UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KELONIA THERAPEUTICS, INC.
Petitioners

v.

INTERIUS BIOTHERAPEUTICS, INC.
Patent Owner

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

DECLARATION OF PROFESSOR JOHN K. ROSE, PHD IN SUPPORT OF PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 11,767,366

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I, John K. Rose, declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for the Petitioners as an independent expert consultant in this proceeding before the United States Patent and Trademark Office, which I understand involves U.S. Patent No. 11,767,366 ("the '366 patent") (Ex. 1001).[1]

2. I am being compensated at my normal consulting rate of $800 per hour for my work.

3. My compensation is in no way contingent on the nature of my findings, the presentation of my findings in testimony, or the outcome of this or any other proceeding. I have no other interest in this proceeding.

4. I have been asked to consider whether certain references disclose or suggest the features recited in claims 1-30 of the '366 Patent. My opinions are set forth below.

II. PROFESSIONAL BACKGROUND AND QUALIFICATIONS

5. I am an independent consultant. All of my opinions stated in this declaration are based on my own personal knowledge and professional judgment. In

[1] Where appropriate, I refer to exhibits that I understand to be attached to the petition for post-grant review of the '366 patent.

forming my opinions, I have relied on my knowledge and experience in the structure and function of glycoproteins and the specific targeting of viral vectors.

6. I am over 18 years of age and, if called upon to do so, I would be competent to testify as to the matters set forth herein. I understand that a copy of my current curriculum vitae (Ex. 1003), which details my education and professional and academic experience, is being submitted in this proceeding. The following provides an overview of some of my experience that is relevant to the matters set forth in this declaration.

7. I have significant experience and familiarity with the structure and function of viral glycoproteins, including the vesicular stomatitis virus (VSV) glycoprotein (VSV-G). In 1981 my laboratory reported the first sequence of VSV-G mRNA and protein determined from a cDNA clone. *See* J. Rose and C. Gallione, *Nucleotide Sequences of the mRNAs Encoding the Vesicular Stomatitis Virus G and M Proteins Determined from cDNA Clones Containing the Complete Coding Regions,* 39 J. VIROLOGY 519 (1981) (EX. 1028). We then showed that cells expressing VSV-G protein in the absence of other VSV proteins would fuse at low pH. *See* R. Florkiewicz and J. Rose, *A Cell Line Expressing Vesicular Stomatitis Virus Glycoprotein Fuses at Low pH*, 225 SCIENCE 721 (1984) (Ex. 1029). This was the first direct evidence that VSV-G protein has membrane fusion activity. We later

performed numerous studies using VSV-G mutants to study the signals involved in protein transport from the endoplasmic reticulum to the cell surface.

8. I am currently Professor Emeritus of Pathology and Senior Research Scientist at Yale University School of Medicine in New Haven, CT. I have held this role since 2019, and to this day operate a laboratory engaged in research on VSV.

9. For over thirty years my laboratory at Yale has been concerned with novel approaches to vaccine development based on recombinant viruses and on specific targeting of viral vectors. In particular, my laboratory has developed methodology for generating recombinants of VSV starting from plasmid DNA. VSV is a simple membrane-enveloped, negative-strand RNA virus that grows to high titers in most animal cells. These recombinant VSVs expressing foreign viral proteins induce potent cellular and humoral immune responses to the foreign proteins in animals and protect from infection or disease caused by other viruses such as influenza, measles, respiratory syncytial virus, SARS, and a monkey AIDS virus. My laboratory has also performed research into the mechanisms by which the recombinants of VSV generate such strong immune responses and in ways to enhance these responses further while improving vector safety. My laboratory has also developed novel priming and boosting vaccine vectors based on propagating replicons of positive-strand RNA viruses.

10. Prior to my current role at Yale University School of Medicine, I was a Professor of Pathology and Cell Biology at Yale School of Medicine from 1986 to 2019. Before that position, from 1982 to 1986, I was an Associate Professor at the Salk Institute. From 1979 to 1982, I was an Assistant Professor at the Salk Institute.

11. Previously I was a Research Associate at the Massachusetts Institute of Technology with Dr. David Baltimore from 1976 to 1978. From 1974 to 1975, I was a Postdoctoral Fellow at the Massachusetts Institute of Technology in the laboratories of Drs. Harvey Lodish and Dr. David Baltimore. From 1969 to 1973, I was a Predoctoral trainee in the U.S. Public Health Service with Dr. Charles Yanofsky at Stanford University.

12. I was awarded a B.A in Biology from Brandeis University in 1969, and a Ph.D. in Biology and Biochemical Genetics in 1973 from Stanford University.

13. I have published over 200 peer-reviewed papers and reviews.

14. I have served on the Editorial Board of the *Journal of Virology* from 1980 to 2011 and *Virology* from 1994 to 2014.

15. I have also held various titles in professional activities at Yale. From 1987 to 1992 I was the Director of Graduate Studies in Experimental Pathology. From 1992 to 2000 I was the Director of the Yale Medical School HIV research facility. From 1994 to 1999 I was the Co-director of the Yale Graduate Program in

Microbiology. From 2005 to 2015 I was the Director of the Program in Virology and Vaccine Development at Yale University.

16. I am not an attorney and offer no legal opinions, but in the course of my work, I have had experience studying and analyzing patents and patent claims from the perspective of a person of ordinary skill in the art (which I define in Section IV below).

III. MATERIALS REVIEWED

17. The opinions in this Declaration are based on the documents I reviewed, my knowledge and experience, and professional judgment. In forming my opinions expressed in this Declaration, I have reviewed the documents and other materials referred to herein. I understand that the documents and materials I reviewed and refer to herein are being submitted as exhibits attached to the petition for Post Grant Review of the ’366 patent, and are listed in Appendix A (Table of Cited Exhibits).

18. My opinions have been guided by my understanding of how one of ordinary skill in the art would have understood claims 1-30 and the specification of the ’366 patent at the time of the alleged invention, which I have been asked to consider as of the 2021 timeframe (including December 15, 2021, the filing date of U.S. Provisional Application No. 63/289,888 (“the ’888 application”) and U.S. Provisional Application No. 63/289,977 (“the ’977 patent”), which is the earliest filing date to which the ’366 patent claims priority). My opinions reflect how one

of ordinary skill in the art would have understood the ’366 patent, the prior art to that patent, and the state of the art at the time of the alleged invention.

19. Based on my review of the materials in view of my experience and expertise, it is my opinion that the references identified below taught a mutant VSV-G envelope protein with a I182E or I182D mutation, including all of the elements recited in claims 1-30 of the ’366 patent, as I discuss in detail below.

IV. PERSON OF ORDINARY SKILL IN THE ART

20. I have been asked to assume that the relevant timeframe for the alleged inventions of the ’366 patent is 2021, including the time period up to and including December 15, 2021, the filing date of the earliest applications (the ’888 and the ’977 applications) to which the ’366 patent claims priority (referred to herein as “the relevant timeframe”). I applied that understanding in my analysis.

21. I am familiar with the level of ordinary skill in the art with respect to the technology disclosed and claimed in the ’366 patent during the relevant timeframe. Based on my review of the ’366 patent, the technology, the educational level and experience of active workers in the field, the types of problems faced by professionals in the field, the solutions found to those problems, the sophistication of the technology in the field, and drawing on my own experience, I believe one of ordinary skill in the art 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. All of my opinions in this declaration are from the perspective of one of ordinary skill in the art as I have defined it here. My opinions expressed in this declaration would be the same if this definition was altered to some extent to account for a slightly greater or lesser level of skill in the art, at least because of the clear prior art disclosures discussed herein.

V. BACKGROUND OF TECHNOLOGY, THE '366 PATENT AND PROSECUTION HISTORY, AND THE PRIOR ART

A. Gene Therapy with Lentiviral Vectors

22. 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.)[2] 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.)

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

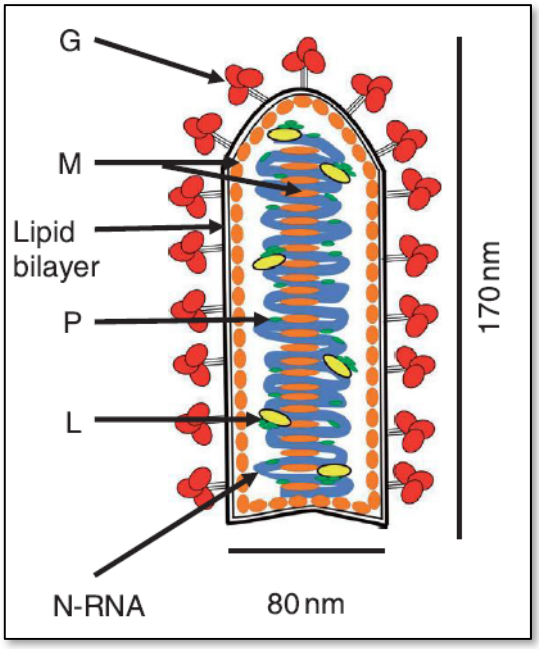
23. By the 2020s, lentiviral vectors were known to be "among the most promising vectors" for cellular therapies and, for certain cells, "the tools of choice." (*See, e.g.*, Ex. 1010 at 1; Ex. 1008 at 1.) This stems not only from their stable and effective delivery of genes into cells, also known as cell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

24. 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 "pseudotyping." (*See, e.g.*, Ex. 1010 at 2; Ex. 1012 at 130.) 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.) 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.) 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.*, *id.*)

25. By the 2020s, it was known that pseudotyping lentiviral vectors by the vesicular stomatitis virus envelope glycoprotein G ("VSV-G") was the most common approach for pseudotyping lentiviral vectors. (*See, e.g.,* Ex. 1010 at 9.) 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.)

B. <u>Vesicular Stomatitis Virus Glycoprotein</u>

26. 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.) A schematic illustration of a VSV viral particle is reproduced below for illustration:



27. 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 291-92, 295-96, FIG. 1.) 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.*)

28. 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.) 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.) Subsequently, "the viral envelope fuses with a cellular membrane within the acidic environment of the endosome." (*See, e.g.*, Ex. 1015 at 1717.) 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.)

29. 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).)

30. 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, e.g.,* Ex. 1016 at 7306, 7310.) 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, e.g.,* Ex. 1016 at 7306.) 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 LDL-R. (*See, e.g.*, Ex. 1017 at 1422-23.)

C. Making "Mutations" to Prepare Mutants of VSV-G

31. A person of ordinary skill in the art 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.) A person of ordinary skill in the art also would have understood that polynucleotides are nucleic acid molecules that include both deoxyribonucleic acid ("DNA") and ribonucleic acid ("RNA"). (*See, e.g.,* Ex. 1022 at 39-44.)

32. 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.) A person of ordinary skill in the art 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.*)

33. Proteins are composed of 20 "standard" amino acids. (*See, e.g.*, Ex. 1022 at 74-77.) A person of ordinary skill in the art was also well aware of the abbreviated one-letter symbols for amino acids. (*See, e.g.*, Ex. 1022 at 76-77, 81-

82.) For example, the amino acid "isoleucine" using its one-letter symbol is referred to as "I." (*See, e.g.*, Ex. 1022 at 76.)

34. Wild-type VSV-G includes a 16 amino acid signal peptide (also referred to as a "signal sequence") that is cleaved in the endoplasmic reticulum of a eukaryotic cell. (*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). 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).) 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.*, *id.*)

35. A person of ordinary skill in the art would have understood that mutations at a single amino acid residue can be easily represented by the one-letter amino acid symbol. 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.) 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.

D. Engineering of VSV-G Pseudotyped Lentiviral Vectors

36. 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.) 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.)

37. Importantly, Nikolic *et al.* reported in 2018 the crystal structure of VSV-G bound to the LDL-R. (*See* Ex. 1018 at 1.)[3] 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.) 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 activity of VSV-G, thereby suggesting a pathway for "develop[ing] recombinant VSVs with

[3] The crystal structures of VSV-G bound to the LDL receptor was submitted to the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Databank (PDB) ("*RCSB PDB*") and made publicly available in March 2018. (*See, e.g.*, Exs. 1024, 1025, 1026.)

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").)

38. 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.) 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].)

39. 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.) 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].) 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.)

E. Overview of the ’366 Patent

40. 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.

41. The ’366 patent claims a combination of disclosed technologies relating to the mutation of VSV-G and related viral applications. Independent claim 1 of the ’366 patent 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.

42. Claim 2 of the ’366 patent is the same as claim 1 of the ’366 patent, but recites a I182D mutation instead of a I182E mutation.

43. The dependent claims of independent claim 1, including claims 3-5 and 9-21, and the dependent claims of independent claim 2, including claims 6-8 and 22-30, in my opinion 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 (Ex. 1001 at

146:17-40), and known additional mutations to provide protection against serum inactivation of VSV-G in a lentiviral vector (Ex. 1001 at 145:19-40.).

F. Overview of the '366 Patent Prosecution History

44. 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. (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.)

45. 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 other prior art such as *Perkins*, which expressly disclosed a mutation at ***residue 182***.

G. Overview of *Perkins*

46. *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.) 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; Ex. 1006 at 1.)

47. *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.) For example, that "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.*,

[4] Citations to Ex. 1006 are to the internal page numbers of the specification of the '639 application.

Ex. 1005 at 19:29-20:2; Ex. 1006 at 16.) *Perkins* specifically disclosed that the mutated VSV-G envelope protein includes a mutation at "I182," among other amino acid positions.[5] (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18.)

48. *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.) *Perkins* disclosed that the lentiviral vector 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, 18.) *Perkins* also disclosed that, "in further specific embodiments, the transgene encodes a chimeric antigen receptor (CAR)." (*Id.*)

H. <u>Overview of *Perkins*' Provisional Application</u>

49. I was also asked to review U.S. Provisional Application No. 63/154,639 ("the '639 application") (*see* Ex. 1006 at Cover) to determine if it contained support for claim 1 as seen in *Perkins*.

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[5] As explained in *Perkins*, the position and nature of the "I182" mutation is in reference to the VSV-G envelope protein absent its 16 amino acid N-terminal signal sequence. (*See, e.g.*, Ex. 1005 at 20:17-28.)

50. In my opinion, claim 1 of *Perkins* finds support in the ’639 application. The chart below demonstrates this support:

***Perkins* at Claim 1 (Ex. 1005 at 117:1-10)**	**Support in the ’639 Application (Ex. 1006)**
A lentiviral vector, comprising:	*See, e.g.*, Ex. 1006 at 75 (claim 1); *see also id.* at 16
(a) a viral envelope comprising:	*See, e.g.*, Ex. 1006 at 75 (claim 1); *see also id.* at 16-18
a heterologous lymphocyte targeting protein, the lymphocyte targeting protein comprising:	*See, e.g.*, Ex. 1006 at 75 (claim 1); *see also id.* at 16, 18-19
an extracellular domain comprising a lymphocyte targeting domain; and	*See, e.g.*, Ex. 1006 at 75 (claim 1); *see also id.* at 16, 18-19
a transmembrane domain; and	*See, e.g.*, Ex. 1006 at 75 (claim 1); *see also id.* at 16, 18-19, 29-32
(b) a mutated VSV-G envelope protein that exhibits inhibited binding to an LDL-R but mediates membrane fusion; and	*See, e.g.*, Ex. 1006 at 75 (claim 1); *see also id.* at 16-18
(c) an expression cassette that comprises a heterologous transgene.	*See, e.g.*, Ex. 1006 at 75 (claim 1); *see also id.* at 16, 26, 29-32, 41-42, 52

51. In addition, as seen in my supporting citations in this declaration, each of the statements in *Perkins* I rely on below were carried forward from the ’639 application.

I. Overview of the *RCSB PDB*

52. 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.) 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.*)

53. 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.) This included accession code "5OY9" for VSV-G bound to the CR3 domain (Ex. 1025), and accession "5OYL" for VSV-G bound to the CR2 domain (Ex. 1026).)

54. I navigated to the *RCSB PDB* and downloaded the crystal structures associated with accession codes 5OY9 and 5OYL, which are in a *.pdb file format. 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.

55. 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.) As of 2021, free navigation tools were commonly used to view and analyze structural data on the *RCSB PDB*. I 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 person of ordinary skill in the art would have done at the relevant time.

J. Overview of *Hwang*

56. *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.)

57. *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.)

[6] A person of ordinary skill in the art 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. Thus, *Hwang*'s disclosure of "T230N + T368A" is equivalent to "T214N + T352A" in a VSV-G envelope protein without its signal sequence.

58. *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 812-813.) *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.)

VI. THE PRIOR ART DISCLOSED, TAUGHT, OR SUGGESTED CLAIMS 1-30 OF THE '366 PATENT

59. I have reviewed several references, discussed further below, that I understand were available to a person of ordinary skill in the art as of the 2021 priority date of the '366 patent, which is the relevant timeframe. In my opinion these references disclosed, taught, or suggested all of the elements of claims 1-30 of the '366 patent.

A. ***Perkins* Disclosed All of the Elements of Claims 1-3 and 10-25 of the '366 Patent**

60. In my opinion, a person of ordinary skill in the art would have understood that *Perkins* disclosed all of the elements of claims 1-2 and 10-25 of the '366 patent, as set forth in the claim charts below.

1. Claim 1

i) [1.a] "A polypeptide"

61. *Perkins* disclosed "[a] polypeptide."

Claim Language	*Perkins*
1. "A polypeptide"	*Perkins* disclosed that "the nucleic acid and amino acid sequences set forth in Table 10 provide references sequences for a wild type VSV-G envelope protein and examples of mutated VSV-G envelope proteins according to the present disclosure. . . . SEQ ID NO: 88 is an amino acid sequence of the cleavable signal peptide of the reference VSV-G envelope protein. . . . SEQ ID NO: 90 is an amino acid sequence of a reference VSV-G envelope protein absent the sequence." (Ex. 1005 at 20:11-21, 74-75 (SEQ ID NO: 90); Ex. 1006 at 9-10, 17, 50 (SEQ ID NO: 72), 51 (SEQ ID NO: 78).

62. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "a polypeptide."

63. *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 SQFINGKCSNYICPTVHNSTTWHSD 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).)

64. The ’639 application described SEQ ID NO: 90 in *Perkins*. 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
DYSLCQETWSKIRAGLPISPVDLSYLAPKNPGT
GPAFTIINGTLKYFETRYIRVDIAAPILSRMVGMIS
GTTTERELWDDWAPYEDVEIGPNGVLRTSSGY
KFPLYMIGHGMLDSDLHLSSKAQVFEHPHIQDA
ASQLPDDESLFFGDTGLSKNPIELVEGWFSSWK
SSIASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQI
YTDIEMNRLGK (SEQ ID NO: 78)

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

65. 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).)

66. The '639 application expressly contemplates an amino acid sequence without the "signal sequence." (Ex. 1005 at 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"). A person of ordinary skill in the art would have understood that SEQ ID NO: 78 without the signal sequence (SEQ ID NO: 72) results in SEQ ID NO: 90 in *Perkins*.

67. A person of ordinary skill in the art would have also recognized that 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).) 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.) As stated above, *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.) Therefore while the '639 application does not reproduce SEQ ID NO: 90 like *Perkins* does, a person of ordinary skill in the art would have understood that the '639 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.[7]

[7] I note that the '366 patent similarly described an amino acid sequence at SEQ ID NO: 1 which is the "full length protein" of VSV-G, identical to SEQ ID NO: 78 in the '639 application, and states that the "16-mer signal peptide of

68. 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 at 17.) However, there is no "H" at position 8, no "N" at position 9, or "Q" at position 10 in SEQ ID NO: 78. (*Id.* at 51.) It is only when one removes the first 16 amino acids (*i.e.*, the signal sequence) and begins counting with "K" at position 1 does one arrive at H8, N9, Q10. Moreover, a person of ordinary skill in the art 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. SEQ ID NO: 78 is processed to it mature form, SEQ ID NO: 90, which is then expressed on the viral envelope.

69. *Perkins* disclosed 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.) A person of ordinary skill in the art would have understood the ***amino acid sequence*** in SEQ ID

MKCLLYLAFLFIGVNC . . . is cleaved leaving a protein of SEQ ID NO: 2." (*See* Ex. 1001 at 17:33-39.) SEQ ID NO: 2 in the '366 patent is identical to SEQ ID NO: 90 (*see* Section VI.A.1.ii below) resulting from the removal of the "signal sequence" (SEQ ID NO: 72) from SEQ ID NO: 78 in the '639 application.

NO: 90, as well as the reference to "VSV-G envelope ***protein***" to represent "a polypeptide."

70. A person of ordinary skill in the art would have understood these disclosures from *Perkins* to disclose "a polypeptide."

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

71. *Perkins* disclosed "comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2."

Claim Language	***Perkins***
1) "comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2"	*Perkins* disclosed that "the nucleic acid and amino acid sequences set forth in Table 10 provide references sequences for a wild type VSV-G envelope protein and examples of mutated VSV-G envelope proteins according to the present disclosure. . . . SEQ ID NO: 88 is an amino acid sequence of the cleavable signal peptide of the reference VSV-G envelope protein. . . . SEQ ID NO: 90 is an amino acid sequence of a reference VSV-G envelope protein absent the sequence." (Ex. 1005 at 20:11-21, 74-75 (SEQ ID NO, 90); Ex. 1006 at 9-10 ("For polypeptide sequences disclosures

Claim Language	*Perkins*
	herein, where a signal sequence is noted, the polypeptide sequence absent the signal sequence or having a partial sequence is also contemplated"), 17, 50 (SEQ ID NO: 72), 51 (SEQ ID NO: 78). *Perkins* disclosed the amino acid sequence of WT VSV-G without its signal sequence at SEQ ID NO: 90: **WT VSV-G without signal sequence** **Amino acid** KFTIVFPHNQKGNWKNVPSNYHYC PSSSDLNWHNDLIGTALQVKMPKS HKAIQADGWMCHASKWVTTCDFR WYGPKYITHSIRSFTPSVEQCKESIE QTKQGTWLNPGFPPQSCGYATVTD AEAVIVQVTPHHVLVDEYTGEWVD SQFINGKCSNYICPTVHNSTTWHSD YKVKGLCDSNLISMDITFFSEDGEL SSLGKEGTGFRSNYFAYETGGKAC KMQYCKHWGVRLPSGVWFEMAD KDLFAAARFPECPEGSSISAPSQTSV DVSLIQDVERILDYSLCQETWSKIR AGLPISPVDLSYLAPKNPGTGPAFTI INGTLKYFETRYIRVDIAAPILSRMV GMISGTTTERELWDDWAPYEDVEI GPNGVLRTSSGYKFPLYMIGHGML DSDLHLSSKAQVFEHPHIQDAASQL PDDESLFFGDTGLSKNPIELVEGWF SSWKSSIASFFFIIGLIIGLFLVLRVGI HLCIKLKHTKKRQIYTDIEMNRLGK (SEQ ID NO: 90)

Claim Language	***Perkins***
	(Ex. 1005 at 74-75 (SEQ ID NO: 90); Ex. 1006 at 9-10, 17, 50 (SEQ ID NO: 72), 51 (SEQ ID NO: 78).)

72. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2."

73. 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, e.g.*, Ex. 1005 at 20:11-21, 74-75 (SEQ ID. NO: 90); Ex. 1006 at 9-10, 17, 50 (SEQ ID NO: 72), 51 (SEQ ID NO: 78).) SEQ ID NO: 90 from *Perkins* is reproduced below:

KFTIVFPHNQKGNWKNVPSNYHYC
PSSSDLNWHNDLIGTALQVKMPKS
HKAIQADGWMCHASKWVTTCDFR
WYGPKYITHSIRSFTPSVEQCKESIE
QTKQGTWLNPGFPPQSCGYATVTD
AEAVIVQVTPHHVLVDEYTGEWVD
SQFINGKCSNYICPTVHNSTTWHSD
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).

74. The '366 patent disclosed that "SEQ ID NO: 2 is the ectodomain[8] of the VSV-G protein," where "[t]he 16-mer signal peptide . . . is cleaved leaving a

[8] While the '366 patent refers to SEQ ID NO: 2 as "the ectodomain of the VSV-G protein," a person of ordinary skill in the art would have understood that the "ectodomain" of native VSV-G actually contained less than the 495 amino acids in SEQ ID NO: 2. (*See, e.g.*, Ex. 1012 at 118.) The '366 patent appears to recognize this elsewhere, describing in background that VSV-G contains "an ectodomain of about 450 amino acids, a single alpha helical transmembrane segment and a small intraviral carboxy-terminal domain." (*See* Ex. 1001 at 1:32-39.)

protein of SEQ ID NO: 2." (*See, e.g.*, Ex. 1001 at 17:33-39.) 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 KGNWKNVPSN YHYCPSSSDL NWHNDLIGTA LQVKMPKSHK AIQADGWMCH  60
ASKWVTTCDF RWYGPKYITH SIRSFTPSVE QCKESIEQTK QGTWLNPGFP PQSCGYATVT  120
DAEAVIVQVT PHHVLVDEYT GEWVDSQFIN GKCSNYICPT VHNSTTWHSD YKVKGLCDSN  180
LISMDITFFS EDGELSSLGK EGTGFRSNYF AYETGGKACK MQYCKHWGVR LPSGVWFEMA  240
DKDLFAAARF PECPEGSSIS APSQTSVDVS LIQDVERILD YSLCQETWSK IRAGLPISPV  300
DLSYLAPKNP GTGPAFTIIN GTLKYFETRY IRVDIAAPIL SRMVGMISGT TTERELWDDW  360
APYEDVEIGP NGVLRTSSGY KFPLYMIGHG MLDSDLHLSS KAQVFEHPHI QDAASQLPDD  420
ESLFFGDTGL SKNPIELVEG WFSSWKSSIA SFFFIIGLII GLFLVLRVGI HLCIKLKHTK  480
KRQIYTDIEM NRLGK                                                   495
```

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

75. A person of ordinary skill in the art would have understood that SEQ ID NO: 90 in *Perkins* and SEQ ID NO: 2 in the '366 patent 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. Based on this identical amino acid sequence, a person of ordinary skill in the art 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.

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

76. *Perkins* disclosed "and a I182E mutation as compared to SEQ ID NO: 2."

Claim Language	***Perkins***
1) "and a I182E mutation as compared to SEQ ID NO: 2."	*Perkins* disclosed that "[l]entiviral vectors as described herein are pseudotyped with a mutated heterologous viral envelope protein that, in the absence of mutation, mediates both cellular attachment and membrane fusion. In particular embodiments, the mutated 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.) *Perkins* disclosed "[i]n some embodiments, the mutated VSV-G envelope protein includes a mutation at amino acid position H8, N9, QI0, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and Q10, an insertion of GGS

Claim Language	***Perkins***
	between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and/or a deletion of residues 1-8." (Ex. 1005 at 20:29-21:2; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n certain embodiments, the VSV-G envelope protein includes two or more mutations at amino acid positions selected from H8, N9, QI0, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (*See, e.g.*, Ex. 1005 at 21:2-8; Ex. 1006 at 17-18.)

Claim Language	***Perkins***
	Perkins disclosed [i]n other embodiments, the VSV-G envelope protein includes three or more mutations at amino acid positions selected from H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (*See, e.g.*, Ex. 1005 at 21:8-14; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n still other embodiments, the VSV-G envelope protein includes one or more mutations selected from N9, Q10, K50, A51, Sl83, SI79, N180, I182, M184, I347, T350, T352, and E353, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT

Claim Language	*Perkins*
	between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (Ex. 1005 at 21:16-22; Ex. 1006 at 17-18.) *Perkins* disclosed "in yet other embodiments, the VSV-G envelope protein includes two or more mutations selected from a mutation at one or more of N9, Q10, K50, A51, S183, S179, N180, I182, M184, I347, T350, T352, and E353, an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (Ex. 1005 at 21:22-27; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n some embodiments, the mutated VSV-G envelope protein comprises a N180 mutation, a

Claim Language	***Perkins***
	I182 mutation, a T352 mutation, and a E353 mutation." (Ex. 1005 at 22:2-3; Ex. 1006 at 17-18).

77. As shown by the above disclosures, a person of ordinary skill in the art would have understood that *Perkins* disclosed "a I182E mutation as compared to SEQ ID NO: 2."

78. A person of ordinary skill in the art would have understood that "I182E mutation" simply means that position 182 has an amino acid referenced by the letter "I" which is substituted (*i.e.*, mutated) with an amino acid referenced by the letter "E." 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
SQFINGKCSNYICPTVHNSTTWHSD
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) (annotated to show "I" at position 182).)

79. *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.) *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 (disclosing a mutation at "N9, Q10, K50, A51, S183, S179, N180, **I182**, M184, I347, T350, T352, and E353" (emphasis added).) *Perkins* also disclosed a mutated VSV-envelope protein comprising a mutation at only four amino acid positions, including "a I182 mutation." (Ex. 1005 at 22:2-3; Ex. 1006 at 17-18.)

80. *Perkins* disclosed that "[i]n particular embodiments, 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.) *Perkins* also 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.)

81. *Perkins* expressly disclosed that "the position and nature of VSV-G mutations ***disclosed herein*** are described in reference to . . . the amino acid sequence provided by . . . SEQ ID NO: 78 absent the N-terminal signal sequence of SEQ ID NO: 88. . . . Thus, reference to a position 1 of the VSV-G env amino acid sequence for the purpose of identifying mutation position refers to position 17 of the wildtype VSV-G amino acid sequence of SEQ ID NO: 78, which is a lysine (K), or position 1 of the wildtype VSV-G amino acid sequence of SEQ ID NO: 90." (*See, e.g.*, Ex. 1005 at 20:21-28 (emphasis added).)

82. A person of ordinary skill in the art would have thus understood that the positions disclosed for making amino acid mutations to VSV-G in both *Perkins* and the '639 provisional application were in reference to the amino acid sequence of VSV-G without its signal sequence, *i.e.*, SEQ ID. NO: 90 in *Perkins*. (*See, e.g.*, Ex. 1005 at 20:11-22:14; Ex. 1006 at 9-10, 17-18). 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. (*See, e.g.*, Ex. 1005 at 74-75 (SEQ ID NO: 90.)

83. A person of ordinary skill in the art would have understood *Perkins'* disclosure of a mutation at amino acid position I182 to mean a substitution of a single amino acid ("I") at position 182 of SEQ ID NO. 90 with another amino acid. While *Perkins* does not specify what "I" is replaced with, a person of ordinary skill in the art would have understood that that, by default, the possible amino acids to which *Perkins* allows for a substituting "I" is any of the other 19 natural amino acids besides isoleucine, if there were no other specified range. (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18.) A person of ordinary skill in the art 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") was one option. (*See, e.g.,* Ex. 1022 at 74-77.) Stated differently, a "I182" mutation includes a "I182E" mutation as one of 19 options.

84. Based on *Perkins*' disclosure of a mutation at amino acid position I182 of SEQ ID NO: 90 and a total number of 19 possible amino acids, a person of ordinary skill in the art would have understood that *Perkins* disclosed "a I182E mutation as compared to SEQ ID NO: 2." (*See, e.g.*, Ex. 1005 at 20:29-21:14, 21:16-27, 22:2-3; Ex. 1006 at 17-18.) *Perkins* disclosed a finite set of possible amino acid

positions for mutating the VSV-G envelope protein, including a mutation at amino acid position number 182. Amino acid position number 182 includes a limited class of 19 amino acids from which a person of ordinary skill in the art would have envisioned each amino acid that falls within it. *Perkins*' disclosures in my opinion would have enabled a person of ordinary skill in the art to arrive at a I182E mutation.

85. Furthermore, a person of ordinary skill in the art 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 recited 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.) 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 person of ordinary skill in the art 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, the mutated sequence 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.).)

86. To the extent even more mutations were made, *Perkins*' VSV-G envelope protein could be mutated at up to 24 different amino acid positions and still

be "at least 95% identical to the amino acid sequence of SEQ ID NO. 2" as in claim 1 of the '366 patent. (*See* Ex. 1001 at 13:31-33.)

87. A person of ordinary skill in the art would have understood these disclosures from *Perkins* to disclose "and a I182E mutation as compared to SEQ ID NO: 2."

2. Claim 2

i) [2.a] "A polypeptide"

88. *Perkins* disclosed this limitation. As discussed in Section VI.A.1.i, *Perkins* disclosed a polypeptide at SEQ ID NO: 90.

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

89. *Perkins* disclosed this limitation. As discussed in Section VI.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) [2.c] "and a I182D mutation as compared to SEQ ID NO: 2."

90. *Perkins* disclosed "and a I182D mutation as compared to SEQ ID NO: 2."

Claim Language	***Perkins***
2) "and a I182D mutation as compared to SEQ ID NO: 2."	*Perkins* disclosed that "[l]entiviral vectors as described herein are pseudotyped with a mutated heterologous viral envelope protein that, in the absence of mutation, mediates both cellular attachment and membrane fusion. In particular embodiments, the mutated 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.) *Perkins* disclosed "[i]n some embodiments, the mutated VSV-G envelope protein includes a mutation at amino acid position H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of

Claim Language	*Perkins*
	GGS between N208 and Y209, and/or a deletion of residues 1-8." (Ex. 1005 at 20:29-21:2; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n certain embodiments, the VSV-G envelope protein includes two or more mutations at amino acid positions selected from H8, N9, QI0, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (*See, e.g.*, Ex. 1005 at 21:2-8; Ex. 1006 at 17-18.) *Perkins* disclosed [i]n other embodiments, the VSV-G envelope protein includes three or more mutations at amino acid positions selected from H8, N9, QI0, K47, K50, A51,

Claim Language	*Perkins*
	S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (*See, e.g.*, Ex. 1005 at 21:8-14; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n still other embodiments, the VSV-G envelope protein includes one or more mutations selected from N9, Q10, K50, A51, S183, S179, N180, I182, Ml 84, I347, T350, T352, and E353, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and

Claim Language	*Perkins*
	a deletion of residues 1-8." (Ex. 1005 at 21:16-22; Ex. 1006 at 17-18.) *Perkins* disclosed "in yet other embodiments, the VSV-G envelope protein includes two or more mutations selected from a mutation at one or more of N9, Q10, K50, A51, S183, S179, N180, I182, M184, I347, T350, T352, and E353, an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (Ex. 1005 at 21:22-27; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n some embodiments, the mutated VSV-G envelope protein comprises a N180 mutation, a I182 mutation, a T352 mutation, and a E353 mutation." (Ex. 1005 at 22:2-3; Ex. 1006 at 17-18).

91. As shown by the above disclosures, a person of ordinary skill in the art would have understood that *Perkins* disclosed a I182D mutation as compared to SEQ ID NO: 2

92. As discussed above for claim 1 of the ’366 patent (Section VI.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.) A person of ordinary skill in the art 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.)

93. Based on *Perkins*’ disclosure of “a mutation at amino acid position . . . I182” and a total number of 19 possible amino acids, a person of ordinary skill in the art would have understood that *Perkins* disclosed “a I182D mutation as compared to SEQ ID NO: 2” for the same reasons discussed above for claim 1 of the ’366 patent. (*See* Section VI.A.1.iii; Ex. 1005 at 20:29-21:14, 21:16-27; Ex. 1006 at 17-18).

94. Furthermore, for the same reasons discussed above in Section VI.A.1.iii, a person of ordinary skill in the art 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; Ex. 1006 at 17-18.)

95. To the extent even more mutations were made, *Perkins*' VSV-G envelope protein could be mutated at up to 24 different amino acid positions and still be "at least 95% identical to the amino acid sequence of SEQ ID NO. 2" as in claim 2 of the '366 patent.

96. A person of ordinary skill in the art would have understood these disclosures from *Perkins* to disclose "and a I182D mutation as compared to SEQ ID NO: 2."

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.[9]"

97. *Perkins* disclosed "[t]he 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."

[9] 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.

Claim Language	***Perkins***
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 that "[l]entiviral vectors as described herein are pseudotyped with a mutated heterologous viral envelope protein that, in the absence of mutation, mediates both cellular attachment and membrane fusion. In particular embodiments, the mutated 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.) *Perkins* disclosed "[i]n some embodiments, the mutated VSV-G envelope protein includes a mutation at amino acid position H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of

Claim Language	*Perkins*
	GGS between N208 and Y209, and/or a deletion of residues 1-8." (Ex. 1005 at 20:29-21:2; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n certain embodiments, the VSV-G envelope protein includes two or more mutations at amino acid positions selected from H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (*See, e.g.*, Ex. 1005 at 21:2-8; Ex. 1006 at 17-18.) *Perkins* disclosed [i]n other embodiments, the VSV-G envelope protein includes three or more mutations at amino acid positions selected from H8, N9, Q10, K47, K50, A51,

Claim Language	*Perkins*
	S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (*See, e.g.*, Ex. 1005 at 21:8-14; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n still other embodiments, the VSV-G envelope protein includes one or more mutations selected from N9, Q10, K50, A51, Sl83, S179, N180, I182, M184, I347, T350, T352, and E353, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and

Claim Language	*Perkins*
	a deletion of residues 1-8." (Ex. 1005 at 21:16-22; Ex. 1006 at 17-18.) *Perkins* disclosed "in yet other embodiments, the VSV-G envelope protein includes two or more mutations selected from a mutation at one or more of N9, Q10, K50, A51, S183, S179, N180, I182, M184, I347, T350, T352, and E353, an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (Ex. 1005 at 21:22-27; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n some embodiments, the mutated VSV-G envelope protein comprises a N180 mutation, a I182 mutation, a T352 mutation, and a E353 mutation." (Ex. 1005 at 22:2-3; Ex. 1006 at 17-18).

98. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he 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."

99. *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.) *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. *Perkins* also 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.)

100. As described above in Section VI.A.1, a person of ordinary skill in the art 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.

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

101. *Perkins* disclosed "[a] nucleic acid molecule encoding the polypeptide of claim 1."

Claim Language	*Perkins*
10. "A nucleic acid molecule encoding the polypeptide of claim 1."	*Perkins* disclosed "[t]he nucleic acid and amino acid sequences set forth in Table 10 provide references sequences for a wild type VSV-G envelope protein and examples of mutated VSV-G envelope proteins according to the present disclosure." (Ex. 1005 at 20:11-13; Ex. 1006 at 17.) *Perkins* disclosed the nucleic acid sequence of WT VSV-G without its signal sequence at SEQ ID NO: 89: **WT VSV-G without signal sequence** **Nucleotide** AAGTTCACTATCGTGTTTCCGCACA ACCAAAAGGGCAACTGGAAAAACG TGCCTTCAAATTACCATTATTGCCC CAGCAGCTCGGACCTGAACTGGCA CAATGACCTCATTGGAACCGCGCTG CAGGTGAAGATGCCAAAGAGCCAC AAGGCTATCCAGGCTGACGGATGG ATGTGCCACGCGTCAAAATGGGTG

Claim Language	*Perkins*
	. . . . GGGTGGGAATTCATCTGTGCATCAA GCTCAAGCACACTAAGAAGCGGCA AATCTACACTGATATCGAGATGAAT CGCCTGGGCAAG (SEQ ID NO: 89) (Ex. 1005 at 74-76 (SEQ ID NO: 89); Ex. 1006 at 9-10, 17, 50 (SEQ ID NO: 71), 51-52 (SEQ ID NO: 77).)

102. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "a nucleic acid molecule encoding the polypeptide of claim 1."

103. *Perkins* disclosed 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).) 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).)

104. *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 person of ordinary skill in the art 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). Thus for the reasons explained as to claim 1 (Section VI.A.1), a person of ordinary skill in the art 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."

105. The '639 application includes the same disclosure as *Perkins*. For example, the '639 application disclosed 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, 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*.

106. Thus for the reasons explained as to claim 1 (Section VI.A.1), a person of ordinary skill in the art would have understood that the I182E mutation also applied 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.”

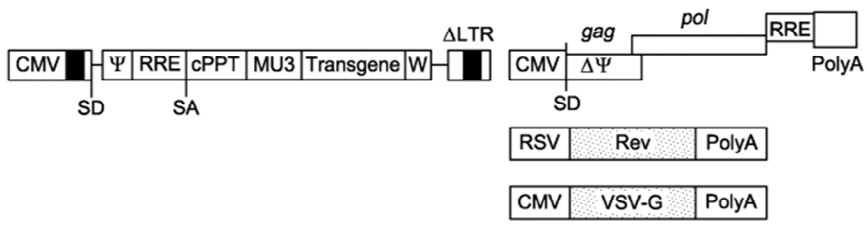
5. Claim 11: “A vector comprising the nucleic acid molecule of claim 10.”

107. *Perkins* disclosed “[a] vector comprising the nucleic acid molecule of claim 10.”

Claim Language	***Perkins***
11. “A vector comprising the nucleic acid molecule of claim 10.”	*Perkins* disclosed “[l]entivirus is a genus of retroviruses that typically gives rise to slowly developing diseases due to their ability to incorporate into a host genome. Modified lentiviral genomes are useful as viral vectors for the delivery of a nucleic acids to a host cell. (Ex. 1005 at 19:10-13; Ex. 1006 at 16.) *Perkins* disclosed “[t]he present disclosure provides self-inactivating lentiviral vectors (“LVV”) that include a viral

Claim Language	*Perkins*
	envelope comprising a mutated, heterologous envelope protein and a tropism defining molecule (also referred to as a "targeting protein"). The LVV described herein 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. In some embodiments, the LVV may carry more than one transgene. In further specific embodiments, the transgene encodes a chimeric antigen receptor (CAR)." (Ex. 1005 at 19:14-21; Ex. 1006 at 16.) *Perkins* disclosed "[m]ethods for producing the LVV disclosed are provided herein. LVV have been developed and based on the retroviral genome by combining its components into recombinant plasmid DNA vectors. The plasmid DNA vectors can then be transfected into producer cell lines to transfer genes required for lentiviral particle production. LVV packaging systems generally comprise a transfer plasmid encoding the

Claim Language	*Perkins*
	transgene of interest, an envelope plasmid (e.g., VSV-G), and packaging plasmid(s). Second generation LVV packaging systems contain a single packaging plasmid encoding Gag, Pol, Rev, and Tat genes and a separate Env plasmid. In some embodiments, the methods described herein utilize a third generation vector system for producing LVV." (Ex. 1005 at 54:9-17; Ex. 1006 at 41.) *Perkins* disclosed "[p]roductive lentiviral particles are harvested from the producer cell culture media. Exemplary materials and methods for producing LVV particles are described in *Production of Lentiviral Vectors,* Merten et al., Molecular Therapy - Methods & Clinical Development (2016), 3, 16017, the contents of which are incorporated herein by reference. Third generation production systems are used for research and development and clinical purposes. Schematic representations of helper plasmids suitable for use in a third

Claim Language	*Perkins*
	generation LVV production system are provided in **FIG. 1.”** (Ex. 1005 at 56:8-14; Ex. 1006 at 41.) FIG. 1 of *Perkins* is shown below:  *FIG. 1* (Ex. 1005 at FIG. 1; Ex. 1006 at FIG. 1) *Perkins* disclosed “[i]n some embodiments of a four plasmid LVV system, the VSV-G env plasmid includes a tandem expression cassette that encodes a mutated VSV-G envelope protein and a targeting protein as disclosed herein.” (Ex. 1005 at 56:25-27; Ex. 1006 at 42.)

108. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed “[a] vector comprising the nucleic acid molecule of claim 10.”

109. *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; Ex. 1006 at 16. The "mutated, heterologous envelope protein" is the mutated VSV-G envelope protein (e.g., the VSV-G with a I182 mutation). However, a person of ordinary skill in the art 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. 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.

110. *Perkins*' description of 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.) *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 person of ordinary skill in the art 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).)

111. *Perkins* further disclosed that "[m]ethods for producing the ***LVV disclosed*** are provided herein." (*See, e.g.*, Ex. 1005 at 54:8-11; 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 person of ordinary skill in the art would understand to be a vector including a nucleic acid sequence that 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 then subsequently harvested as LVV particles. (Ex. 1005 at 54:14-56:14; Ex. 1006 at 41.)

112. *Perkins* at FIG. 1 shows a schematic representation of "helper plasmids" for LVV production which includes a nucleic acid molecule which encodes for "VSV-G." (*See, e.g.*, Ex. 1005 at 56:13-14, FIG. 1; Ex. 1006 at 41, FIG. 1.) *Perkins* further disclosed that in "a four plasmid LVV system, the ***VSV-G env plasmid*** includes a tandem expression cassette that ***encodes a mutated VSV-G envelope protein*** and a target protein ***as disclosed herein***." (*See, e.g.*, Ex. 1005 at

56:25-27; Ex. 1006 at 42.) A person of ordinary skill in the art 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 as explained in Sections VI.A.1. and VI.A.4, described a nucleic acid molecule encoding the polypeptide of claim 1.

113. A person of ordinary skill in the art would have understood that *Perkins* disclosed, as claimed in the '366 patent, "a vector comprising the nucleic acid molecule of claim 10."

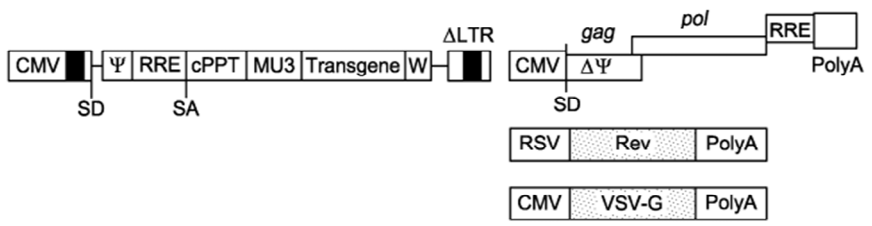
6. Claim 12: "A cell comprising the nucleic acid molecule of claim 10."

114. *Perkins* disclosed "[a] cell comprising the nucleic acid molecule of claim 10."

Claim Language	***Perkins***
12. "A cell comprising the nucleic acid molecule of claim 10."	*Perkins* disclosed "[l]entivirus is a genus of retroviruses that typically gives rise to slowly developing diseases due to their ability to incorporate into a host genome. Modified lentiviral genomes are useful as viral vectors for the delivery of a nucleic acids to a host cell. (Ex. 1005 at 19:10-13; Ex. 1006 at 16.)

Claim Language	***Perkins***
	Perkins disclosed "[t]he present disclosure provides self-inactivating lentiviral vectors ("LVV") that include a viral envelope comprising a mutated, heterologous envelope protein and a tropism defining molecule (also referred to as a "targeting protein"). The LVV described herein 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. In some embodiments, the LVV may carry more than one transgene. In further specific embodiments, the transgene encodes a chimeric antigen receptor (CAR)." (Ex. 1005 at 19:14-21; Ex. 1006 at 16.) *Perkins* disclosed "[m]ethods for producing the LVV disclosed are provided herein. LVV have been developed and based on the retroviral genome by combining its components into recombinant plasmid DNA vectors. The plasmid DNA vectors can then be transfected into producer cell lines to transfer genes

Claim Language	*Perkins*
	required for lentiviral particle production. LVV packaging systems generally comprise a transfer plasmid encoding the transgene of interest, an envelope plasmid (e.g., VSV-G), and packaging plasmid(s). Second generation LVV packaging systems contain a single packaging plasmid encoding Gag, Pol, Rev, and Tat genes and a separate Env plasmid. In some embodiments, the methods described herein utilize a third generation vector system for producing LVV." (Ex. 1005 at 54:9-17; Ex. 1006 at 41.) *Perkins* disclosed "[p]roductive lentiviral particles are harvested from the producer cell culture media. Exemplary materials and methods for producing LVV particles are described in *Production of Lentiviral Vectors,* Merten et al., Molecular Therapy - Methods & Clinical Development (2016), 3, 16017, the contents of which are incorporated herein by reference. Third generation production systems are used for research and development and clinical purposes. Schematic

Claim Language	*Perkins*
	representations of helper plasmids suitable for use in a third generation LVV production system are provided in **FIG. 1.”** (Ex. 1005 at 56:8-14; Ex. 1006 at 41.) FIG. 1 of *Perkins* is shown below:  *FIG. 1* (Ex. 1005 at FIG. 1; Ex. 1006 at FIG. 1) *Perkins* discloses that “[p]roducer cells that may be used for making LVV of the present disclosure include human embryonic kidney (HEK) 293 cells and derivatives thereof. Producer cells may be an adherent cell line, such as HEK293T producer cells, or a suspension cell line, such as HEK293T/l7 SF producer cells.” (Ex. 1005 at 55:14-17; Ex. 1006 at 41, 71.)

115. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[a] cell comprising the nucleic acid molecule of claim 10."

116. *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.) *Perkins* further disclosed that its LVVs "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.) A person of ordinary skill in the art 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.

117. As described in Section VI.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; Ex. 1006 at 41.) The envelope plasmid (a vector) discussed above in Section VI.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.*) *Perkins* goes on to disclose producer cell lines that may be used for producing LVV particles, such as HEK293 cells. (Ex. 1005 at 55:14-17; Ex, 1006 at 41, 71).

118. 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 person of ordinary skill in the art 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.)

119. A person of ordinary skill in the art would have thus understood that *Perkins* disclosed, and as claimed in the '366 patent, "[a] cell comprising the nucleic acid molecule of claim 10."

7. Claim 13: "A viral particle comprising the polypeptide of claim 1."

120. *Perkins* disclosed "[a] viral particle comprising the polypeptide of claim 1."

Claim Language	***Perkins***
13. "A viral particle comprising the polypeptide of claim 1."	*Perkins* disclosed "Example 1: Methods for generating lentiviral vectors with defined tropism." (Ex. 1005 at 110:23; Ex. 1006 at 71.) *Perkins* disclosed "[s]elf-inactivating lentiviral vectors (LVV) ***as described herein*** are produced using a third generation production system. An expression plasmid that contains the gene sequences desired for delivery by the LVV is combined at defined ratios with three packaging plasmids, ***VSV-G***, GagPol, and Rev, and used to transfect HEK293 producer cells. ***Productive viral particles*** are harvested from the HEK293 culture media 2-3 days later." (Ex. 1005 at 110:24-29; Ex. 1006 at 71) (emphasis added).

Claim Language	***Perkins***
	Perkins disclosed "[t]he tropism of the resulting LVV was tested to determine whether it can be redirected using a non-viral targeting protein as described herein expressed from one of three packaging plasmids or by addition of a fifth plasmid to the transfection mix. The ***LVV vector includes a mutated VSV-G envelope protein***, where the ***mutated VSVG includes mutations that abolish binding of the mutated VSV-G to its native receptor*** such that viral entry occurs via the non-viral, tropism defining targeting protein." (Ex. 1005 at 110:30-111:4; Ex. 1006 at 71) (emphasis added). *Perkins* disclosed "[m]ethods for producing the LVV disclosed are provided herein. LVV have been developed and based on the retroviral genome by combining its components into recombinant plasmid DNA vectors. The plasmid DNA vectors can then be transfected into producer cell lines to transfer genes required for lentiviral particle production. LVV packaging

Claim Language	*Perkins*
	systems generally comprise a transfer plasmid encoding the transgene of interest, an envelope plasmid (e.g., VSV-G), and packaging plasmid(s). Second generation LVV packaging systems contain a single packaging plasmid encoding Gag, Pol, Rev, and Tat genes and a separate Env plasmid. In some embodiments, the methods described herein utilize a third generation vector system for producing LVV." (Ex. 1005 at 54:9-17; Ex. 1006 at 41.) *Perkins* disclosed "[i]n some embodiments of a four plasmid LVV system, the VSV-G env plasmid includes a tandem expression cassette that encodes a mutated VSV-G envelope protein and a targeting protein as disclosed herein." (Ex. 1005 at 56:25-27; Ex. 1006 at 42.)

121. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[a] viral particle comprising the polypeptide of claim 1."

122. *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; Ex. 1006 at 71) (emphasis added). A person of ordinary skill in the art 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. *Perkins* also disclosed, as discussed above, that "[t]he 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* Ex. 1005 at 111:2-4; Ex. 1006 at 71.) A person of ordinary skill in the art would have thus made a viral particle, as in Example 1, using the polypeptide of claim 1, as discussed above.

123. Additionally, as discussed above in Section VI.A.5, *Perkins* disclosed "[m]ethods for producing the ***LVV disclosed*** are provided herein," which included plasmid components, including an envelope plasmid, which is transfected into a producer cell and harvested as LVV particles. (Ex. 1005 at 54:8-56:14; Ex. 1006 at 41.) As described in Section VI.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 VI.A.1).

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

125. A person of ordinary skill in the art would thus have understood *Perkins*' disclosure of "viral particles," as claimed in the '366 patent, to comprise "the polypeptide of claim 1."

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

126. *Perkins* disclosed "[t]he viral particle of claim 13, wherein the viral particle is a lentivirus comprising the polypeptide."

Claim Language	***Perkins***
14. "The viral particle of claim 13, wherein the viral particle is a lentivirus	*Perkins* disclosed "Example 1: Methods for generating lentiviral vectors with defined tropism." (Ex. 1005 at 110:23; Ex. 1006 at 71.) *Perkins* disclosed "[s]elf-inactivating ***lentiviral vectors (LVV) as described herein*** are produced using a third

Claim Language	***Perkins***
comprising the polypeptide."	generation production system. An expression plasmid that contains the gene sequences desired for delivery by the LVV is combined at defined ratios with three packaging plasmids, VSV-G, GagPol, and Rev, and used to transfect HEK293 producer cells. Productive viral particles are harvested from the HEK293 culture media 2-3 days later." (Ex. 1005 at 110:24-29; Ex. 1006 at 71) (emphasis added). *Perkins* disclosed "[t]he tropism of the resulting LVV was tested to determine whether it can be redirected using a non-viral targeting protein as described herein expressed from one of three packaging plasmids or by addition of a fifth plasmid to the transfection mix. The LVV vector includes a mutated VSV-G envelope protein, where the mutated VSVG includes mutations that abolish binding of the mutated VSV-G to its native receptor such that viral entry occurs via the non-viral, tropism defining targeting protein." (Ex. 1005 at 110:30-111:4; Ex. 1006 at 71).

127. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he viral particle of claim 13, wherein the viral particle is a lentivirus comprising the polypeptide."

128. As discussed in Section VI.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.) *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.)

129. As discussed in Section VI.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 person of ordinary skill in the art to include the production of mutant VSV-G in the form of the polypeptide of claim 1. *Perkins* defines "lentiviral vector" as "a vector derived from a ***lentivirus*** and includes one or more lentiviral packaging proteins and/or one or more lentiviral proteins," and thus *Perkins*' disclosures of methods of producing LVV particles would result in a lentivirus. (*See* Ex. 1001 at 14:21-25.)

130. A person of ordinary skill in the art 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."

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."

131. *Perkins* disclosed "[t]he viral particle of claim 13, wherein the viral particle further comprises a heterologous nucleic acid molecule encoding a heterologous molecule of interest."

Claim Language	***Perkins***
15. "The viral particle of claim 13, wherein the viral particle further comprises a heterologous nucleic acid molecule encoding a	*Perkins* disclosed "Example 1: Methods for generating lentiviral vectors with defined tropism." (Ex. 1005 at 110:23; Ex. 1006 at 71.) *Perkins* disclosed "[s]elf-inactivating ***lentiviral vectors (LVV) as described herein*** are produced using a third generation production system. An expression plasmid that contains the gene sequences desired for delivery by the LVV is combined at defined ratios with three packaging plasmids,

Claim Language	***Perkins***
heterologous molecule of interest."	VSV-G, GagPol, and Rev, and used to transfect HEK293 producer cells. Productive viral particles are harvested from the HEK293 culture media 2-3 days later." (Ex. 1005 at 110:24 29; Ex. 1006 at 71) (emphasis added). *Perkins* disclosed "[t]he tropism of the resulting LVV was tested to determine whether it can be redirected using a non-viral targeting protein as described herein expressed from one of three packaging plasmids or by addition of a fifth plasmid to the transfection mix. The LVV vector includes a mutated VSV-G envelope protein, where the mutated VSVG includes mutations that abolish binding of the mutated VSV-G to its native receptor such that viral entry occurs via the non-viral, tropism defining targeting protein." (Ex. 1005 at 110:30-111:4; Ex. 1006 at 71). *Perkins* disclosed "[t]he lentiviral vectors described herein include a transgene encoding one or more proteins that is

Claim Language	*Perkins*
	delivered to and expressed by a lymphocyte (e.g., T cell, B cell, or NK cell) targeted by the vector. In particular embodiments, the transgene encodes a chimeric antigen receptor (CAR)." (Ex. 1005 at 41:5-8; Ex. 1006 at 29.) *Perkins* disclosed "[m]ethods for producing the LVV disclosed are provided herein. LVV have been developed and based on the retroviral genome by combining its components into recombinant plasmid DNA vectors. The plasmid DNA vectors can then be transfected into producer cell lines to transfer genes required for lentiviral particle production. LVV packaging systems generally comprise a transfer plasmid encoding the transgene of interest, an envelope plasmid (e.g., VSV-G), and packaging plasmid(s). Second generation LVV packaging systems contain a single packaging plasmid encoding Gag, Pol, Rev, and Tat genes and a separate Env plasmid. In some embodiments, the methods described herein utilize a third

Claim Language	***Perkins***
	generation vector system for producing LVV." (Ex. 1005 at 54:9-17; Ex. 1006 at 41.)

132. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he viral particle of claim 13, wherein the viral particle further comprises a heterologous nucleic acid molecule encoding a heterologous molecule of interest."

133. As discussed in Section VI.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.) Additionally, as described above in Sections VI.A.5 and VI.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.) 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.)

134. *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.) *Perkins* also disclosed that that the transfer plasmid "may ***encode*** a single ***heterologous protein*** (e.g., a single ***CAR*** as described herein.)" (Ex. 1005 at 56:21-22; Ex. 1006 at 42.)

135. A person of ordinary skill in the art 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.) 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 person of ordinary skill in the art 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.

136. A person of ordinary skill in the art would have understood that *Perkins*' disclosure of viral particles containing LVVs, including a transgene encoding a chimeric antigen receptor, disclosed, as claimed in the '366 patent, "[t]he viral particle of claim 14, wherein the viral particle further comprises a heterologous nucleic acid molecule encoding a heterologous molecule of interest."

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."

137. *Perkins* disclosed "[t]he 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."

Claim Language	***Perkins***
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	*Perkins* disclosed "Example 1: Methods for generating lentiviral vectors with defined tropism." (Ex. 1005 at 110:23; Ex. 1006 at 71.) *Perkins* disclosed "[s]elf-inactivating ***lentiviral vectors (LVV) as described herein*** are produced using a third generation production system. An expression plasmid that contains the gene sequences desired for delivery by the LVV is combined at defined ratios with three packaging plasmids, VSV-G, GagPol, and Rev, and used to transfect HEK293 producer cells. Productive viral particles are harvested from the HEK293 culture media 2-3 days later." (Ex. 1005 at 110:24 29; Ex. 1006 at 71) (emphasis added).

Claim Language	***Perkins***
combination thereof."	*Perkins* disclosed "[t]he tropism of the resulting LVV was tested to determine whether it can be redirected using a non-viral targeting protein as described herein expressed from one of three packaging plasmids or by addition of a fifth plasmid to the transfection mix. The LVV vector includes a mutated VSV-G envelope protein, where the mutated VSVG includes mutations that abolish binding of the mutated VSV-G to its native receptor such that viral entry occurs via the non-viral, tropism defining targeting protein." (Ex. 1005 at 110:30-111:4; Ex. 1006 at 71). *Perkins* disclosed "[t]he lentiviral vectors described herein include a transgene encoding one or more proteins that is delivered to and expressed by a lymphocyte (e.g., T cell, B cell, or NK cell) targeted by the vector. In particular embodiments, the transgene encodes a chimeric antigen receptor (CAR)." (Ex. 1005 at 41:5-8; Ex. 1006 at 29.)

138. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he 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."

139. *Perkins* disclosed this limitation for the reasons described above in Section VI.A.8, including that *Perkins* disclosed viral particles containing LVVs with a transgene encoding a "chimeric antigen receptor." A person of ordinary skill in the art would have understood a chimeric antigen receptor to be, a 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.)

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

140. *Perkins* disclosed "[t]he viral particle of claim 15, wherein the heterologous molecule of interest is a chimeric antigen receptor ('CAR')."

Claim Language	***Perkins***
17. "The viral particle of claim 15, wherein the	*Perkins* disclosed "Example 1: Methods for generating lentiviral vectors with defined tropism." (Ex. 1005 at 110:23; Ex. 1006 at 71.)

Claim Language	***Perkins***
heterologous molecule of interest is a chimeric antigen receptor ('CAR')."	*Perkins* disclosed "[s]elf-inactivating ***lentiviral vectors (LVV) as described herein*** are produced using a third generation production system. An expression plasmid that contains the gene sequences desired for delivery by the LVV is combined at defined ratios with three packaging plasmids, VSV-G, GagPol, and Rev, and used to transfect HEK293 producer cells. Productive viral particles are harvested from the HEK293 culture media 2-3 days later." (Ex. 1005 at 110:24 29; Ex. 1006 at 71) (emphasis added). *Perkins* disclosed "[t]he tropism of the resulting LVV was tested to determine whether it can be redirected using a non-viral targeting protein as described herein expressed from one of three packaging plasmids or by addition of a fifth plasmid to the transfection mix. The LVV vector includes a mutated VSV-G envelope protein, where the mutated VSVG includes mutations that abolish binding of the mutated VSV-

Claim Language	*Perkins*
	G to its native receptor such that viral entry occurs via the non-viral, tropism defining targeting protein." (Ex. 1005 at 110:30-111:4; Ex. 1006 at 71). *Perkins* disclosed "[t]he lentiviral vectors described herein include a transgene encoding one or more proteins that is delivered to and expressed by a lymphocyte (e.g., T cell, B cell, or NK cell) targeted by the vector. In particular embodiments, the transgene encodes a chimeric antigen receptor (CAR)." (Ex. 1005 at 41:5-8; Ex. 1006 at 29.)

141. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he viral particle of claim 15, wherein the heterologous molecule of interest is a chimeric antigen receptor ('CAR')."

142. *Perkins* disclosed this limitation for the reasons described above in Section VI.A.9, including that *Perkins* disclosed viral particles containing LVVs, including a transgene encoding a "chimeric antigen receptor." Accordingly, a person of ordinary skill in the art 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’).”

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.”

143. *Perkins* disclosed “[t]he 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.”

144. A person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed “[t]he 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.” As described above in Section VI.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; Ex. 1006 at 17-18.) A person of ordinary skill in the art 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.).)

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."

145. *Perkins* disclosed "[t]he 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."

146. A person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he 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." As described above in Section VI.A.12, a person of ordinary skill in the art 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.).)

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."

147. *Perkins* disclosed "[t]he 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."

148. A person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he 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." As described above in Section VI.A.12, a person of ordinary skill in the art 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.).)

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."

149. *Perkins* disclosed "[t]he 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."

150. A person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he 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." As described above in Section VI.A.12, a person of ordinary skill in the art 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.).)

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."

151. *Perkins* disclosed "[t]he 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."

152. A person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he 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." As described above Section VI.A.2.iii, *Perkins* disclosed a mutant VSV-G envelope proteins 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.) A person of ordinary skill in the art 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.).)

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."

153. *Perkins* disclosed "[t]he 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."

154. A person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he 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." As described above in Section VI.A.16, a person of ordinary skill in the art 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.).)

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."

155. *Perkins* disclosed "[t]he 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."

156. A person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he 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." As described above in Section VI.A.16, a person of ordinary skill in the art 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.).)

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."

157. *Perkins* disclosed "[t]he 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."

158. A person of ordinary skill in the art at the relevant time would have understood that *Perkins* disclosed "[t]he 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." As described above in Section VI.A.16, a person of ordinary skill in the art 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.).)

B. ***Perkins* and *Hwang* Taught or Suggested All of the Elements of Claims 3-9 and 26-30 of the '366 Patent**

159. In my opinion, a person of ordinary skill in the art would have understood that *Perkins* and *Hwang* taught or suggested all of the elements recited in claims 3-9 and 26-30 of the '366 patent, as set forth in the claim charts below:

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."

160. *Perkins* and *Hwang* disclosed or suggested "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."

Claim Language	*Perkins* and *Hwang*
3. "The polypeptide of claim 1, wherein the polypeptide	*Perkins* disclosed that "[l]entiviral vectors as described herein are pseudotyped with a mutated heterologous viral envelope protein that, in the absence of mutation, mediates both cellular attachment and membrane fusion. In

Claim Language	***Perkins* and *Hwang***
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."	particular embodiments, the mutated 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.) *Perkins* disclosed "[i]n some embodiments, the mutated VSV-G envelope protein includes a mutation at amino acid position H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and/or a deletion of residues 1-8." (Ex. 1005 at 20:29-21:2; Ex. 1006 at 17-18.)

Claim Language	*Perkins* and *Hwang*
	Perkins disclosed "[i]n certain embodiments, the VSV-G envelope protein includes two or more mutations at amino acid positions selected from H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (*See, e.g.*, Ex. 1005 at 21:2-8; Ex. 1006 at 17-18.) *Perkins* disclosed [i]n other embodiments, the VSV-G envelope protein includes three or more mutations at amino acid positions selected from H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS

Claim Language	*Perkins* and *Hwang*
	between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (*See, e.g.*, Ex. 1005 at 21:8-14; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n still other embodiments, the VSV-G envelope protein includes one or more mutations selected from N9, Q10, K50, A51, Sl83, S179, N180, I182, M184, I347, T350, T352, and E353, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (Ex. 1005 at 21:16-22; Ex. 1006 at 17-18.)

Claim Language	*Perkins* and *Hwang*
	Perkins disclosed "in yet other embodiments, the VSV-G envelope protein includes two or more mutations selected from a mutation at one or more of N9, Q10, K50, A51, S183, S179, N180, I182, M184, I347, T350, T352, and E353, an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (Ex. 1005 at 21:22-27; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n other embodiments, the mutated VSV-G envelope protein is as described in Nikolic et al., "Structural basis for the recognition of LDL-receptor family members by VSV glycoprotein." *Nature Comm.,* 2018, 9: 1029, the relevant disclosures of which are incorporated by reference herein. (*See, e.g.*, Ex. 1005 at 22:16-19 (citing Ex. 1018); Ex. 1006 at 18 (citing Ex. 1018).)

Claim Language	*Perkins* and *Hwang*
	Perkins disclosed "[t]he various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, including but not limited to U.S. Provisional Patent Application No. 63/154,639, filed on February 26, 2021, are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and publications to provide yet further embodiments. (Ex. 1005 at 116, 10-17.) *Hwang* disclosed "vesicular stomatitis virus G glycoprotein (VSV-G) is the most widely used envelope protein for retroviral and lentiviral vector pseudotyping; however,

Claim Language	*Perkins* and *Hwang*
	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 neutralization." (Ex. 1007 at 807.) *Hwang* disclosed "analysis of a number of combined mutants revealed that VSV-G harboring T230N + T368A or K66T + S162T + T230N + T368A mutations exhibited both higher *in vitro* resistance to human serum and higher thermostability, as well as enhanced resistance to rabbit and mouse serum. Finally, lentiviral vectors pseudotyped with these variants were more resistant to human serum in a murine model. These serum-resistant and thermostable VSV-G variants may aid the application of retroviral and lentiviral vectors to gene therapy." (Ex. 1007 at 807.)

Claim Language	***Perkins* and *Hwang***
	Hwang disclosed "[i]mportantly, mutants T230N + T368A or K66T + S162T + T230N + T368A had higher combined thermostability and serum resistance than wild-type VSV-G." (Ex. 1007 at 809.) *Hwang* disclosed "[i]n this study, we evolved VSV-G and successfully created variants with higher resistance to human, rabbit and mouse sera in vitro and human serum in vivo. This work therefore further establishes the power of directed evolution to improve viral vectors, and these results may enhance the utility of retroviral and lentiviral vectors to treat human disease. In addition, 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." (Ex. 1007 at 812-13.)

161. As shown by the above disclosures, a person of ordinary skill in the art at the relevant time would have understood that *Perkins* and *Hwang* disclosed or suggested "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."

162. As described above in Section VI.A.3, *Perkins* disclosed mutations at amino acid positions I182 and T352, 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. As yet another exemplary teaching, *Perkins* and *Hwang* disclosed or suggested this limitation. *Hwang* disclosed a combined "T230N + T368A"[10] mutant VSV-G protein which demonstrated "higher combined thermostability and serum resistance than wild-type VSV-G." (*See, e.g.*, Ex. 1007 at 809.)

163. A person of ordinary skill in the art 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

[10] As indicated at footnote 6, above, *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.

always substantial." (*See, e.g.*, Ex. 1020 at 218, 221.) A person of ordinary skill in the art 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.)

164. 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*, a person of ordinary skill in the art 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- 16, 96:18-98:17, 115:18-116:9; Ex. 1006 at 54, 56-58, 73-74.) 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.) A person of ordinary skill in the art would have accordingly looked to *Hwang* to enhance *Perkins'* disclosed lentiviral vectors containing a mutant VSV-G protein for *in vivo* applications, including the treatment of human cancer. This combination would have been understood to provide *Perkins*' VSV-G protein not only the de-targeting effect of a I182E mutation, but also protection against serum inactivation when used *in vivo*.

165. A person of ordinary skill in the art would 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. *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.) Additionally, while not required by claim 3, a person of ordinary skill in the art would not believe that *Hwang*'s T214N and T352A mutations would lead to a loss of fusogenic function of VSV-G protein. *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.) A person of ordinary skill in the art would also 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).)

166. 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.) A person of ordinary skill in the art 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].)

167. A person of ordinary skill in the art 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, including *Perkins* and *Hwang*, to make these mutations[11]

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."

168. *Perkins* and *Hwang* disclosed or suggested this limitation, as discussed in Section VI.B.1.

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."

169. *Perkins* and *Hwang* disclosed or suggested this limitation, as discussed in Section VI.B.1.

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[11] I note that 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.)

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."

170. *Perkins* and *Hwang* disclosed or suggested this limitation, as discussed in Section VI.B.1. While the polypeptide of claim 2 incorporates a I182D mutation instead of I1821E mutation, aspartic acid and glutamic acid are of similar charge and functionality, and would not have changed the reasons as to why a person of ordinary skill in the art would have understood that *Perkins* and *Hwang* disclosed or suggested the limitations of claim 6. (Ex. 1022 at 76-77.)

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."

171. *Perkins* and *Hwang* disclosed or suggested this limitation, as discussed in Section VI.B.1 and VI.B.4.

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."

172. *Perkins* and *Hwang* disclosed or suggested this limitation, as discussed in Section VI.B.1 and VI.B.4.

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

173. *Perkins* and *Hwang* disclosed or suggested this limitation. 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). 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 AYENGGKACK MQYCKHWGVR LPSGVWFEMA  240
DKDLFAAARF PECPEGSSIS APSQTSVDVS LIQDVERILD YSLCQETWSK IRAGLPISPV  300
DLSYLAPKNP GTGPAFTIIN GTLKYFETRY IRVDIAAPIL SRMVGMISGT TAERELWDDW  360
APYEDVEIGP NGVLRTSSGY KFPLYMIGHG MLDSDLHLSS KAQVFEHPHI QDAASQLPDD  420
ESLFFGDTGL SKNPIELVEG WFSSWKSSIA SFFFIIGLII GLFLVLRVGI HLCIKLKHTK  480
KRQIYTDIEM NRLGK                                                   495
```

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

174. As discussed in Sections VI.A.3 and VI.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. *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.) *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.)

175. A person of ordinary skill in the art 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 VI.B.1. These mutations would result in "a polypeptide comprising the amino acid sequence of SEQ ID NO: 23" as claimed in the '366 patent.

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

176. *Perkins* and *Hwang* disclosed or suggested this limitation. 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 NO: 23).) 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 VHNSTTWHSD YKVKGLCDSN  180
LDSMDITFFS EDGELSSLGK EGTGFRSNYF AYENGGKACK MQYCKHWGVR LPSGVWFEMA  240
DKDLFAAARF PECPEGSSIS APSQTSVDVS LIQDVERILD YSLCQETWSK IRAGLPISPV  300
DLSYLAPKNP GTGPAFTIIN GTLKYFETRY IRVDIAAPIL SRMVGMISGT TAERELWDDW  360
APYEDVEIGP NGVLRTSSGY KFPLYMIGHG MLDSDLHLSS KAQVFEHPHI QDAASQLPDD  420
ESLFFGDTGL SKNPIELVEG WFSSWKSSIA SFFFIIGLII GLFLVLRVGI HLCIKLKHTK  480
KRQIYTDIEM NRLGK                                                   495
```

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

177. As explained in Section VI.B.7, a person of ordinary skill in the art 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 Section VI.C.4. These mutations would result in "a polypeptide comprising the amino acid sequence of SEQ ID NO: 22" as claimed in the '366 patent.

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

178. *Perkins* and *Hwang* disclosed or suggested this limitation. As discussed in Section VI.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 T352. As explained in Sections VI.A.5, VI.A.7, and VI.B.7, *Perkins* and *Hwang* disclosed or suggested to a person of ordinary skill in the art to make the polypeptide of claim 9.

179. As discussed above in Section VI.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; Ex. 1006 at 41.) As described in Section VI.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 VI.B.7).

180. As discussed above in Section VI.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 target protein ***as disclosed herein***." (*See, e.g.*, Ex. 1005 at 56:25-27; Ex. 1006 at 42.) This plasmid would be transfected into cells to produce viral particles, using *Perkins*' above described methods of producing LVVs.

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

181. *Perkins* and *Hwang* disclosed or suggested this limitation. As described above in Sections VI.A.9 and VI.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. *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; Ex. 1006 at 29. *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; Ex. 1006 at 42.)

182. Based on these disclosures, *Perkins* and *Hwang* disclosed or suggested to a person of ordinary skill in the art to incorporate a transgene (*i.e.*, nucleic acid molecule) encoding the CAR into the viral particle of claim 27 for the same seasons discussed above.

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

183. *Perkins* and *Hwang* disclosed or suggested this limitation, as discussed in Section VI.B.9. While the polypeptide of claim 26 incorporates a I182D mutation instead of I1821E mutation, it would not have changed the reasons as to why *Perkins* and *Hwang* disclosed or suggested to a person of ordinary skill in the art the limitation of claim 29. (Ex. 1022 at 76-77.) As explained above in Section VI.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; Ex. 1006 at 41.) A person of ordinary skill in the art would have understood *Perkins*' disclosures for producing viral particles would be equally applicable to the polypeptide of claim 26.

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

184. *Perkins* and *Hwang* disclosed or suggested this limitation, as discussed in Section VI.B.10. As discussed above in Sections VI.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.) A person of ordinary skill in the art would have understood *Perkins*' disclosures on the use of transgenes encoding CAR to be equally applicable to the viral particle of claim 29.

C. *Perkins* and the *RCSB PDB* Taught or Suggested All of the Elements of Claims 1-3 and 10-25 of the '366 Patent

185. In my opinion, a person of ordinary skill in the art would have understood that *Perkins* and the *RCSB PDB* taught or suggested all of the elements recited in claims 1-3 and 10-25 of the '366 patent, as set forth in the claim charts below:

1. Claim 1

i) [1.a] "A polypeptide"

186. *Perkins* disclosed "[a] polypeptide" for the reasons discussed above in Section VI.A.1.i.

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

187. *Perkins* disclosed "comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2" for the reasons discussed above in Section VI.A.1.ii.

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

188. *Perkins* and the *RCSB PBD* disclosed or suggested "and a I182E mutation as compared to SEQ ID NO: 2."

Claim Language	*Perkins* and the *RCSB PDB*
1) "and a I182E mutation as compared to SEQ ID NO: 2."	*Perkins* disclosed that "[l]entiviral vectors as described herein are pseudotyped with a mutated heterologous viral envelope protein that, in the absence of mutation, mediates both cellular attachment and membrane fusion. In particular embodiments, the mutated envelope protein includes at least one mutation that inhibits the envelope

Claim Language	*Perkins* and the *RCSB PDB*
	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.) *Perkins* disclosed "[i]n some embodiments, the mutated VSV-G envelope protein includes a mutation at amino acid position H8, N9, QI0, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and/or a deletion of residues 1-8." (Ex. 1005 at 20:29-21:2; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n certain embodiments, the VSV-G envelope protein includes two or more mutations at amino acid positions selected from H8, N9, QI0, K47, K50, A51,

Claim Language	*Perkins* and the *RCSB PDB*
	S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (*See, e.g.*, Ex. 1005 at 21:2-8; Ex. 1006 at 17-18.) *Perkins* disclosed [i]n other embodiments, the VSV-G envelope protein includes three or more mutations at amino acid positions selected from H8, N9, QI0, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, R354, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion

Claim Language	***Perkins* and the *RCSB PDB***
	of residues 1-8." (*See, e.g.*, Ex. 1005 at 21:8-14; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n still other embodiments, the VSV-G envelope protein includes one or more mutations selected from N9, Q10, K50, A51, S183, S179, N180, I182, M184, I347, T350, T352, and E353, an insertion of TT between N9 and QI0, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and QI0, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (Ex. 1005 at 21:16-22; Ex. 1006 at 17-18.) *Perkins* disclosed "in yet other embodiments, the VSV-G envelope protein includes two or more mutations selected from a mutation at one or more of N9, Q10, K50, A51, S183, S179, N180, I182, M184, I347, T350, T352, and

Claim Language	*Perkins* and the *RCSB PDB*
	E353, an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, an insertion of GGS between N208 and Y209, and a deletion of residues 1-8." (Ex. 1005 at 21:22-27; Ex. 1006 at 17-18.) *Perkins* disclosed "[i]n some embodiments, the mutated VSV-G envelope protein comprises a N180 mutation, a I182 mutation, a T352 mutation, and a E353 mutation." (Ex. 1005 at 22:2-3; Ex. 1006 at 17-18). *Perkins* disclosed "[i]n other embodiments, the mutated VSV-G envelope protein is as described in Nikolic et al., "Structural basis for the recognition of LDL-receptor family members by VSV glycoprotein." *Nature Comm.,* 2018, 9: 1029, the relevant disclosures of which are incorporated by

Claim Language	*Perkins* and the *RCSB PDB*
	reference herein. (*See, e.g.*, Ex. 1005 at 22:16-19 (citing Ex. 1018); Ex. 1006 at 18 (citing Ex. 1018).) *Perkins* disclosed "[t]he various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, including but not limited to U.S. Provisional Patent Application No. 63/154,639, filed on February 26, 2021, are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and publications to provide yet further embodiments. (Ex. 1005 at 116, 10-17.)

Claim Language	***Perkins* and the *RCSB PDB***
	RCSB PDB disclosed the 3D crystal structures first published in Nikolic *et al.* (Ex. 1018) of VSV-G bound the CR3 and CR2 domains of the LDL receptor. ((Ex. 1025 ("5OY0") and Ex. 1026 ("5OYL"), respectively.)) These structures disclose the position of I182 and its nearby amino acid residues, including the distances between them.

189. As shown by the above disclosures, a person of ordinary skill in the art would have understood that *Perkins* and the *RCSB PDB* disclosed or suggested "a I182E mutation as compared to SEQ ID NO: 2."

190. A person of ordinary skill in the art 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. A person of ordinary skill in the art 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.)

191. With respect to the mutated VSV-G envelope protein, as described in Section VI.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.) *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.) *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.)

192. Based on any of these disclosures in *Perkins* of a mutation at I182 among a finite set, *Perkins* disclosed or suggested to a person of ordinary skill in the art to make a I182 mutation to *Perkins*' VSV-G envelope protein. As explained above in Section VI.A.1.iii, a person of ordinary skill in the art would have understood *Perkins*' disclosure of a mutation at amino acid position I182 to mean 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.)

193. A person of ordinary skill in the art 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 envelope protein to bind its native target. (*See, e.g.*, Ex. 1005 at 19:26-29; Ex. 1006 at 16.) 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.)

194. *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 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.)

195. A person of ordinary skill in the art 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.) Amino acids I, L, and V are similar in structure and function, and thus represent the most conservative substitutions. A person of ordinary skill in the art would not have considered a mutation of I182L or I182V to be an option where *Perkins*' intention is to alter VSV-G binding characteristics. 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.)

196. In my opinion, the potential amino acids that a person of ordinary skill in the art 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.) It would have also excluded cysteine (C), which could potentially have introduced 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 which includes 12

cysteine residues engaged in 6 disulfide bonds).) A person of ordinary skill in the art therefore would have considered I182P or I182C mutations to be less viable options in the context of *Perkins*' disclosure.

197. 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, *Perkins* would have at least disclosed or suggested to a person of ordinary skill in the art to make "a I182E mutation as compared to SEQ ID NO: 2" as in claim 1 of the '366 patent.

198. However, even if *Perkins* did not disclose or suggest a I182E mutation to a person of ordinary skill in the art based on *Perkins*' express disclosure, this would have been disclosed or suggested to a person of ordinary skill in the art 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, LDL-R, which was available to a person of ordinary skill in the art in the *RCSB PDB*. (*See, e.g.*, Ex. 1005 at 19:26-29; Ex. 1006 at 16; Ex. 1025 at 1; 1026 at 1.)

199. A person of ordinary skill in the art would have looked to the structure of VSV-G in their ordinary course of research at the relevant time. I further note that *Perkins* states that it incorporates by reference the disclosures of Nikolic *et al.*

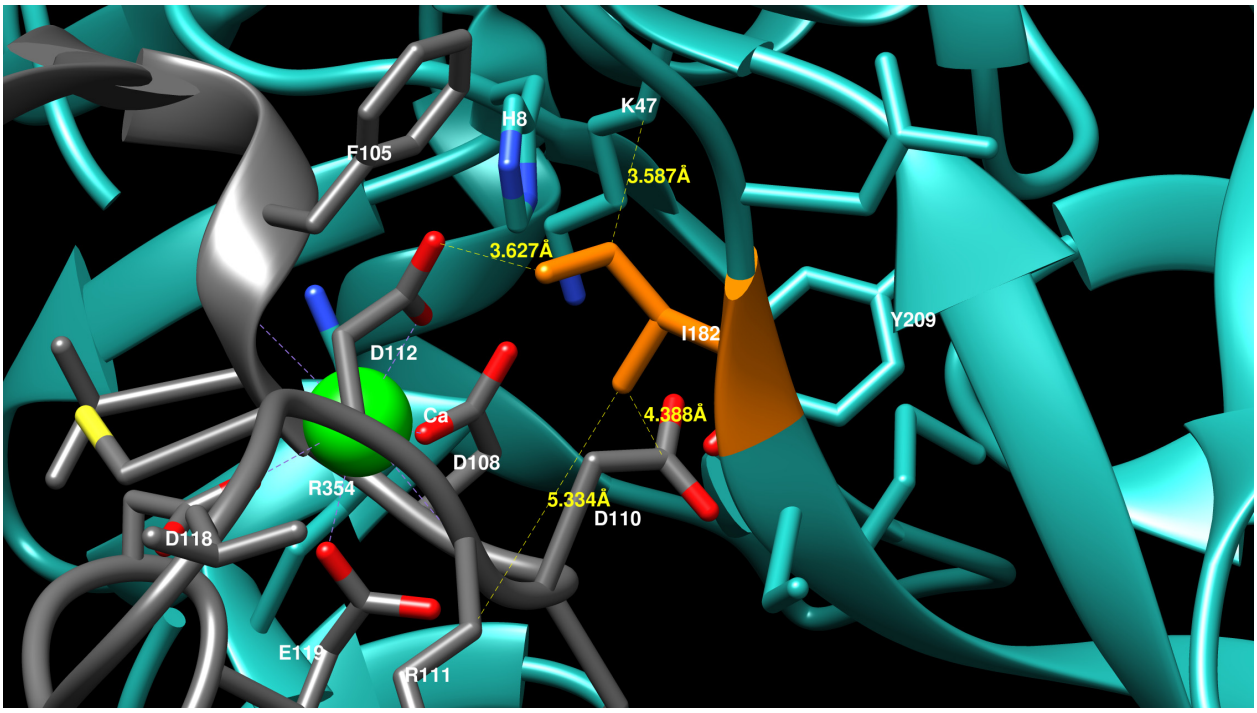
(Ex. 1018), which is a state of the art publication underpinning the published crystal structures of VSV-G bound to its native LDL-R.[12] (*See, e.g.*, Ex. 1005 at 22:16-19, 116:10-17; Ex. 1006 at 18; Ex. 1018 at 4, 11; Ex. 1025 at 1; Ex. 1026 at 1.)

200. 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 the LDL-R, respectively. (Ex. 1025; Ex. 1026.) A person of ordinary skill in the art at the relevant time would have routinely navigated these crystal structures using well-known visualization software, for example UCSF Chimera, 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.)

201. For example, below is a snapshot of I182 and its nearby amino acid residues, including distance apart as measured in angstroms (Å), using UCSF Chimera visualization software that was well known to a person of ordinary skill in the art at the relevant time, and the published "5OY9" crystal structure of VSV-G (blue green) bound to the CR3 domain of the LDL receptor (grey):

[12] 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). All other relevant materials are available from the authors." (Ex. 1018 at 11.)

I182 and Nearby Residues in VSV-G Bound to CR3

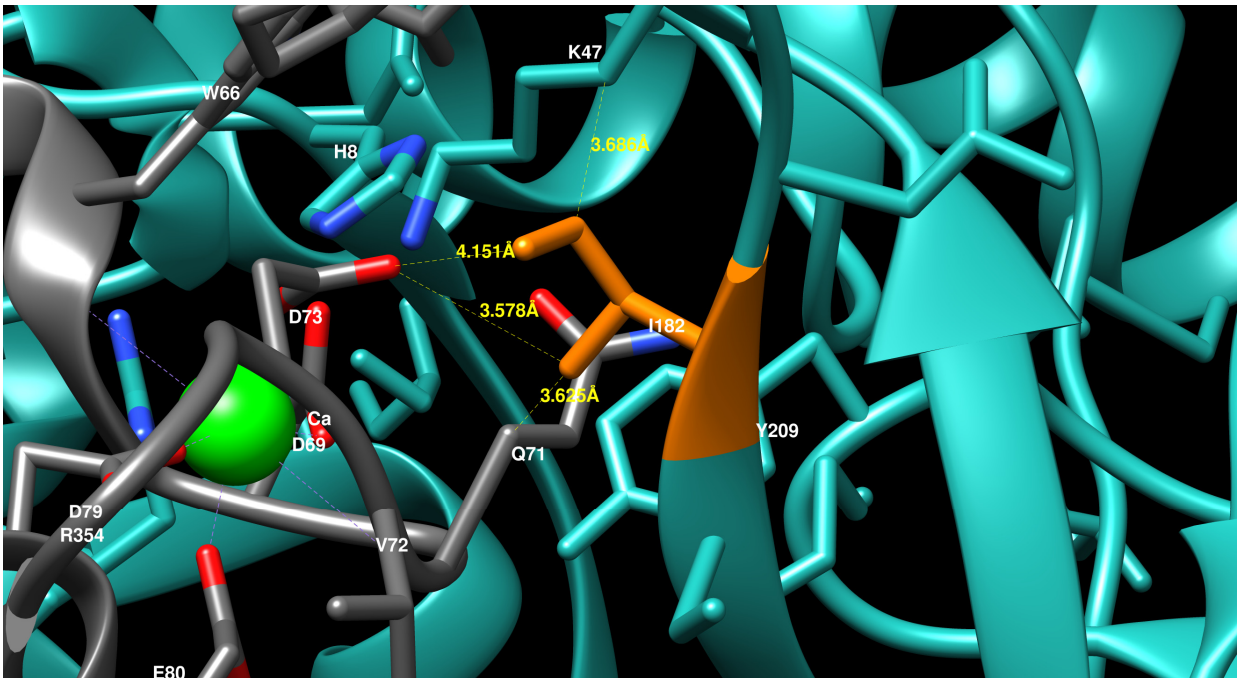


(*See* Ex. 1025 at 1; *see also* Appendix B (Image 1).)

202. A person of ordinary skill in the art would have immediately recognized from the crystal structure that I182 is nearby D110 and D112, both of which are aspartic acid. A person of ordinary skill in the art would have expected an interaction between the carboxyl portions of these aspartic acid residues and I182 at this distance. A person of ordinary skill in the art would have also understood that D110 and D112 are believed to be involved in the binding of VSV-G to the CR3 domain, as they appear in structural images in Nikolic *et al*. (Ex. 1018 at 5, FIG. 4c.)

203. A person of ordinary skill in the art would have similarly navigated the published "5OYL" crystal structure and identified I182 and its nearby amino acid residues. This is shown in the below snapshot for VSV-G (blue-green) bound to the CR2 domain of the LDL receptor (grey):

I182 and Nearby Residues in VSV-G Bound to CR2



(*See* Ex. 1026 at 1; *see also* Appendix B (Image 2).)

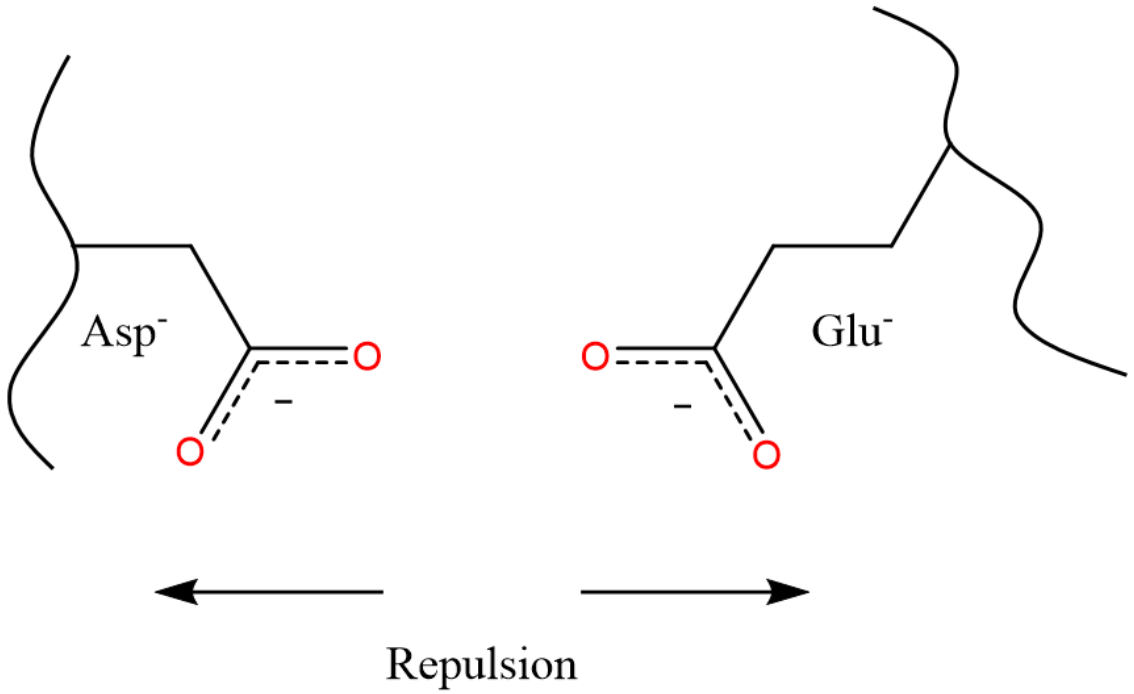
204. A person of ordinary skill in the art would have immediately recognized from this crystal structure that I182 is nearby the carboxyl portion of D73, which is aspartic acid, and the first methylene of Q71, which is glutamine. A person of ordinary skill in the art would have expected some interaction between the carboxyl portion of D73 and I182 at this distance. A person of ordinary skill in the art would have also understood that residues D73 and Q71 were believed to be involved in the

binding of VSV-G to the CR2 domain from the crystal structure, as they appear in the structural images in Nikolic *et al.* (Ex. 1018 at 5, FIG. 4b.)

205. In my opinion, a person of ordinary skill in the art would have been motivated to modify *Perkins* based on the VSV-G crystal structures in the *RCSB PDB*. *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.) The VSV-G crystal structures in the *RCSB PDB* taught that I182 is nearby negatively charged amino acids on the LDL-R. Thus, a person of ordinary skill in the art 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.)

206. A person of ordinary skill in the art 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.) Accordingly, it would have been immediately apparent to a person of ordinary skill in the art 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. The concept of anionic repulsion between two negatively residues, such as aspartic

acid and glutamic acid,[13] would have been well known to a person of ordinary skill in the art to occur at pH 6. This concept is demonstrated in the image below:



207. A person of ordinary skill in the art would have had only two options out of the naturally occurring amino acids—glutamic acid (E) and aspartic acid (D)—to incorporate in place of isoleucine at position 182 to oppose an interaction with negatively charged residues through anionic repulsion. (Ex. 1022 at 76-77; Ex. 1023 at 10. In my opinion, it would have been common sense for a person of

[13] The anionic forms of aspartic acid ("aspartate") and glutamic acid ("glutamate") are indicated in the figure above by "Asp-" and "Glu-," respectively.

ordinary skill in the art to make a I182E mutation in view of the finite number of options that would be known to introduce anionic repulsion and ablate the interaction with the LDL receptor.

208. A person of ordinary skill in the art in my opinion would also have had a good reason to focus on *Perkins*' express disclosure of a I182 mutation. For instance, *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 person of ordinary skill in the art 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; Appendix B (Image 3).)[14] These positions are also contained within *Perkins*'

[14] While *Perkins*' also discloses potential "insertions" and a "deletion" at 21:16-27, a person of ordinary skill in the art 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

mutant VS-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.)

209. A person of ordinary skill in the art would have recognized that I182 is the closest out of the 13 disclosed positions in *Perkins* to the carboxyl portion of a charged amino acid residue known to be involved the coordination of calcium in the CR3 domain, specifically D112 at a distance of ~3.627 Å. (*See, e.g.*, Ex. 1005 at 21:16-27; Ex. 1006 at 17-18; Ex. 1018 at 7 (describing that "D108 and D112 on CR3" as "two acidic residues which belong to the octahedral calcium cage"); Appendix B (Image 3).) Additionally, I182 was the only amino acid out of the 13 disclosed amino acid positions in *Perkins* that was close (~4.388 Å) to a second negatively charged amino acid in the CR3 domain, D110. These interactions are shown in the image above and in Appendix B (Images 1 and 3). (*See supra* ¶ 201.)

210. A person of ordinary skill in the art would thus have concluded that I182 was as one of the best of the 13 disclosed options in *Perkins* for disrupting the interaction with the CR3 domain of the LDL-R, which as discussed above was most

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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.)

likely through anionic repulsion. (*See supra* ¶¶ 205-207.) While another disclosed position,[15] M184, was also close to the carboxyl portion of D110 (as close as ~3.180 Å), I182 had the advantage of potentially interacting with both D112 and D110.

211. Similarly, while routinely navigating the published 5OYL crystal structure, a person of ordinary skill in the art 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. 1026 at 1; Appendix B (Image 4).) A person of ordinary skill in the art would have recognized that I182 is the closest out of the 13 disclosed positions in *Perkins* to the carboxyl portion of a charged amino acid residue involved the coordination of calcium in the CR2 domain, specifically D73 at a distance of ~3.578 Å. (*See, e.g.*, Ex. 1005 at 21:16-27; Ex. 1006 at 17-18; Ex. 1018 at 7 (describing that "D69 and D73 on CR2" as "two acidic residues which belong to the octahedral calcium cage.") This interaction is shown in the image above and in Appendix B (Images 2 and 4). (*See supra* ¶ 203.)

[15] Appendix B (Image 3) is an exemplary image from the analysis of 13 potential positions for a mutation disclosed in *Perkins.* Potential mutation positions have been colored in cornflower blue, with the exception of I182, which is colored in orange.

212. A person of ordinary skill in the art would have similarly concluded that I182 was one of the best of the 13 disclosed options in *Perkins* for disrupting the interaction with the CR2 domain of the LDL-R, most likely through anionic repulsion. While one of the disclosed options,[16] T352, was also close to a negatively charged amino acid on CR2 known to be involved in the binding of calcium, E80 at ~3.582 Å (*see* Ex. 1018 at 5, FIG. 4(a)), I182 had the advantage of a better position when taking into account both of the published 5OY9 and 5OYL crystal structures.

213. A person of ordinary skill in the art in my opinion would have been interested in amino acids such as I182 that interact with the octahedral calcium cage of the LDL-R CR domains. For instance, a person of ordinary skill in the art was aware that "[t]he LDL-R gene family consists of trans-membrane receptors that . . . require Ca^{2+} for ligand binding." (*See, e.g.*, Ex. 1018 at 4.) Nikolic *et al.* reported that "the presence of Ca^{2+} was mandatory for the correct folding of the proteins." (*See, e.g., id.* at 5.) As the calcium cage appears to mediate binding, a person of ordinary skill in the art would have looked to residues in close proximity. (*See, e.g., id.* at 9.)

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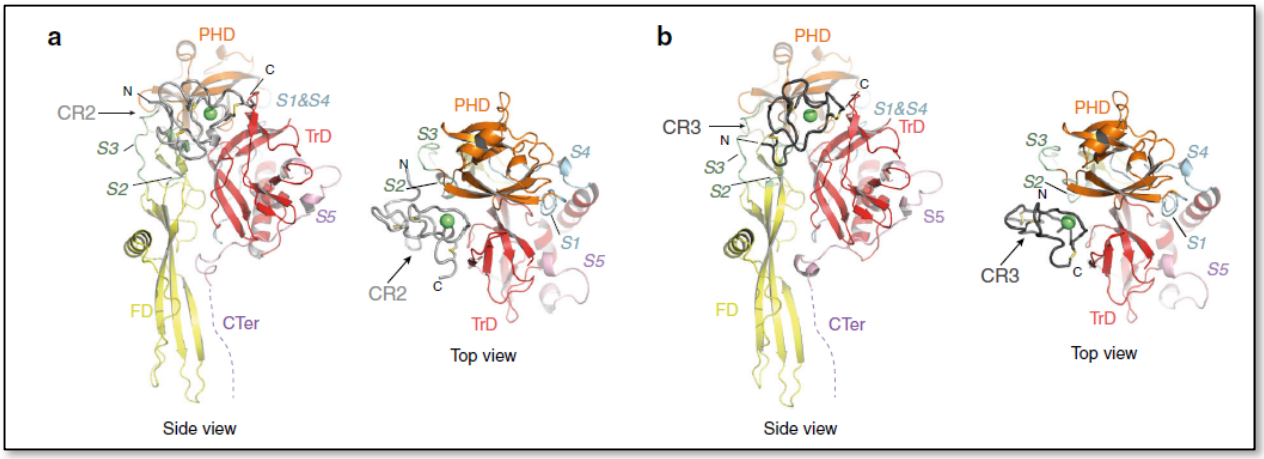
[16] Appendix B (Image 4) is an exemplary image from the analysis of the 13 potential positions for a mutation disclosed in *Perkins*. Potential mutation positions have been colored in cornflower blue, with the exception of I182, which is colored in orange.

214. A person of ordinary skill in the art would have had a reasonable expectation of success in making the I182E mutation to the VSV-G protein disclosed in *Perkins* for multiple reasons. For instance, as discussed above, a person of ordinary skill in the art would have reason to believe that a I182E mutation would have resulted in a defect in LDL receptor binding. Additionally, while not required by claim 1, a person of ordinary skill in the art would not have believed that a I182E mutation would lead to a loss of VSV-G protein fusogenic function.

215. A person of ordinary skill in the art 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). Figure 3a and b from Nikolic *et al.* is reproduced below:



(Ex. 1018 at 4, FIGs. 3a and b.)

216. As shown in this select portion of Figure 3 of Nikolic *et al.*, the I182 residue sits near the indicated "CR2" and "CR3" domains, which are at the top

portion of VSV-G (in gray and black, respectively), whereas the fusion domain (in yellow) is located near the bottom of VSV-G.

217. A person of ordinary skill in the art 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.) 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).)

218. A person of ordinary skill in the art 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.) *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.)

219. In my opinion, a person of ordinary skill in the art 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 among other things 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 person of ordinary skill in the art at the relevant time.

2. Claim 2

i) [1.a] "A polypeptide"

[17] The '366 patent states that it identified I182 through "structure-guided design" using published crystal structures 5OYL and 5OY9. (*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 how *Perkins* and the *RCSB PDB* disclose or suggest a I182E mutation.

220. *Perkins* and the *RCSB PBD* disclosed or suggested "[a] polypeptide" for the reasons discussed above in Section VI.C.2.i.

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

221. *Perkins* disclosed "comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2" for the reasons discussed above in Section VI.C.1.ii.

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

222. *Perkins* disclosed "and a I182D mutations as compared to SEQ ID NO: 2" as discussed in Section VI.A.2.iii. To the extent *Perkins*' disclosure of mutating VSV-G at amino acid position I182 is found not to expressly meet "a I182D mutation as compared to SEQ ID NO: 2," *Perkins* and the *RCSB PDB* at a minimum disclosed or suggested this limitation.

223. A person of ordinary skill in the art 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 VI.C.1.iii with respect to glutamic acid. 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.) A person of ordinary skill in the art would have understood that the concept of anionic repulsion behaved similarly whether the opposed residues were glutamic acid or aspartic acid.

224. Accordingly, *Perkins* and the *RCSB PDB* disclosed or suggested to a person of ordinary skill in the art a I182D mutation the same reasons that *Perkins* and the *RCSB PDB* disclosed or suggested a I182E mutation.

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."

225. *Perkins* and 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. *See* Section VI.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 VI.A.3.

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

226. *Perkins* and 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. *See* Section VI.C.1.iii. *Perkins* further disclosed the nucleic acid molecule encoding SEQ ID NO: 90 with the I182E mutation, as discussed in Section VI.A.4.

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

227. *Perkins* and the *RCSB PDB* disclosed or suggested the nucleic acid molecule, as discussed in Section VI.C.4 and *Perkins* further disclosed a vector comprising such a nucleic acid molecule as discussed in Section VI.A.5.

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

228. *Perkins* and the *RCSB PDB* disclosed or suggested the nucleic acid molecule, as discussed in Section VI.C.4, and *Perkins* further disclosed a cell comprising such a nucleic acid molecule as discussed in Section VI.A.6.

7. Claim 13: "A viral particle comprising the polypeptide of claim 1."

229. *Perkins* and the *RCSB PDB* disclosed or suggested the polypeptide of claim 1 in Section VI.C.1 and *Perkins* further disclosed a viral particle comprising such a polypeptide as discussed in in Section VI.A.7.

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

230. *Perkins* and the *RCSB PDB* disclosed or suggested this claim for the reasons discussed above in Sections VI.C.7 and VI.A.8.

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."

231. *Perkins* and the *RCSB PDB* disclosed or suggested this claim for the reasons discussed above in Sections VI.C.7 and VI.A.9.

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."

232. *Perkins* and the *RCSB PDB* disclosed or suggested this claim for the reasons discussed above in Sections VI.C.7, VI.C.9, and Section VI.A.10.

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

233. *Perkins* and the *RCSB PDB* disclosed or suggested this claim for the reasons discussed above in Sections VI.C.7, VI.C.9, and VI.A.11.

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."

234. *Perkins* and the *RCSB PDB* disclosed or suggested the polypeptide of claim 1. *See* Section VI.C.1.iii. Such a polypeptide satisfies claim 18 as discussed in Section VI.A.12.

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."

235. *Perkins* and the *RCSB PDB* disclosed or suggested the polypeptide of claim 1. *See* Section VI.C.1.iii. Such a polypeptide satisfies claim 19 as discussed in Section VI.A.13.

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."

236. *Perkins* and the *RCSB PDB* disclosed or suggested the polypeptide of claim 1. *See* Section VI.C.1.iii. Such a polypeptide satisfies claim 20 as discussed in Section VI.A.14.

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."

237. *Perkins* and the *RCSB PDB* disclosed or suggested the polypeptide of claim 1. *See* Section VI.C.1.iii. Such a polypeptide satisfies claim 21 as discussed in Section VI.A.15.

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."

238. *Perkins* and the *RCSB PDB* disclosed or suggested the polypeptide of claim 2. *See* Section VI.C.2.iii. Such a polypeptide satisfies claim 22 as discussed in Section VI.A.16.

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."

239. *Perkins* and the *RCSB PDB* disclosed or suggested the polypeptide of claim 2. *See* Section VI.C.2.iii. Such a polypeptide satisfies claim 23 as discussed in Section VI.A.17.

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."

240. *Perkins* and the *RCSB PDB* disclosed or suggested the polypeptide of claim 2. *See* Section VI.C.2.iii. Such a polypeptide satisfies claim 24 as discussed in Section VI.A.18.

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."

241. *Perkins* and the *RCSB PDB* disclosed or suggested the polypeptide of claim 2. *See* Section VI.C.2.iii. Such a polypeptide satisfies claim 25 as discussed in Section VI.A.19.

D. ***Perkins*, the *RCSB PDB*, and *Hwang* Taught or Suggested All of the Elements of Claims 3-9 and 26-30 of the '366 Patent**

242. For the reasons described in Section VI.C, *Perkins* and the *RCSB PDB* disclosed or suggested independent claims 1 and 2 of the '366 patent. 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. However, *Perkins*, the *RCSB PDB,* and *Hwang* disclosed or suggested claims 3-9 and 26-30 for reasons similar to those I have set forth in Section VI.B.

243. A person of ordinary skill in the art in would have been motivated to further modify *Perkins* and the *RCSB PDB* with *Hwang* and would have arrived at claims 3-9 and 26-30 with a reasonable expectation of success for the reasons described in Section VI.B. 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 person of ordinary skill in the art 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 VI.B and VI.C.

VII. CONCLUSION

244. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: October 31, 2023

John K. Rose, Ph.D.

APPENDIX A

Table of Cited Exhibits

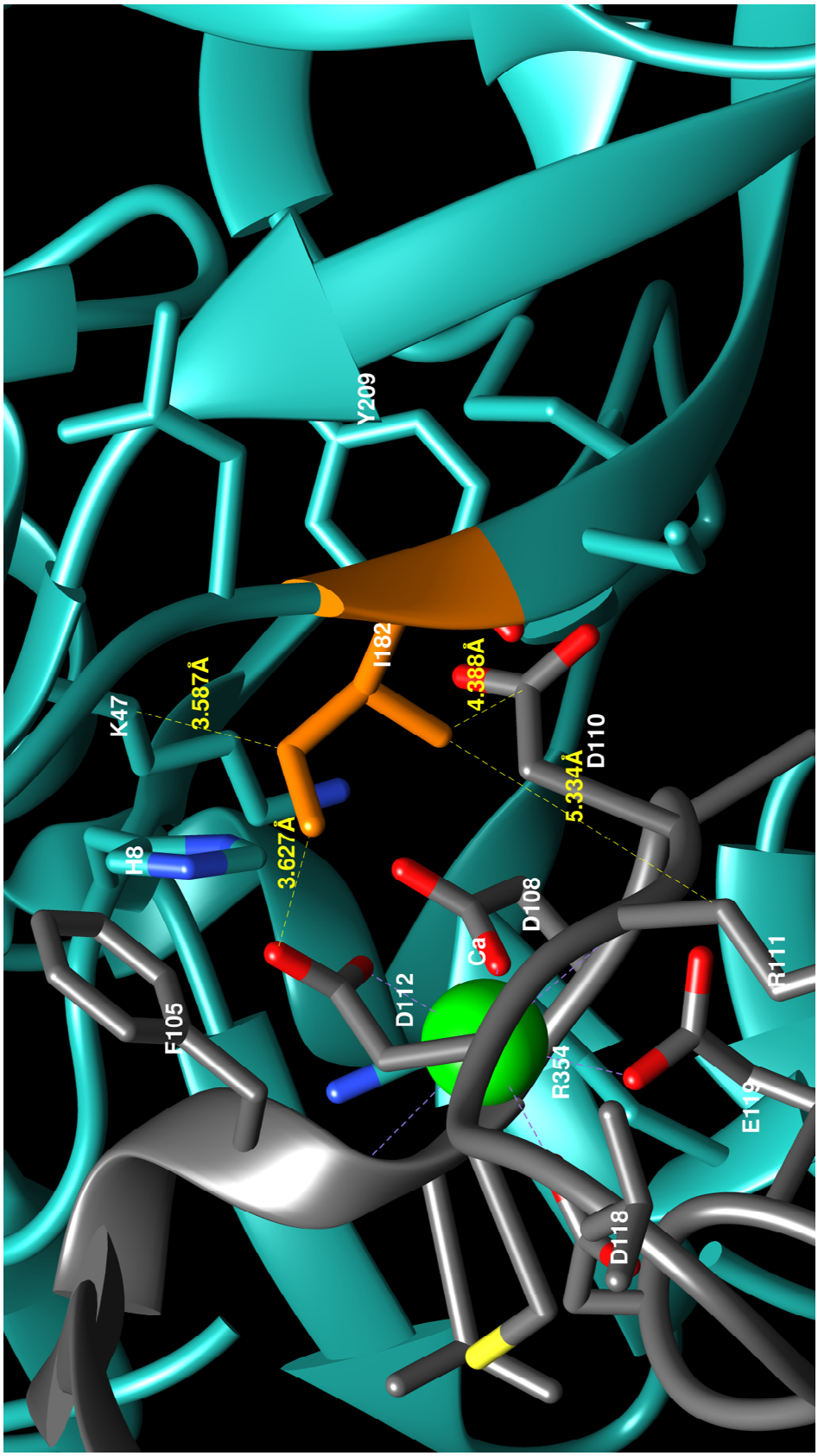
Ex. 1001	U.S. Patent No. 11,767,366 ("the '366 patent")
Ex. 1002	Declaration of Professor John K. Rose, Ph.D.
Ex. 1003	Curriculum Vitae of Professor John K. Rose, Ph.D.
Ex. 1004	File History of the '366 Patent
Ex. 1005	International Application Pub. No. WO 2022/183072 ("Perkins")
Ex. 1006	Provisional Application No. 63/154639 ("the '639 Application")
Ex. 1007	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. 1008	C. Dunbar *et al.*, *Gene therapy comes of age*, 359 SCIENCE 1 (2018)
Ex. 1009	L. Naldini *et al.*, *In Vivo Gene Delivery and Stable Transduction of Nondividing Cells by a Lentiviral Vector*, 272 SCIENCE 263 (1996)
Ex. 1010	A. Duverge and M. Negroni, *Pseudotyping Lentiviral Vectors: When the Clothes Make the Virus*, 12 VIRUSES 1311 (2020)
Ex. 1011	S. P. J. Whelan, *Vesicular Stomatitis Virus*, ENCYCLOPEDIA OF VIROLOGY 291 (Elsevier Ltd) (2008)
Ex. 1012	A. Albertini *et al.*, *Molecular and Cellular Aspects of Rhabdovirus Entry*, 4 VIRUSES 117-139 (2012)
Ex. 1013	S. Roche *et al.*, *Structure of the Prefusion Form of Vesicular Stomatitis Virus Glycoprotein G*, 315 SCIENCE 843 (2007)
Ex. 1014	S. Roche *et al.*, *Crystal Structure of the Low-pH Form of the Vesicular Stomatitis Virus Glycoprotein G*, 313 SCIENCE 187 (2006)
Ex. 1015	S. Roche *et al.*, *Structures of vesicular stomatitis virus glycoprotein: membrane fusion revisted*, 65 CELL. MOL. LIFE SCI. 1716 (2008)

Ex. 1016	D. Finkelshtein *et al.*, *LDL receptor and its family members serve as the cellular receptors for vesicular stomatitis* virus, 110 PNAS 7306 (2013)
Ex. 1017	F. Amirache *et al.*, *Mystery solved: VSV-G-LVs do not allow efficient gene transfer into unstimulated T cells, B cells, and HSCs cause they lack the LDL receptor*, 123 BLOOD 1422 (2014)
Ex. 1018	J. Nikolic *et al.*, *Structural Basis for the recognition of LDL-receptor family members by VSV glycoprotein,* 9 NATURE COMMUN. 1029 (2018)
Ex. 1019	U.S. Application Pub. No. 2020/0216502
Ex. 1020	N. Depolo *et al.*, *VSV-G Pseudotyped Lentiviral Vector Produced in Human Cells Are Inactivated by Human Serum*, 2 Molecular Therapy 218 (2000)
Ex. 1021	U.S. Application Pub. No. 2018/0036429
Ex. 1022	Donald J. Voet *et al.*, FUNDAMENTALS OF BIOCHEMISTRY (2008), Chapters 3 and 4, 39-82.
Ex. 1023	International Application Pub. No. WO 1997009433
Ex. 1024	C. Zardecki *et al.*, *RCSB Protein Data Bank: A Resource for Chemical, Biochemical, and Structural Explorations of Large and Small Biomolecules*, 93 J. CHEM. EDUC. 569 (2016)
Ex. 1025	5OY9, RCSB Protein Data Bank, https://www.rcsb.org/structure/5OY9 (last accessed October 11, 2023)
Ex. 1026	5OYL, RCSB Protein Data Bank, https://www.rcsb.org/structure/5oyl (last accessed October 11, 2023)
Ex. 1027	E. Pettersen *et al.*, *UCSF Chimera—A visualization system for exploratory research and analysis*, 25 J. COMP. CHEM. 1605 (2004)
Ex. 1028	J. Rose and C. Gallione, *Nucleotide Sequences of the mRNAs Encoding the Vesicular Stomatitis Virus G and M Proteins Determined from cDNA Clones Containing the Complete Coding Regions,* 39 J. VIROLOGY 519 (1981)
Ex. 1029	R. Florkiewicz and J. Rose, *A Cell Line Expressing Vesicular Stomatitis Virus Glycoprotein Fuses at Low pH*, 225 SCIENCE 721 (1984)

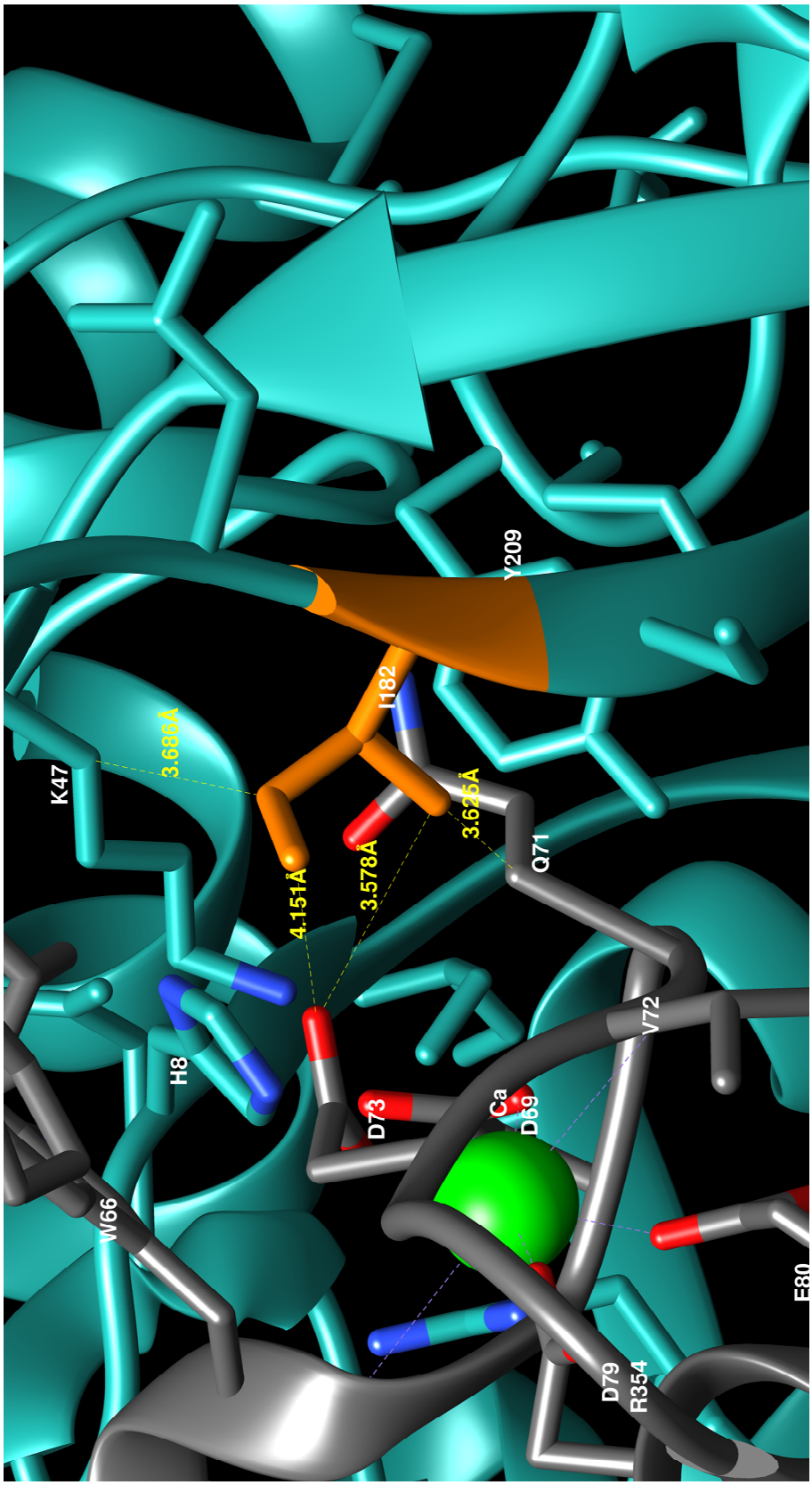
APPENDIX B

Crystal Structure Analysis

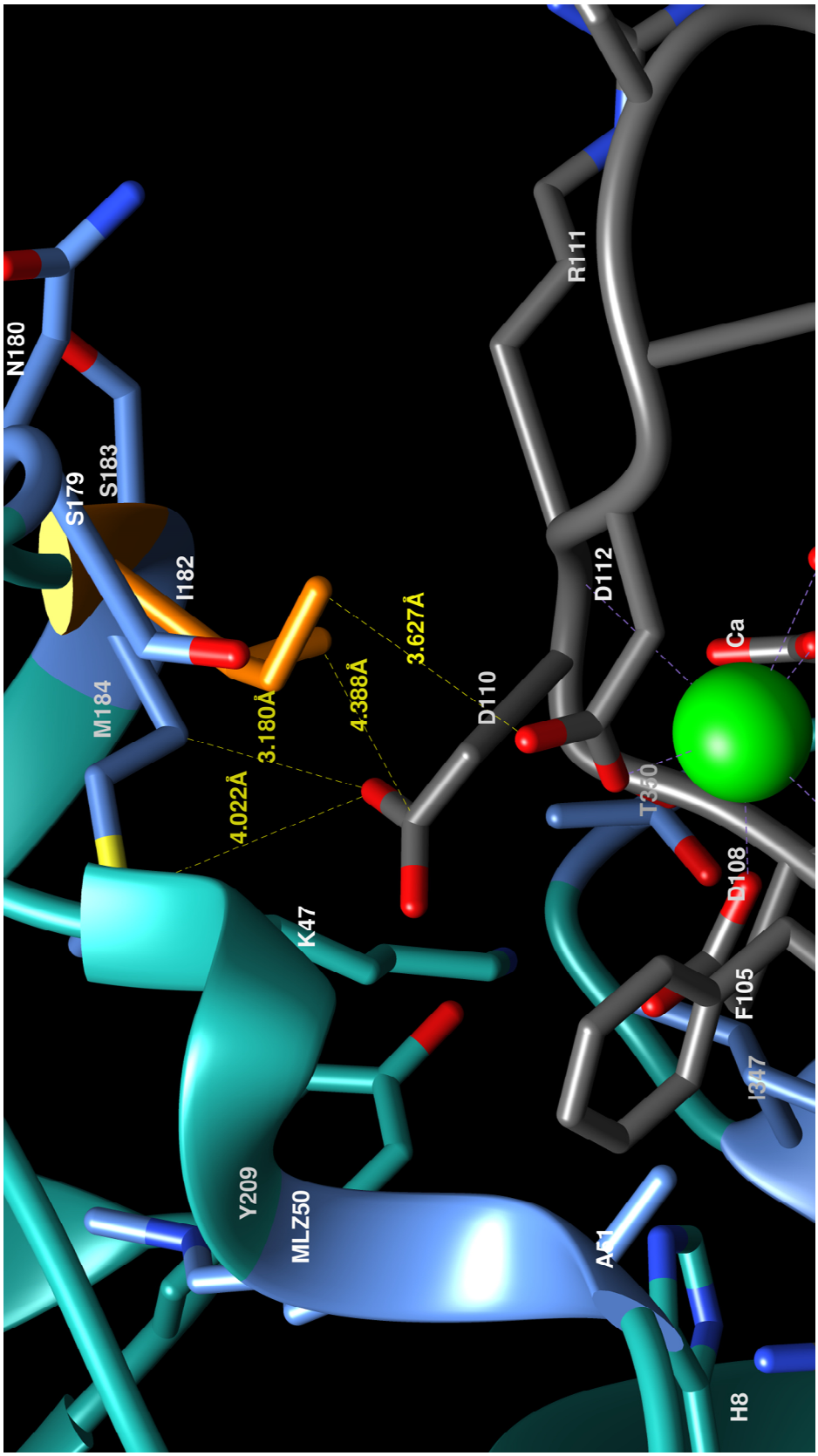
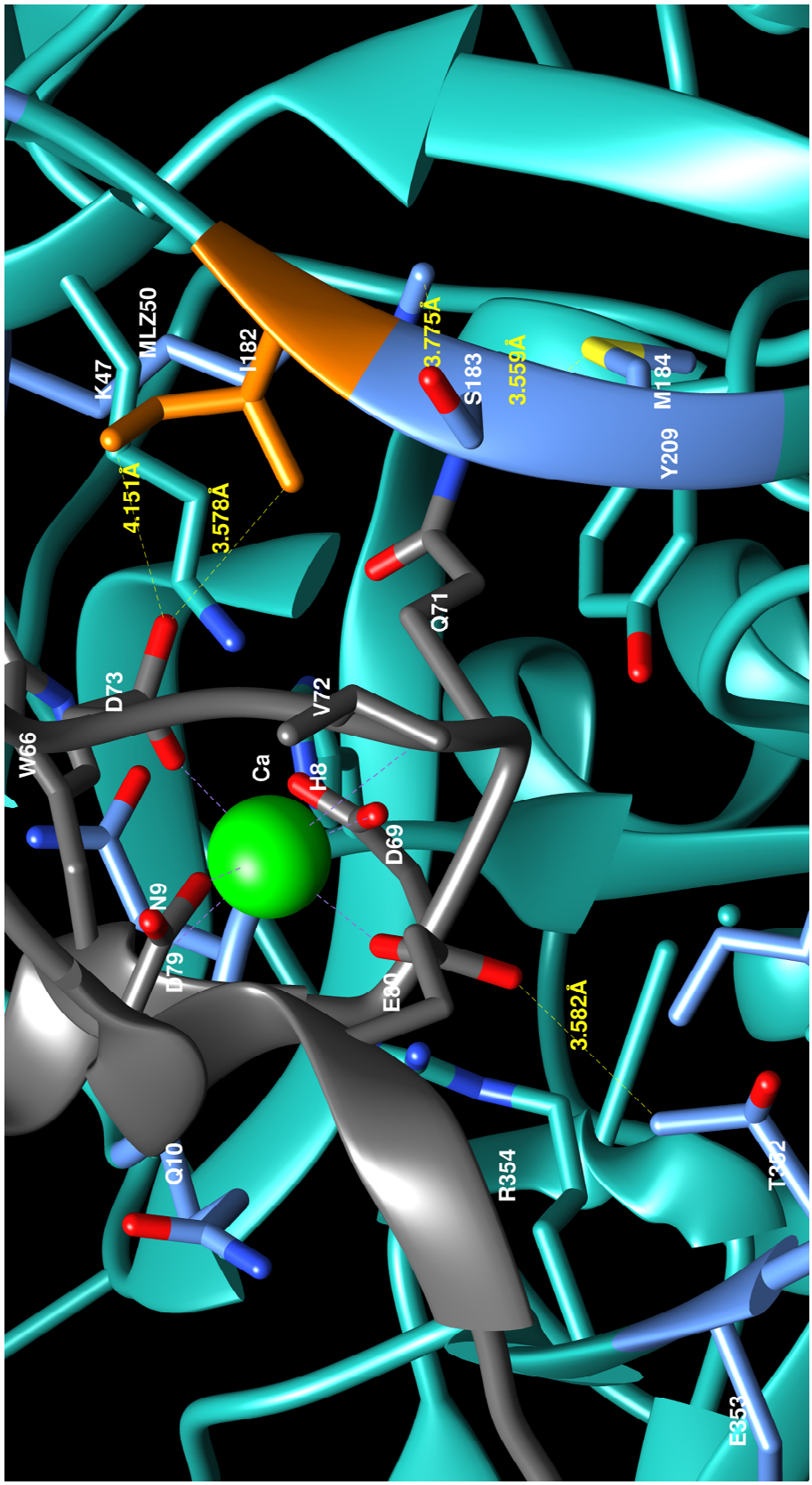
I182 and Nearby Residues in VSV-G Bound to CR3 (Image 1)



I182 and Nearby Residues in VSV-G Bound to CR2 (Image 2)



I182 and Other Potential Mutation Positions in VSV-G Bound to CR3 (Image 3)



I182 and Other Potential Mutation Positions in VSV-G Bound to CR2 (Image 4)