—to a negatively charged amino acid such as glutamic acid (E) would have been likely to ablate any interaction between VSV-G and the LDL-R, as instructed by the prior art. Ex. 1002 at ¶ 206.) The concept of anionic repulsion between two negatively residues, such as aspartic acid and glutamic acid,¹⁵ would have been well known to a POSA to occur at pH 6. (Ex. 1002 at ¶ 206.) This concept is demonstrated in the image below:



(Ex. 1002 at ¶ 206.)

A POSA would have had only two options out of the naturally occurring amino acids—glutamic acid (E) and aspartic acid (D)—to incorporate in lieu of

¹⁵ The anionic forms of aspartic acid (“aspartate”) and glutamic acid (“glutamate”) are indicated in the figure above by “Asp-” and “Glu-,” respectively.

isoleucine at position 182 and oppose an interaction with negatively charged residues through anionic repulsion. (Ex. 1022 at 76-77; Ex. 1023 at 10; 1002 at ¶ 207.) It would have been common sense for a POSA to make a I182E mutation in view of the finite number of predictable options for solving a problem that was expressly called out by the prior art. (See Ex. 1002 at ¶ 207); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-21 (2007) (“When there is design need or market pressure to solve a problem and there are finite number of identified, predictable solutions, person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense”).

A POSA would also have had a good reason to focus on *Perkins*’ express disclosure of a I182 mutation. (Ex. 1002 at ¶ 208). As discussed above, *Perkins* in certain embodiments disclosed a narrowed list of 13 positions for an amino acid mutation which includes I182 as one option. (See, e.g., Ex. 1005 at 21:16-27 (disclosing a mutation at “N9, Q10, K50, A51, S183, S179, N180, **I182**, M184, I347, T350, T352, and E353” (emphasis added); Ex. 1006 at 17-18.) While routinely navigating the published 5OY9 crystal structure, a POSA could have easily checked the 13 amino acid positions disclosed in *Perkins* for making a mutation. (See, e.g.,

Ex. 1005 at 21:16-27; Ex. 1006 at 17-18; Ex. 1025 at 1; Ex. 1002 at ¶ 208.)¹⁶ These positions are also contained within *Perkins*' mutant VSV-G envelope protein containing only four mutations at N180, **I182**, T352, and E353. (*See, e.g.*, Ex. 1005 at 22:2-3; Ex. 1006 at 17-18.)

As explained by Dr. Rose, a POSA would have recognized that I182 is the closest out of the 13 disclosed amino acid positions in *Perkins* to an important aspartic acid residue in the CR3 domain. (*See, e.g.*, Ex. 1005 at 21:16-27; Ex. 1006 at 17-18; Ex. 1018 at 7; Ex. 1002 at ¶ 209.) Additionally, I182 was the only amino acid out of the 13 disclosed amino acid positions that could potentially interact with a second negatively charged amino acid in the CR3 domain. (Ex. 1002 at ¶ 209.) A POSA would thus have concluded that I182 was as one of the best of the 13 disclosed amino acid positions in *Perkins* for disrupting the interaction with the CR3 domain

¹⁶ While *Perkins* also discloses potential “insertions” and a “deletion” at 21:16-27, a POSA would have first focused on the point mutations (*i.e.*, single amino acid changes), as they are easy to check in the VSV-G crystal structures found in the *RCSB PDB* and the effect of the substitutions or deletion on VSV-G protein folding are difficult to model and would require more time to investigate. State of the art reference Nikolic *et al.* also expressly indicates that a “point mutation” should be made which ablates the natural receptor tropism. (*See, e.g.*, Ex. 1018 at 10.)

of the LDL-R, which as discussed above was most likely through anionic repulsion. (*See supra* pages 77-79; Ex. 1002 at ¶ 210.)

Similarly, while routinely navigating the published 5OYL crystal structure, a POSA could have easily checked the 13 amino acid positions disclosed in *Perkins* for making a mutation. (*See, e.g.*, Ex. 1005 at 21:16-27; Ex. 1006 at 17-18; Ex. 1002 at ¶ 211). As explained by Dr. Rose, a POSA would have recognized that I182 is the closest out of the 13 disclosed positions in *Perkins* to an important aspartic acid residue in the CR2 domain. (*See, e.g.*, Ex. 1005 at 21:16-27; Ex. 1006 at 17-18; Ex. 1018 at 7; Ex. 1002 at ¶ 211). A POSA would have similarly concluded that I182 was one of the best of the 13 disclosed amino acid positions in *Perkins* for disrupting the interaction with the CR2 domain of the LDL-R, most likely through anionic repulsion. (Ex. 1002 at ¶ 212).

Accordingly, the *RCSB PDB* provided ample reason for a POSA to focus on *Perkins*' disclosure of a I182 mutation, and to the make a I182E mutation based on the location of I182 in the crystal structures and the limited options to effectively accomplish *Perkins*' stated goal of inhibiting LDL-R binding. (Ex. 1002 at ¶¶ 208-213); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1363-64, 1366 (Fed. Cir. 2007) (holding claims obvious where prior art references provided "ample motivation to narrow the genus of 53 pharmaceutically acceptable anions" disclosed in a primary reference to a much smaller group with a reasonable expectation of success); *see*

also Altana Pharma AG v. Teva Pharms. USA, Inc., 566 F.3d 999, 1008 (Fed. Cir. 2009) (finding that it was not clearly erroneous for a POSA to have looked to one lead compound as a “natural choice for further development efforts” among 18 lead compounds because it was “one of the more potent” lead compounds, even though potency was just “a factor”).

A POSA would have had a reasonable expectation of success in making the I182E mutation to the VSV-G protein disclosed in *Perkins* for multiple reasons. (Ex. 1002 at ¶ 214.) While not required by claim 1, a POSA would have reason to believe that a I182E mutation would have resulted in a defect in LDL receptor binding. (Ex. 1002 at ¶ 214.) Additionally, while not required by claim 1, a POSA would not have believed that a I182E mutation would lead to a loss of VSV-G protein fusogenic function. (Ex. 1002 at ¶ 214.) A POSA would have appreciated that I182 is located in a different portion of the VSV-G crystal structure than the domains that were known to be involved in fusion. (*See, e.g.*, Ex. 1018 at 4 (FIG. 3); Ex. 1002 at ¶¶ 215-216.)

A POSA would also have appreciated that Nikolic *et al.* reported several mutations that were made at the VSV-G LDL-R interface (K47A, K47Q, R354A, and R354Q), which inhibited binding but retained the ability of the VSV-G protein to mediate membrane fusion. (*See, e.g.*, Ex. 1018 at 7-9; Ex. 1002 at ¶ 217.) Indeed, laboratories studying the amino acid residues which had an impact on the fusogenic

function of VSV-G did not indicate I182. (*See, e.g.*, Ex. 1015 at 1722, Table 1, 1723, FIG. 6; *see also* Ex. 1018 at 8-9 (“it is possible *to uncouple* G fusion protein activity and receptor recognition”), 10 (“[t]he demonstration that the receptors of VSV are all members of the LDL-R family together with the characterization of the molecular basis of CR domains recognition by G *paves the way to develop recombinant VSVs with modified tropism.*”) (emphasis added); Ex. 1002 at ¶ 217.)

A POSA would have reasonably believed that a change from isoleucine to glutamic acid was likely to alter binding characteristics at position 182, and that incorporation of anionic repulsion was consistent with *Perkins*’ guidance that mutations inhibit binding of VSV-G to the LDL-R while preserving the VSV-G protein’s fusogenic function. (Ex. 1005 at 19:29-20:2; Ex. 1006 at 16; 1002 at ¶ 218.) *Perkins* also makes clear that inhibition of binding between VSV-G and its native target encompasses a range of reductions, including as low as 10%. (*See* Ex. 1005 at 20:3-10; Ex. 1006 at 16; Ex. 1002 at ¶ 218.)

A POSA therefore would have had ample motivation to make a I182E mutation to the VSV-G protein disclosed in *Perkins*, as well as a reasonable expectation of success in making the mutation, based on *inter alia* the express disclosures of *Perkins* to mutate at position I182, crystal structure characterizations

of the VSV-G protein showing compatibility,¹⁷ and the knowledge and experience of a POSA at the relevant time. (Ex. 1002 at ¶ 219.)

2. Claim 2

i) [1.a] “A polypeptide”

Perkins disclosed this limitation. (Ex. 1002, ¶ 220.) As discussed in Section X.A.2.i, *Perkins* disclosed a polypeptide at SEQ ID NO: 90.

ii) [1.b] “comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO. 2”

Perkins disclosed this limitation. (Ex. 1002, ¶ 221.) As discussed in Section X.A.2.ii, *Perkins* disclosed at SEQ ID NO: 90 a polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO. 2.

¹⁷ The '366 patent states that it identified I182 through “structure-guided design” using published crystal structures 50YL and 50Y9. (See Ex. 1001 at 104:47-51.) The '366 patent also provides snapshots of the binding interface of VSV-G and the CR3 and CR2 domains. (See *id.* at FIGs. 1A and 1B.) The '366 patent, however, does not identify the nearby amino acid residues or disclose distances, which would have demonstrated the obviousness of a I182E mutation. (See Ex. 1002 at ¶ 219.)

iii) [1.c] “and a I182D mutation as compared to SEQ ID NO: 2.”

Perkins disclosed this limitation, as discussed in Section X.A.2.iii. (Ex. 1002 at ¶ 222.) Any argument that *Perkins*’ disclosure of a mutant VSV-G envelope protein including “a mutation at amino acid position . . . I182” does not disclose “a I182D mutation as compared to SEQ ID NO: 2” is incorrect. (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18.) But even if *Perkins*’ disclosure of mutating VSV-G at amino acid position I182 is found not to expressly meet “a I182E mutation as compared to SEQ ID NO: 2,” it would at a minimum have been obvious in view of the *RCSB PDB*. (Ex. 1002 at ¶ 222.)

A POSA would have possessed ample motivation to make a I182D mutation to the VSV-G envelope protein disclosed in *Perkins*, as well as a reasonable expectation of success in making the mutation, for the reasons discussed in Section X.B.1.iii with respect to glutamic acid. (Ex. 1002 at ¶ 223.) Aspartic acid (D) was one of only two options, along with glutamic acid (E), to directly oppose an interaction between a glutamic acid residue and position 182 through anionic repulsion. (Ex. 1022 at 76-77; Ex. 1023 at 10; 1002 at ¶ 223.) A POSA would have understood that the concept of anionic repulsion behaved similarly whether the opposed residues were glutamic acid or aspartic acid. (Ex. 1002, ¶ 223.) Accordingly, a I182D mutation would have been obvious to a POSA for the same reasons that a I182E mutation would have been obvious. (Ex. 1002, ¶ 224.)

3. Claim 3

Perkins in view of the *RCSB PDB* disclosed or suggested the polypeptide of claim 1 that includes the VSV-G amino acid sequence (SEQ ID NO: 90) with an I182E mutation. *Supra* Section X.C.1.iii. *Perkins* further disclosed the polypeptide of claim 1 that includes the VSV-G amino acid sequence (SEQ ID NO: 90) with an I182E mutation and a T352 mutation, as discussed in Section X.A.3. (Ex. 1002, ¶ 225.)

4. Claim 10

Perkins in view of the *RCSB PDB* disclosed or suggested the polypeptide of claim 1 that includes the VSV-G amino acid sequence (SEQ ID NO: 90) with an I182E mutation. *Supra* Section X.C.1.iii. *Perkins* further disclosed the nucleic acid molecule encoding SEQ ID NO: 90 with the I182E mutation, as discussed in Section X.A.4. (Ex. 1002, ¶ 226.)

5. Claim 11

Perkins in view of the *RCSB PDB* disclosed or suggested the nucleic acid molecule, as discussed in Section X.C.4 and *Perkins* further disclosed a vector comprising such a nucleic acid molecule as discussed in Section X.A.5. (Ex. 1002, ¶ 227.)

6. Claim 12

Perkins in view of the *RCSB PDB* disclosed or suggested the nucleic acid molecule, as discussed in Section X.C.4, and *Perkins* further disclosed a cell comprising such a nucleic acid molecule as discussed in Section X.A.6. (Ex. 1002, ¶ 228.)

7. Claim 13

Perkins in view of the *RCSB PDB* disclosed or suggested the polypeptide of claim 1 in Section X.C.1 and *Perkins* further disclosed a viral particle comprising such a polypeptide as discussed in in Section X.A.7. (Ex. 1002, ¶ 229.)

8. Claim 14

Perkins in view of the *RCSB PDB* disclosed or suggested this claim for the reasons discussed above in Sections X.C.7 and X.A.8. (Ex. 1002, ¶ 230.)

9. Claim 15

Perkins in view of the *RCSB PDB* disclosed or suggested this claim for the reasons discussed above in Sections X.C.7 and X.A.9. (Ex. 1002, ¶ 231.)

10. Claim 16

Perkins in view of the *RCSB PDB* disclosed or suggested this claim for the reasons discussed above in Sections X.C.7, X.C.9, and Section X.A.10. (Ex. 1002, ¶ 232.)

11. Claim 17

Perkins in view of the *RCSB PDB* disclosed or suggested this claim for the reasons discussed above in Sections X.C.7, X.C.9, and X.A.11. (Ex. 1002, ¶ 233.)

12. Claim 18

Perkins in view of the *RCSB PDB* disclosed or suggested the polypeptide of claim 1. *Supra* Section X.C.1.iii. Such a polypeptide satisfies claim 18 as discussed in Section X.A.12. (Ex. 1002, ¶ 234.)

13. Claim 19

Perkins in view of the *RCSB PDB* disclosed or suggested the polypeptide of claim 1. *Supra* Section X.C.1.iii. Such a polypeptide satisfies claim 19 as discussed in Section X.A.13. (Ex. 1002, ¶ 235.)

14. Claim 20

Perkins in view of the *RCSB PDB* disclosed or suggested the polypeptide of claim 1. *Supra* Section X.C.1.iii. Such a polypeptide satisfies claim 20 as discussed in Section X.A.14. (Ex. 1002, ¶ 236.)

15. Claim 21

Perkins in view of the *RCSB PDB* disclosed or suggested the polypeptide of claim 1. *Supra* Section X.C.1.iii. Such a polypeptide satisfies claim 21 as discussed in Section X.A.15. (Ex. 1002, ¶ 237.)

16. Claim 22

Perkins in view of the *RCSB PDB* disclosed or suggested the polypeptide of claim 2. *Supra* Section X.C.2.iii. Such a polypeptide satisfies claim 22 as discussed in Section X.A.16. (Ex. 1002, ¶ 238.)

17. Claim 23

Perkins in view of the *RCSB PDB* disclosed or suggested the polypeptide of claim 2. *Supra* Section X.C.2.iii. Such a polypeptide satisfies claim 23 as discussed in Section X.A.17. (Ex. 1002, ¶ 239.)

18. Claim 24

Perkins in view of the *RCSB PDB* disclosed or suggested the polypeptide of claim 2. *Supra* Section X.C.2.iii. Such a polypeptide satisfies claim 24 as discussed in Section X.A.18. (Ex. 1002, ¶ 240.)

19. Claim 25

Perkins in view of the *RCSB PDB* disclosed or suggested the polypeptide of claim 2. *Supra* Section X.C.2.iii. Such a polypeptide satisfies claim 25 as discussed in Section X.A.19. (Ex. 1002, ¶ 241.)

D. Ground 4: *Perkins* in View of the *RCSB PDB* and *Hwang* Renders Claims 3-9 and 26-30 Obvious

For the reasons described in Section X.C, independent claims 1 and 2 are obvious over *Perkins* in view of the *RCSB PDB*. Claims 3-9 and 26-30, which depend from either claim 1 or claim 2, concern additional mutations beyond those

recited in claims 1 and 2. But claims 3-9 and 26-30 would have been obvious over *Perkins* and the *RCSB PDB* in further view of *Hwang* for reasons similar to those set forth in Section X.B.

A POSA would have been motivated to further modify *Perkins* and the *RCSB PDB* in view of *Hwang* and would have arrived at claims 3-9 and 26-30 with a reasonable expectation of success for the reasons described in Section X.B. (Ex. 1002 at ¶ 243.) The *RCSB PDB* includes the crystal structures of VSV-G bound to the CR3 and CR2 domains of the LDL-R, and would not present any reason to a POSA as to why *Perkins*, the *RCSB PDB*, and *Hwang* could not be combined to arrive at claims 3-9 and 26-30 with a reasonable expectation of success for the reasons described in Sections X.B and X.C. (Ex. 1002 at ¶ 243.)

XI. DISCRETIONARY DENIAL

A. Discretionary Denial Under *Fintiv* Is Not Appropriate

Fintiv factors are inapplicable because there is no parallel proceeding. *See Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 5-6 (P.T.A.B. Mar. 20, 2020) (precedential).

B. Discretionary Denial Under 35 U.S.C. § 325(d) Is Not Appropriate

Discretionary denial pursuant to 35 U.S.C. § 325(d) is inappropriate under the two-part framework set forth in *Advanced Bionics, LLC v. MED-EL*

Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8-9 (P.T.A.B. Feb. 13, 2020) (precedential).

As to part one of the *Advanced Bionics* framework, this Petition relies on art (*Perkins* and *Hwang*) that was presented to the Office, but was not substantively considered. The Examiner's July 26, 2023 Notice of Allowance from prosecution of the '366 patent suggests the Examiner was not aware of *Perkins*. (See Section VI.C.) *RCSB PDB* was not presented to the Office.

Regardless of whether part one of the *Advanced Bionics* framework is satisfied, the Office materially erred in allowing the claims of the '366 patent under part two of the *Advanced Bionics* framework. *Perkins* and *Hwang* were cited in an information disclosure, but there is no indication that they were substantively considered by the Examiner and certainly, were never used to reject the claims. See *Hum Indus. Tech., Inc. v. Amsted Rail Co., Inc.*, IPR2023-00539, Paper 10 at 49-53 (P.T.A.B. July 26, 2023) (declining to exercise discretion under § 325(d)).

In fact, the Examiner issued a single rejection during the prosecution of the application that issued as the '366 patent, which only objected to claim language and raised a provisional double patenting rejection. (Ex. 1004 at 161-166.) The Examiner did not raise an anticipation or obviousness rejection based upon the Petitioner's prior art grounds in this petition, and factors (d), (e), and (f) therefore weigh against discretionary denial under 35 U.S.C. § 325(d). See *Progenity, Inc. v.*

Natera, Inc., IPR2021-00279, Paper 12 at 41-45 (P.T.A.B. Jun. 11, 2021). As this Petition and supporting testimony demonstrates, *Perkins* anticipates claims 1-3 and 10-25 and renders the same claims obvious in view of the *RCSB PDB*. *Perkins* and *Hwang*, or *Perkins* and the *RCSB PDB* in view of *Hwang* render claims 3-9 and 26-30 obvious. Thus, the Office materially erred by allowing the claims over the prior art cited in this Petition.

XII. CONCLUSION

Petitioner requests institution of PGR for claims 1-30 of the '366 patent.

Respectfully submitted,

Dated: October 31, 2023

By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)
Counsel for Petitioner

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for Post-Grant Review of U.S. Patent No. 11,767,366 contains, as measured by the word-processing system used to prepare this paper, 18,656 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Respectfully submitted,

Dated: October 31, 2023

By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)
Counsel for Petitioner

CERTIFICATE OF SERVICE

I hereby certify that on October 31, 2023, I caused a true and correct copy of the foregoing Petition for Post-Grant Review of U.S. Patent No. 11,767,366 and supporting exhibits to be served via express mail on the Patent Owner at the following correspondence address of record as listed on Patent Center:

51414 - GOODWIN PROCTER LLP
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By: /Naveen Modi/
Naveen Modi (Reg. No. 46,224)