

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KELONIA THERAPEUTICS, INC.,
Petitioner,

v.

INTERIUS BIOTHERAPEUTICS, INC.,
Patent Owner.

PGR2024-00008
Patent 11,767,366 B1

Before SHERIDAN K. SNEDDEN, SUSAN L. C. MITCHELL, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

DECISION

Denying Institution of Post-Grant Review
35 U.S.C. § 324, 37 C.F.R. § 42.4

I. INTRODUCTION

A. Background and Summary

Kelonia Therapeutics, Inc. (“Petitioner”) filed a Petition requesting a post-grant review of claims 1–30 of U.S. Patent No. 11,767,366 B1 (“the ’366 patent,” Ex. 1001). Paper 1 (“Pet.”). Interius Biotherapeutics, Inc. (“Patent Owner”) filed a Patent Owner’s Preliminary Response. Paper 6 (“Prelim. Resp.”). With our authorization (Paper 7), Petitioner filed a Reply (Paper 9) and Patent Owner filed a Sur-Reply (Paper 10) addressing discretionary denial under 35 U.S.C. § 325(d).¹

We have authority under 35 U.S.C. § 324(a), which provides that a post-grant review may not be instituted “unless . . . the information presented in the petition . . . , if such information is not rebutted, would demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” Upon considering the arguments and evidence presented by the parties, we determine Petitioner has not shown that it is more likely than not that at least one of the claims challenged in the Petition is unpatentable. Accordingly, we deny institution of post-grant review.

B. Real Parties in Interest

Each party identifies itself as the sole real party in interest. Pet. 2; Paper 3, 2.

¹ Because we deny institution of trial on the merits, we do not further address the parties’ arguments concerning discretionary denial.

C. Related Matters

Petitioner indicates that there are no related matters. Pet. 2. Patent Owner identifies U.S. App. No. 18/157,421 as a pending patent application “that may be affected by a decision in this proceeding.” Paper 3, 2.

D. The ’366 patent (Ex. 1001)

The ’366 patent issued on September 26, 2023, and is titled “PSEUDOTYPED VIRAL PARTICLES, COMPOSITIONS COMPRISING THE SAME, AND USES THEREOF.” Ex. 1001, codes (45), (54). The ’366 patent is directed to mutant VSV-G polypeptides, compositions comprising mutant VSV-G polypeptides, and methods of using mutant VSV-G polypeptides. *Id.* at Abstract. The ’366 patent also describes polypeptides and compositions that bind to CD7 and/or CD8 and uses thereof. *Id.*

The ’366 patent explains that “[v]esicular stomatitis virus (VSV) is an enveloped, negative-strand RNA virus that belongs to the Vesiculovirus genus of the Rhabdovirus family. It is an arbovirus which can infect insects, cattle, horses and pigs. VSV genome encodes five structural proteins among which include a single transmembrane glycoprotein (G),” (“VSV-G”). Ex. 1001, 1:27–32. The ’366 patent further explains that “low-density lipoprotein receptor (LDL-R) and other members of this receptor family serve as VSV receptors.” *Id.* at 2:1–6.

According to the ’366 patent,

VSV-G can be used for pseudotyping other viruses and VSV-G-pseudotyped lentiviruses (VSV-G-LVs) exhibit the same broad tropism as VSV. However, this broad tropism can inhibit the selective targeting of specific cell types. Therefore, there is a need, for modified (mutated or mutant) VSV-G proteins that can

be used to pseudotype viruses that abrogate its binding to the LDL receptor.

Id. at 2:9–15. The '366 patent describes mutant VSV-G proteins that can be used to transduce a target cell and deliver a heterologous molecule to the targeted cells and “show[s] that a mutant VSV-G protein comprising a mutation at position 182 can be used to pseudotype a virus and transduce a cell when the virus comprises a targeting moiety.” *Id.* at 17:23–26. The '366 patent discloses that a mutation at position 182 inhibits or reduces the VSV-G affinity to LDL-R. *Id.* at 17:26–28.

Additionally, the '366 patent describes a VSV-G protein

that comprises a mutation at position 198 as compared to SEQ ID NO: 1 or at position 182 as compared to SEQ ID NO: 2. SEQ ID NO: 1 is the full length protein and SEQ ID NO: 2 is the ectodomain of the VSV-G protein. The 16-mer signal peptide of MKCLLYLAFLFIGVNC (SEQ ID NO: 26) as shown at the N-terminus of SEQ ID NO: 1 is cleaved leaving a protein of SEQ ID NO: 2. Thus, although a mutation may be referred to in the context of SEQ ID NO: 2, it should be understood to also be made in the context of SEQ ID NO: 1, which contains the leader sequence, and thus would be a position number that is 16 more than the position recited for SEQ ID NO: 2. In some embodiments, the mutation inhibits or decreases the binding of the VSV-G protein to the LDL receptor (LDL-R). In some embodiments, the mutation is a I182D mutation as compared to SEQ ID NO: 2. In some embodiments, the mutation is a I182E mutation as compared to SEQ ID NO: 2.

Id. at 17:32–49. Sequence listings of SEQ ID NO: 1 and SEQ ID NO: 2 are reproduced below.

SEQUENCE LISTING

Sequence total quantity: 81

SEQ ID NO: 1 moltype = AA length = 511
FEATURE Location/Qualifiers
source 1..511
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 1

MKCLLYLAFL	FIGVNCKFTI	VFPHNQKGNW	KNVPSNYHYC	PSSSDLNWHN	DLIGTALQVK	60
MPKSHKAIQA	DGWMCHASKW	VTTCDFRWYG	PKYITHSIRS	FTPSVEQCKE	SIEQTKQGTW	120
LNPGFPPQSC	GYATVTDAEA	VIVQVTPHHV	LVDEYTGGEV	DSQFINGKCS	NYICPTVHNS	180
TTWHSYKVK	GLCDSNLISM	DITFFSEGE	LSSLGKEGTG	FRSNYFAYET	GGKACKMQYC	240
KHWGVRLPSG	VWFEMADKDL	FAAARFPECP	EGSSISAPSQ	TSVDVSLIQD	VERILDYSLC	300
QETWSKIRAG	LPISPVDLSY	LAPKNPGTGP	AFTIINGTLK	YFETRYIRVD	IAAPILSRMV	360
GMISGTTTER	ELWDDWAPYE	DVEIGPNGVL	RTSSGYKFPL	YMIGHGMLDS	DLHLSSKAQV	420
FEHPHIQDAA	SQLPDDESLF	FGDTGLSKNP	IELVEGWFS	WKSSIASFFF	IIGLIIGLFL	480
VLRVGIHLCI	KLKHTKKRQI	YTDIEMNRLG	K			511

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	VHNSTTWHS	YKVKGLCDSN	180
LISMDITFFS	EDGELSSLGK	EGTGFRSNYF	AYETGGKACK	MQYCKHWGVR	LPSGVWFEMA	240
DKDLFAAARF	PECPEGSSIS	APSQTSVDVS	LIQDVERILD	YSLCQETWSK	IRAGLPISPV	300
DLSYLAPKNP	GTGPAFTIIN	GTLKYFETRY	IRVDIAAPIL	SRMVGMI	SGT TTERELWDDW	360
APYEDVEIGP	NGVLR	TSSGY KFPLYMIGHG	MLDS	DLHLSS KAQVFEHPHI	QDAASQLPDD	420
ESLFFGDTGL	SKNPIELVEG	WFSSWKSSIA	SFFFIIGLII	GLFLVLRVGI	HLCIKLKHTK	480
KRQIYTDIEM	NRLGK					495

Id. at col. 121. The sequences above provide, respectively, a listing of the amino acids comprising SEQ ID NO: 1 and SEQ ID NO: 2.

The '366 patent's filing date is December 15, 2022; however, it claims priority to Provisional Application No. 63/267,039, filed on January 21, 2022; Provisional Application No. 63/266,044, filed on December 27, 2021; Provisional Application No. 63/289,977, filed on December 15, 2021; and Provisional Application No. 63/289,888, filed on December 15, 2021. Ex. 1001, codes (22), (60). Petitioner assumes, for purposes of its challenge, a priority date of December 15, 2021. *See* Pet. 4 ("The earliest application

to which the '366 patent purports to claim priority has a filing date of December 15, 2021. Even if claims 1-30 of the '366 patent are entitled to a priority date of December 15, 2021—which Petitioner does not concede. . .”).

E. Prosecution History of the '366 Patent

The Examiner issued only one rejection during prosecution of the '366 patent. On June 23, 2023, the Examiner made a non-final rejection of some of the pending claims based on nonstatutory double patenting over claims 71–78 and 82–89 of Application No. 18/157,421, which was copending at that time. Ex. 1004, 1484–89.² The Examiner also objected to certain informalities in the Applicant's claims, namely that “the claims recite, or depend upon claims that recite, a polypeptide that ‘. . . comprises a mutation that corresponds to a mutation at position 182. . .,’” which “is grammatically clumsy and potentially confusing, primarily due to the duplicative use of the term ‘mutation’ in the relevant phrase wherein a single use of the term would suffice.” *Id.* at 1486.

On June 28, 2023, the Applicant responded to the non-final rejection. Ex. 1004, 1522–28. The Applicant amended the claims to overcome the Examiner's objections and cancelled the claims at issue in the non-statutory double patenting rejection. *Id.* In response, the Examiner issued a Notice of Allowance on July 26, 2023. *Id.* at 1616–22.

F. Challenged Claims

Petitioner challenges claims 1–30. Representative independent claims 1 and 2 are reproduced below.

² Page number citations for Exhibit 1004 correspond to the page numbers stamped on the bottom corner on the left of each page.

1. 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.

2. 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 I182D mutation as compared to SEQ ID NO: 2.

Ex. 1001, 145:11–18. Claims 3–30 depend, directly or indirectly, from either claim 1 or claim 2. *Id.* at 145:19–146:51.

G. Evidence

Petitioner relies upon information that includes the following:

Ex. 1005, Perkins et al., WO 2022/183072 A1, published September 1, 2022 (“Perkins”);

Ex. 1007, B-Y Hwang et al., *Engineering a Serum-Resistant and Thermostable Vesicular Stomatitis Virus G Glycoprotein for Pseudotyping Retroviral and Lentiviral Vectors*, 20(8) GENE THERAPY 807–15 (2013) (“Hwang”); and

Ex. 1025, 5OY9, Research Collaboratory for Structural Bioinformatics (“RCSB”) Protein Databank (“PDB”) (2018) (*available at* <https://www.rcsb.org/structure/5oy9>) and Ex. 1026, 5OYL, RCSB PDB (2018) (*available at* <https://www.rcsb.org/structure/5oyl>) (collectively, “RCSB PDB”).

Petitioner also relies on the Declaration of Professor John K. Rose, Ph.D. in Support of Petition for Post-Grant Review of U.S. Patent No. 11,767,366 (Ex. 1002) to support its contentions.

H. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–30 are unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–3, 10–25	102	Perkins
2	3–9, 26–30	103	Perkins, Hwang
3	1–3, 10–25	103	Perkins, RCSB PDB
4	3–9, 26–30	103	Perkins, RCSB PDB, Hwang

I. Claim Construction

The Board applies the same claim construction standard that would be used to construe the claims in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.200(b) (2019). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Petitioner contends that “the Board need not construe any terms of the challenged claim[s] to resolve the underlying controversy, as any reasonable construction reads on the prior art.” Pet. 25. Patent Owner contends it “does not believe that the Board needs to construe any claim terms at this stage of the proceeding because the challenged claims are not invalid in view of the asserted prior art under any reasonable construction.” Prelim. Resp. 7.

We agree with the parties and determine that it is unnecessary to expressly construe any claim term for purposes of rendering this Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

J. Level of Ordinary Skill in the Art

Petitioner proposes that a person of ordinary skill in the art (“POSA”) at the time of the invention

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

Pet. 15. Patent Owner does not dispute Petitioner’s proposal about the POSA’s qualifications. *See generally* Prelim. Resp.

For this Decision, we adopt and apply Petitioner’s proposal above, which appears to be consistent with the level of skill reflected in the asserted prior art.

II. POST-GRANT ELIGIBILITY

As a threshold matter, we must determine whether the ’366 patent is eligible for post-grant review. The post-grant review provisions set forth in section 6(d) of the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (September 16, 2011) (“AIA”), apply only to patents subject to the first-inventor-to-file provisions of the AIA. *See* AIA § 6(f)(2)(A) (stating that the provisions of section 6(d) “shall apply only to patents described in section 3(n)(1)”). Patents subject to the first-inventor-to-file provisions are those that issue from applications that contain or contained at any time—

(A) a claim to a claimed invention that has an effective filing date as defined in section 100(i) of title 35, United States Code, that is on or after [March 16, 2013]; or

(B) a specific reference under section 120, 121, or 365(c) of title 35, United States Code, to any patent or application that contains or contained at any time such a claim.

AIA § 3(n)(1).

Our rules require that each petitioner for post-grant review certify that the challenged patent is available for post-grant review. 37 C.F.R.

§ 42.204(a) (“The petitioner must certify that the patent for which review is sought is available for post-grant review . . .”). In addition, “[a] petition for a post-grant review may only be filed not later than the date that is 9 months after the date of the grant of the patent or of the issuance of a reissue patent (as the case may be).” 35 U.S.C. § 321(c).

Petitioner certifies that the ’366 patent is available for post-grant review. Pet. 3. Patent Owner does not dispute Petitioner’s assertion. *See generally* Prelim. Resp.

Because the claims of the ’366 patent have an effective filing date after March 16, 2013, and because the Petition was filed within nine months of the ’366 patent’s issue date on September 26, 2023, we find that the ’366 patent is eligible for post-grant review. *See* Ex. 1001, codes (45), (60).

III. ANALYSIS

A. Summary of the Cited Prior Art

1. Perkins (Ex. 1005)

Perkins is titled “LYMPHOCYTE TARGETED LENTIVIRAL VECTORS.” Ex. 1005, code (54).³ Perkins claims priority to U.S. Provisional Application No. 63/154,639 (“Perkins Provisional”), filed on February 26, 2021. *Id.* at code (30); Ex. 1006, 1. Perkins provides

³ Page number citations for Exhibit 1005 correspond to the original page numbers centered on the bottom of each page.

“lentiviral vectors comprising a mutated, heterologous envelope protein, a targeting protein, and at least one transgene for delivery to and expression by a cell characterized by the targeting protein.” Ex. 1005, code (57). Perkins also describes methods of treating a disease such as cancer in a subject comprising administering an effective amount of an LVV, a CAR modified lymphocyte (e.g., T cell, B cell, or NK cell), or pharmaceutical compositions thereof. *Id.* at 96:1–17. Such treatment may be combined with one or more additional therapeutic agents. *Id.*

Perkins describes lentiviral vectors (“LVV”) that “include a mutated, heterologous envelope protein, a targeting protein, and at least one transgene for delivery to and expression by a cell characterized by the targeting protein. In some embodiments, the targeting protein is selected to target an immune cell, including, for example a lymphocyte or a T cell.” *Id.* at 4:2–6; *see also id.* at 19:14–21. The mutated envelope protein may include “at least one mutation that inhibits the envelope protein’s ability to bind its native target, while preserving the envelope protein’s fusogenic properties,” and may be “a vesicular stomatitis virus G protein (‘VSV-G’, ‘VSV-G envelope protein’ or ‘VSV-G protein’) that includes one or more mutations that inhibit binding of VSV-G to the low-density lipoprotein receptor (‘LDL-R’), while preserving the VSV-G protein’s fusogenic function.” *Id.* at 19:27–20:2. According to Perkins, its LVV are “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.” *Id.* at 19:17–19. For example, in some embodiments, the transgene encodes a chimeric antigen receptor (“CAR”). *Id.* at 20–21.

Perkins provides nucleic acid and amino acid reference sequences for a wild type VSV-G envelope protein and examples of mutated VSV-G envelope proteins in Table 10, including SEQ ID NO: 78 and SEQ ID NO: 90, excerpted below. *Id.* at 20:11–21.

Table 10: WT VSV-G reference and mutant sequences

WT VSV-G	
Nucleotide	Amino acid (signal sequence <u>underlined</u>)
ATGAAGTGTCTGCTGTACCTGGCGT TCCTGTTTATCGGGGTGAAC T GCAA GTTCACTATCGTGTTC CGCACAAAC CAAAAGGGCAACTGGAAAAACGTG CCTTCAAATTACCATTATTGCCCA GCAGCTCGGACCTGAACTGGCACA ATGACCTCATTGGAACCGCGCTGCA GGTGAAGATGCCAAAGAGCCACAA GGCTATCCAGGCTGACGGATGGAT GTGCCACGCGTCAAAATGGGTGAC TACCTGCGATTTCCGCTGGTACGGA CCAAAATACATCACGCACAGCATC AGATCATTACCCCGTCAGTGGAAC AATGCAAAGAATCCATCGAACAGA CTAAGCAGGGAACCTGGCTGAACC CTGGATTTCCGCCGCAGTCGTGTGG GTACGCAACCGTGACCGATGCAGA GGCCGTGATCGTGCAAGTCACGCC GCATCACGTGCTTGTGGACGAGTAC ACCGGAGAATGGGTGCGATTCCCAG TTCATCAACGGCAAGTGCTCCAAC ACATTTGCCCAACCGTGCAACACAG CACTACTTGGCACAGCGACTACAA AGTGAAGGGTCTGTGTGATTCCAAC CTGATCTCCATGGATATCACTTTCT TCTCGGAAGACGGCGAACTGTCCTC ACTGGGCAAAGAAGGAACTGGGTT TCGCTCAAATTACTTCGCCTACGAA ACTGGAGGAAAAGCCTGCAAGATG CAGTACTGCAAGCACTGGGGCGTG AGACTACCCAGCGGTGTCTGGTTCG AGATGGCCGATAAGGACCTGTTTGC	<u>MKCLLYLAFLFIGVNCKFTIVFPHN</u> QKGNWKNVPSNYHYCPSSSDLNW HNDLIGTALQVKMPKSHKAIQADG WMCHASKWVTTCDFRWYGPKYIT HSIRSFTPSVEQCKESIEQTKQGTWL NPGFPPQSCGYATVTDAEAVIVQVT PHHVLVDEYTG EWVDSQFINGKCS NYICPTVHNSTTWHS DYKVKGLCD SNLISMDITFFSEDGELSSLGKEGTG FRSNYFAYETGGKACKMQYCKHW GVRLPSGVWFEMADKDLFAAARFP ECPEGSSISAPSQTSVDVSLIQDVERI LDYSLCQETWSKIRAGLPISPVDLS YLAPKNPGTGPAFTIINGTLKYFETR YIRVDIAAPILSRMVGMI SGT TTERE LWDDWAPYEDVEIGPNGVLRTSSG YKFPLYMIGHGMLDSDLHLSSKAQ VFEHPHIQDAASQLPDDES LFFGDT GLSKNPIELVEGW FSSWKSSIASFFF IIGLIIGLFLVLRVGIHLCKLKHTKK RQIYTDIEMNRLGK (SEQ ID NO: 78)

AGCAGCGAGATTCCCGGAATGCCC TGAGGGATCGAGCATCTCCGCTCCA AGCCAAACTTCAGTGGACGTGAGC CTGATCCAGGACGTGGAACGGATT CTCGACTACTCGCTGTGCCAGGAGA CCTGGTCGAAGATCAGAGCGGGAC TGCCCATCTCACCGGTGGACCTGTC CTACCTGGCGCCAAAGAATCCGGG CACTGGACCGGCGTTCACCATCATC AACGGCACCTCAAATACTTCGAG ACGCGGTACATCCGGGTGGACATC GCAGCTCCGATCCTCTCCCGGATGG TGGAATGATCTCGGGGACTACTAC CGAACGCGAGCTCTGGGACGACTG GGCACCTTACGAGGATGTCGAGAT CGGACCTAACGGAGTGCTCCGGAC CTCCTCCGGGTACAAGTTCCCTCTG TACATGATCGGCCATGGCATGCTGG ACTCGGATCTGCATCTGTCTGCTCAA AGCACAGGTGTTTGAACACCCACA CATTCAAGACGCCGCCAGCCAGCT GCCGGACGATGAGTCGCTGTTCTTC GGAGACACGGGCTTGTCAAAGAAT CCCATCGAGCTGGTGAAGGATGG TTTTCATCCTGGAAAAGCAGCATCG CTTCATTCTTCTTCATCATTGGCCTG ATCATCGGCCTATTTCTAGTCCTGC GGGTGGGAATTCATCTGTGCATCAA GCTCAAGCACACTAAGAAGCGGCA AATCTACACTGATATCGAGATGAAT CGCCTGGGCAAG (SEQ ID NO: 77)	
WT VSV-G Signal Sequence	
Nucleotide	Amino acid
ATGAAGTGTCTGCTGTACCTGGCGT TCCTGTTTATCGGGGTGAACTGC (SEQ ID NO: 87)	MKCLLYLAFLFIGVNC (SEQ ID NO: 88)
WT VSV-G without signal sequence	
Nucleotide	Amino acid
AAGTTCACTATCGTGTTTCCGCACA ACCAAAAGGGCAACTGGAAAAACG TGCCTTCAAATTACCATTATTGCC CAGCAGCTCGGACCTGAACTGGCA CAATGACCTCATTGGAACCGCGCTG CAGGTGAAGATGCCAAAGAGCCAC AAGGCTATCCAGGCTGACGGATGG ATGTGCCACGCGTCAAATGGGTG	KFTIVFPHNQKGNWKNVPSNYHYC PSSSDLNWHNDLIGTALQVKMPKS HKAIQADGWMCHASKWVTTCDFR WYGPKYITHSIRSFTPSVEQCKESIE QTKQGTWLNPGFPPQSCGYATVTD AEAVIVQVTPHHVLVDEYTG EWVD SQFINGKCSNYICPTVHNSTTWHS D YKVKGLCDSNLISMDITFFSEDGEL

ACTACCTGCGATTTCGCTGGTACG GACCAAAATACATCACGCACAGCA TCAGATCATTCACCCCGTCAGTGGA ACAATGCAAAGAATCCATCGAACA GACTAAGCAGGGAACCTGGCTGAA CCCTGGATTTCGCCGCGAGTCGTGT GGGTACGCAACCGTGACCGATGCA GAGGCCGTGATCGTGCAAGTCACG CCGCATCACGTGCTTGTGGACGAGT ACACCGGAGAATGGGTGCGATTCCC AGTTCATCAACGGCAAGTGCTCCAA CTACATTTGCCCAACCGTGCAACA AGCACTACTTGGCACAGCGACTAC AAAGTGAAGGGTCTGTGTGATTCCA ACCTGATCTCCATGGATATCACTTT CTTCTCGGAAGACGGCGAACTGTCC TCACTGGGCAAAGAAGGAACTGGG TTTCGCTCAAATTACTTCGCCTACG AAACTGGAGGAAAAGCCTGCAAGA TGCAGTACTGCAAGCACTGGGGCG TGAGACTACCCAGCGGTGTCTGGTT CGAGATGGCCGATAAGGACCTGTTT GCAGCAGCGAGATTCCCGGAATGC CCTGAGGGATCGAGCATCTCCGCTC CAAGCCAAACTTCAGTGGACGTGA GCCTGATCCAGGACGTGGAACGGA TTCTCGACTACTCGCTGTGCCAGGA GACCTGGTCGAAGATCAGAGCGGG ACTGCCCATCTCACCGGTGGACCTG TCCTACCTGGCGCCAAAGAATCCG GCACTGGACCGGCGTTCACCATCAT CAACGGCACCTCAAATACTTCGAG ACGCGGTACATCCGGGTGGACATC GCAGCTCCGATCCTCTCCCGGATGG TGGAATGATCTCGGGGACTACTAC CGAACGCGAGCTCTGGGACGACTG GGCACCTTACGAGGATGTCGAGAT CGGACCTAACGGAGTGCTCCGGAC CTCCTCCGGGTACAAGTCCCTCTG TACATGATCGGCCATGGCATGCTGG ACTCGGATCTGCATCTGTCGTCCAA AGCACAGGTGTTTGAACACCCACA CATTCAAGACGCCGCCAGCCAGCT GCCGGACGATGAGTCGCTGTTCTTC GGAGACACGGGCTTGTCAAAGAAT CCCATCGAGCTGGTGGAAGGATGG TTTTCATCCTGGAAAAGCAGCATCG CTTCATTCTTCTTCATCATTGGCCTG ATCATCGGCCTATTCTAGTCCTGC	SSLGKEGTGFRSNYFAYETGGKAC KMQYCKHWGVRLPSGVWFEMAD KDLFAAARFPECPEGSSISAPSQTSV DVS LIQDVERILDYSLCQETWSKIR AGLPISPVDLSYLAPKNPGTGPAFTI INGTLKYFETRYIRVDIAAPILSRMV GMISGTTTERELWDDWAPYEDVEI GPNGVLRTSSGYKFPLYMIGHGML DSDLHLSSKAQVFEHPHIQDAASQL PDDESLFFGDTGLSKNPIELVEGWF SSWKSSIASFFFIIIGLIIGLFLVLRVGI HLCIKLKHTKKRQIYTDIEMNRLGK (SEQ ID NO: 90)
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GGGTGGGAATTCATCTGTGCATCAA GCTCAAGCACACTAAGAAGCGGCA AATCTACACTGATATCGAGATGAAT CGCCTGGGCAAG (SEQ ID NO: 89)	
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Id. at 73–76. According to Perkins,

SEQ ID NO: 77 is a reference nucleic acid sequence encoding the VSV-G envelope protein, and SEQ ID NO: 78 is an amino acid sequence of a reference VSV-G envelope protein. SEQ ID NO: 87 is a nucleic acid sequence encoding a cleavable signal peptide of the reference VSV-G envelope protein. SEQ ID NO: 88 is an amino acid sequence of the cleavable signal peptide of the reference VSV-G envelope protein. SEQ ID NO: 89 is a reference nucleic acid sequence encoding the VSV-G envelope protein, absent the signal sequence. SEQ ID NO: 90 is an amino acid sequence of a reference VSV-G envelope protein absent the sequence.

Id. at 20:13–21.

Perkins explains that

In 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. In 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 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. In 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 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. . . . In 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 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. 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. In some embodiments, a mutated VSV-G envelope protein is selected from one or more of an H8A, N9A, Q10A, K47A, K47Q, N180A, **I182A**, Y209A, T352A, T352W, E353A, R354A, and R354Q mutation.

Id. at 20:29–22:5 (emphasis added). Additionally, Perkins discloses that “[i]n specific embodiments, the mutant VSV envelope protein comprises a N180A mutation, an **I182A** mutation, a T352A mutation, and an E353A mutation.” *Id.* at 22:23–24 (emphasis added).

2. *Hwang (Ex. 1007)*

Hwang is titled “Engineering a serum-resistant and thermostable vesicular stomatitis virus G glycoprotein for pseudotyping retroviral and

lentiviral vectors.” Ex. 1007, 807.⁴ Hwang explains that “[v]esicular stomatitis virus G glycoprotein (VSV-G) is the most widely used envelope protein for retroviral and lentiviral vector pseudotyping.” *Id.* According to Hwang, “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.” *Id.* at 813.

Hwang states that “serum inactivation of VSV-G pseudotyped vectors is a significant challenge for *in vivo* gene delivery.” *Id.* at 807. To address this problem, Hwang’s authors “conducted directed evolution of VSV-G to increase its resistance to human serum neutralization” and created “serum-resistant and thermostable VSV-G variants [that] may aid the application of retroviral and lentiviral vectors to gene therapy.” *Id.* Hwang reports that the authors “successfully created variants with higher resistance to human, rabbit and mouse sera *in vitro* and human serum *in vivo*.” *Id.* at 812.

Hwang discloses that its “S162T, T230N and T368A mutations enhanced serum resistance, and additionally K66T, T368A and E380K substitutions increased the thermostability of VSV-G pseudotyped retroviral vectors.” *Id.* at 807. Hwang also discloses that its “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,” and “lentiviral vectors pseudotyped with these variants were more resistant to human serum in a murine model.” *Id.*; *see also id.* at 809. According to Hwang, the

⁴ Page number citations for Exhibit 1007 correspond to the original page numbers on the top corner of each page.

authors' work "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." *Id.* at 812–13.

3. *RCSB PDB (Ex. 1025 and Ex. 1026)*

RCSB PDB includes entries 5OY9 and 5OYL which provide structures of VSV G CR3 and VSV G CR2 proteins, respectively, deposited in the Research Collaboratory for Structural Bioinformatics ("RCSB") Protein Databank ("PDB") in September 2017 by Albertini. *See* Ex. 1025, 1; Ex. 1026, 1; *see generally* Ex. 1024 (describing the origins, maintenance, and uses of the PCSB PDB). Entries 5OY9 and 5OYL were released on March 21, 2018 and are discussed in Nikolic. Ex. 1025, 1; Ex. 1026, 1; Ex. 1018, 11. Nikolic describes the crystal structures of VSV G bound to its native LDL-R receptor and indicates that the structures were deposited in the PDB and are available under accession codes 5OYL and 5OY9. *See* Ex. 1018, 4, 11.

B. *Prior Art Status of Perkins*

Petitioner contends Perkins qualifies as prior art to the '366 patent under 35 U.S.C. § 102(a)(2) based on the filing date of the Perkins Provisional. Pet. 4, 18–20.

Patent Owner contends Perkins does not qualify as prior art to the '366 patent because Perkins includes disclosures that are not present in the Perkins Provisional. Prelim. Resp. 15–22. Patent Owner argues that "the priority application must actually describe the subject matter relied on for the earliest filing date to be the effective prior art date of the reference." *Id.* at 17. Patent Owner contends "Perkins *could* be prior art to the '366 patent based on its priority claim to the Perkins provisional application. . . .

However, for the *subject matter* of Perkins to be considered prior art, the priority application—the Perkins Provisional—must ‘describe[] the subject matter’ on which [Petitioner] relies.” *Id.* at 19.

Having considered the parties’ positions and evidence of record, summarized above, we agree with Patent Owner that Perkins is prior art to the ’366 patent only to the extent that the subject matter disclosed in Perkins is likewise described in the Perkins Provisional. Accordingly, we do not consider Petitioner’s arguments that rely on subject matter unsupported by the Perkins Provisional. For example, support for Petitioner’s argument that Perkins discloses “mutant VSV-G envelope protein containing only four mutations at N180, **I182**, T352, and E353” is not found in the Perkins Provisional and is therefore not considered. Pet. 73 (quoted with Petitioner’s emphasis). Thus, insofar as Petitioner is suggesting that Perkins describes a list of mutations that is narrowed to four positions including a mutation at I182, rather than a listing of thirteen potential positions for mutations (and various combinations thereof with hypothetical mutations at a variety positions), we find no such narrower listing in the Perkins Provisional. *Compare* Ex. 1005, 22:2–5, *with* Ex. 1006, 17–18.

C. Ground 1: Anticipation by Perkins

1. Petitioner’s Contentions

Petitioner contends that claims 1–3 and 10–25 are unpatentable as anticipated by Perkins. Pet. 26–53. To support its contentions, Petitioner provides a claim analysis addressing how Perkins discloses each element of claims 1–3 and 10–25. *Id.* With regard to the “I182E mutation” and “I182D mutation” recited in independent claims 1 and 2, Petitioner contends that Perkins discloses a mutation at amino acid position I182 and, while Perkins

does not specify what “I” is replaced with at position 182, a POSA would “understand that Perkins allows substituting amino acid ‘I’ with any of the other 19 natural amino acids besides isoleucine(‘I’).” *Id.* at 33–34, 38 (citing Ex. 1002 ¶¶ 83, 93).

Petitioner relies heavily on *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005) to support the proposition that

the Federal Circuit has repeatedly analyzed each genus in a list separately from the other genera in the list. In *Perricone v. Medicis Pharm. Corp.*, the prior art disclosed a list of fourteen genera of ingredients, with each genera comprising at least twenty members, if not 2000 members. 432 F.3d 1368, 1376 (Fed. Cir. 2005). There, the Federal Circuit held that the prior art anticipated claims that required subgenera of one specific ingredient in that list. 432 F.3d 1368, 1376–77 (Fed. Cir. 2005).

Pet. 35. Petitioner further contends that

Moreover, the Federal Circuit in *In re Gleave* held that the prior art, which comprised a list of more than 1400 members of fifteen-base-long oligodeoxynucleotides that coded for parts of a protein, anticipated specific 18-22 base-pair-long nucleotides that were complementary to the nucleotides that coded for parts of the protein. 560 F.3d 1331, 1333-34, 1337-38 (Fed. Cir. 2009). The Federal Circuit relied on the prior art’s disclosure that “[the complementary] oligonucleotides are preferably between fifteen and twenty-five bases in length,” to show anticipation in view of the list of more than 1400 members. *Id.* at 1333. In other words, the Federal Circuit treated each member of the list of nucleotides that coded for parts of a protein as a separate genus comprising 15-25-base-long oligodeoxynucleotides.

Id.

Thus, according to Petitioner, Perkins discloses the “I182” mutation and a genus of 19 possible mutations. *Id.* at 34. “Because each listed genera is treated separately, a POSA would ‘at once envisage each member of this

limited class.” *Id.* at 36 (citing *In re Petering*, 301 F.2d 676, 681–82 (CCPA 1962)).

2. *Patent Owner’s Contentions*

Patent Owner contends that “[t]he law on anticipation of a claimed species by a disclosed genus is very clear—‘[t]he prior art may be deemed to disclose each member of a genus when, reading the reference, a person of ordinary skill can ***at once envisage each member of this limited class.***’”

Prelim. Resp. 22–23 (citing *Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.*, 50 F.4th 147, 152 (Fed. Cir. 2022) (internal quotations omitted) (emphasis added)). That is, “where the claimed species is explicitly named, but is included among a list of other possibilities, the number of members in the list is will not avoid a finding of anticipation.” *Id.* at 23 (citing *In re Gleave*, 560 F.3d 1331, 1337–38 (Fed. Cir. 2009)).

Patent Owner argues, however, that the law treats lists and genera differently for the purposes of finding anticipation, where the disclosure of a genus is generally not anticipatory to a species encompassed by the genus disclosed in the prior art. *Id.* at 24 (citing *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999–1000 (Fed. Cir. 2006) (Patent Owner relying on the “holding that the district court clearly erred by finding that prior art reference that disclosed temperature range of 100–500° C anticipated claimed range of 330–450° C and explaining ‘[t]here may be many species encompassed within a genus that are not disclosed by a mere disclosure of the genus’”). According to Patent Owner, as “there is no dispute that neither Perkins nor the Perkins Provisional explicitly discloses an anticipatory species,” Petitioner cannot establish anticipation. *Id.* at 24–25.

Replying solely on the disclosure in the Perkins Provisional, Patent Owner contends that “the Perkins Provisional does not contain any disclosure of an I182E or I182D mutation.” *Id.* at 25. Patent Owner further contends that, “[i]n every mention of a mutation at location I182 in the Perkins Provisional, the I182 mutation is listed as one of twenty or more possible mutation cites or changes to the VSV-G envelope protein.” *Id.* Patent Owner further contends that

As [Petitioner] admits, a POSA would have appreciated that there are 20 natural amino acids, meaning that each of the mutations listed in the Perkins Provisional could be switched with any of the 19 other amino acids available. Pet. at 33, 36. Just on its face, the exemplary list quoted above includes 254 possible mutations. . . . Taken together with the fact that the Perkins Provisional discloses that “one or more” of these mutations can be made together, this disclosure explodes to more than 19^{13} , or over 42 quadrillion, possibilities.

Id. at 26–27.

3. Discussion

“[T]he disclosure of a small genus may anticipate the species of that genus even if the species are not themselves recited.” *Bristol–Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1380 (Fed. Cir. 2001); *see also, Atofina*, 441 F.3d at 999 (“[A] very small genus can be a disclosure of each species within the genus.” (citing *In re Petering*, 301 F.2d at 682)). In *Petering*, for example, the prior art disclosed a small genus of only 20 compounds that included the claimed species. *In re Petering*, 301 F.2d at 682. In its discussion concluding that a small genus may anticipate a species of that genus, the Court of Customs and Patent Appeals explained that “it is not the mere number of compounds in this limited class which is significant here, but rather, the total circumstances involved, including such factors as

the limited number of variations for R, only two alternatives for Y and Z, no alternatives for the other ring positions, and a large unchanging parent structural nucleus.” *Id.* at 681–682. Having considered the parties’ positions and evidence of record, summarized above, we do not find that Perkins discloses a limited class as exemplified in *Petering*.

To begin, while it is undisputed that Perkins discloses a class of mutant VSV-G envelope proteins that encompasses the recited I182E or I182D mutations, it is also undisputed that Perkins does not disclose the I182E or I182D mutations. Prelim. Resp. 22. Furthermore, and by contrast to the limited class of compounds at issue in *Petering*, Perkins discloses a class of mutant VSV-G envelope proteins defined as proteins containing one or more of 20 possible mutations or alterations, a class that includes at least 254 proteins. Ex. 1006, 17–18; Prelim. Resp. 26–27. Furthermore, as Patent Owner correctly points out, “[t]he Perkins Provisional does not include any disclosure of the specific mutations to be made at any of these locations. That is, the Perkins Provisional does not indicate the other amino acid(s) to be substituted at the listed locations.” Prelim. Resp. 26. Thus, Perkins fails to provide a POSA with a “‘pattern of preferences’ that serves to narrow the genus.” *See, e.g., Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1377 (Fed. Cir. 2006) (“there is no such clear ‘pattern of preferences’ [as found in *Petering*] that serves to narrow the genus in claim 2 to a narrow class that includes clopidogrel bisulfate”).

We are not persuaded that *Gleave* or *Perricone* supports Petitioner’s proposition that each genus disclosed within a list of genera is analyzed individually for the purposes of accessing anticipation. Pet. 24, 35. Rather, we find *Gleave* or *Perricone* to support Patent Owner’s contentions that,

“where the claimed species is explicitly named, but is included among a list of other possibilities, the number of members in the list [] will not avoid a finding of anticipation.” Prelim. Resp. 23. In *Gleave*, the Federal Circuit expressly addressed the issue of lists of large numbers of compounds, where the “list includes more than 1400 sequences.” The court found that the prior art reference “expressly lists every possible fifteen-base-long oligodeoxynucleotide sequence in IGFBP-2, and under our precedent, this list anticipates Gleave’s claims” encompassing oligodeoxynucleotide sequences contained within the list. *In re Gleave*, 560 F.3d at 1338. In this case, however, it is undisputed that Perkins fails to explicitly list the I182E or I182D mutations.

Additionally, both parties discuss the issues presented in *Perricone*, however, we find that *Perricone* also better supports Patent Owner’s position—*Perricone* involved a claimed species that was explicitly named and thus distinguishable from the facts here. Prelim. Resp. 23–24. In *Perricone*, the Federal Circuit upheld the district court’s finding that claims directed to the “treatment or prevention of various forms of skin damage through topical application of ascorbic acid (Vitamin C) in a fat soluble form” were anticipated by a prior art reference disclosing a cosmetic composition and “eight distinct example compositions with specific concentrations of ingredients.” *Perricone*, 432 F.3d at 1371–76. The challenged patent disclosed “the topical application of ascorbyl fatty acid ester (e.g., ascorbyl palmitate, ascorbyl laurate, ascorbyl myristate, ascorbyl stearate) with a dermatologically acceptable carrier.” *Id.* at 1371. The prior art reference disclosed “a total of fourteen skin benefit ingredients,” one of which was ascorbyl palmitate. *Id.* at 1376. The Federal Circuit “rejecte[d]

the notion that one of these ingredients cannot anticipate because it appears without special emphasis in a longer list.” *Id.* Rather, the Federal Circuit concluded “the disclosure is prior art to the extent of its enabling disclosure.” *Id.* (citing *Hewlett-Packard Co. v. Mustek Sys., Inc.*, 340 F.3d 1314, 1324 n.6 (Fed. Cir. 2003)). The Federal Circuit noted that “the prior art does not merely disclose a genus of skin benefit ingredients without disclosing the particular claimed ingredient. Rather the prior art specifically disclose[d] ascorbyl palmitate.” *Id.* at 1377. Thus, the Federal Circuit concluded “[t]hat specific disclosure, even in a list, makes this case different from cases involving disclosure of a broad genus without reference to the potentially anticipating species.” *Id.*

Moreover, we agree with Patent Owner that the facts in this case are more akin to *Mylan*. Prelim. Resp. 23–24. In *Mylan*, the challenged claims were directed to a sitagliptin dihydrogenphosphate salt (“sitagliptin DHP”) with a 1:1 stoichiometry. *Mylan*, 50 F.4th at 150. “Sitagliptin DHP belongs to the class of dipeptidyl peptidase-IV (“DP-IV”) inhibitors, which can be used for treating non-insulin-dependent (i.e., Type 2) diabetes.” *Id.* at 150. The asserted prior art disclosed a genus of DP-IV inhibitors and 33 species, one of which was a sitagliptin hydrochloride salt (“sitagliptin HCl”), for “the treatment or prevention of diseases . . . such as diabetes.” *Id.* at 151. Upon consideration of these facts, the Federal Circuit upheld the Board’s determination that there was no express disclosure of all of the limitations of the 1:1 sitagliptin DHP salt, and thus, the reference was not anticipatory. *Id.* at 153 (“the Board did not err in determining that [the prior art reference] does not inherently disclose a 1:1 sitagliptin DHP salt”). In doing so, the Federal Circuit noted that the prior art’s “list of 33 compounds, with no

direction to select sitagliptin from among them, plus the eight ‘pharmaceutically preferred’ acids and various stoichiometric possibilities, results in 957 salts . . . [which] is a far cry from the 20 compounds ‘envisaged’ by the narrow genus in *Petering*.” *Id.* at 153–54 (citing *Petering*, 301 F.2d at 681). The Federal Circuit declined to “provide a specific number defining a ‘limited class’,” but noted that “a class of 957 predicted salts that may result from the 33 disclosed compounds and eight preferred acids . . . is insufficient to meet the ‘at once envisage’ standard set forth in *Petering*.” *Id.* at 154.

By comparison, we determine on this record that a genus of at least 254 proteins that may result from mutating a VSV-G envelope protein at the positions disclosed in Perkins—only one of which is I182—to replace the disclosed amino acids with any one of 19 other natural amino acids, and without any attempt to narrow the genus by way of disclosure as to which of the 19 disparate amino acids would achieve common or otherwise desired structural and functional properties does not provide an anticipatory disclosure of the protein with an I182E or I182D mutation as claimed. Petitioner’s argument here is insufficient to meet the “at once envisage” standard set forth in *Petering*.

4. Conclusion

Having considered the evidence and argument presented by the parties, we are not persuaded that Petitioner has shown it is more likely than not that Perkins anticipates the challenged claims.

D. Ground 3: Obviousness over Perkins and RCSB PDB

1. Petitioner's Contentions

Petitioner contends that claims 1–3 and 10–25 would have been obvious over Perkins and RCSB PDB. Pet. 64–82. To support its contentions, Petitioner provides a claim analysis addressing how the combination of Perkins and RCSB PDB discloses each element of claims 1–3 and 10–25. *Id.* Petitioner contends that a person of ordinary skill would have been motivated to make the I182D and I182E mutations to the VSV-G envelope protein disclosed in Perkins with a reasonable expectation of success in making the mutation. *Id.* at 64–78. Petitioner supports its contentions with Dr. Rose's declaration. *Id.* (citing Ex. 1002 ¶¶ 188–218, 223–224).

In particular, Petitioner contends that “Perkins specifically disclosed a mutation at amino acid position I182 of SEQ ID NO: 90, . . . among 13 other amino acid positions for making one, two, or more mutations.” *Id.* at 65 (citing Ex. 1005, 20:29–21:27; Ex. 1006, 17–18). Petitioner contends that Perkins discloses the I182 mutation among a “finite set” and, therefore, “it would have been obvious for a POSA to make a I182 mutation to Perkins' VSV-G envelope protein.” *Id.* Petitioner further contends that a “POSA would have understood Perkins' disclosure of a mutation at amino acid position I182 means a substitution of a single amino acid at position 182 . . . and that, by default, the genus of possible amino acids to be the other 19 natural acids besides isoleucine.” *Id.* at 66 (citing Ex. 1005, 20:29–21:14, 21:16–27; 22:2–3; Ex. 1006, 17–18, 1002 ¶ 192).

Petitioner contends that a POSA would have envisaged “an even smaller subset of amino acids” given the preference in Perkins for mutations

that inhibit the ability of VSV-G to bind its native target. *Id.* (citing Ex. 1005, 19:26–29; Ex. 1006, 16; 1002 ¶ 193.) Specifically, according to Petitioner, a POSA would have not considered leucine (L) and valine (V) mutations, which are conservative substitutions for isoleucine (I) that would likely maintain rather than alter VSV-G binding characteristics. *Id.* at 67 (citing Ex. 1023, 9–10; Ex. 1002 ¶ 195). A POSA would allegedly have also excluded proline (P) and cysteine (C) mutations as these mutations would likely add unwanted changes to the VSV-G protein structure. *Id.* at 68 (citing Ex. 1002 ¶ 196). Thus, according to Petitioner, the genus of suitable amino acids to replace isoleucine is reduced to 15. *Id.* (citing Ex. 1002 ¶ 197).

Petitioner further contends that, based on the guidance in Perkins, it would have been obvious “to make a mutation at I182 to inhibit VSV-G’s ability to bind its native target receptor, coupled with the location of I182 in the 3D crystal structure of VSV-G bound to its native target receptor, LDL-R, which was available to a POSA in the *RCSB PDB*.” Pet. 69 (citing Ex. 1005, 19:26–29; Ex. 1006, 16; Ex. 1025, 1; Ex. 1026, 1; Ex. 1002 ¶ 198). Petitioner contends that,

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

Pet. 70. According to Petitioner, “it would have been immediately apparent to a POSA,” with the understanding of the well-known concept of anionic repulsion, “that mutation of isoleucine—which is neither polar or charged—to a negatively charged amino acid such as glutamic acid (E) [or Aspartic

acid (D)] would have been likely to ablate any interaction between VSV-G and the LDL-R.” *Id.* at 70–71, 78 (citing Ex. 1002 ¶¶ 206, 223–224).

Petitioner contends that a “POSA would also have had a good reason to focus on Perkins’ express disclosure of a I182 mutation.” *Id.* at 72 (citing Ex. 1002 ¶ 208). According to Petitioner, “a POSA could have easily checked the 13 amino acid positions disclosed in Perkins for making a mutation” based on the published crystal structures of the VSV-G bound to the LDL-R. *Id.* at 72–73 (Ex. 1025, 1; Ex. 1002 ¶ 208). In doing so, “a POSA would have recognized that I182 is the closest out of the 13 disclosed amino acid positions in Perkins to an important aspartic acid residue in the CR3 domain” and that “I182 was the only amino acid out of the 13 disclosed amino acid positions that could potentially interact with a second negatively charged amino acid in the CR3 domain.” *Id.* at 73 (citing Ex. 1018, 7 (describing that “D108 and D112 on CR3” as “two acidic residues which belong to the octahedral calcium cage”)); Ex. 1002 ¶ 209 (Dr. Rose stating that “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.”). Petitioner contends that a “POSA would thus have concluded that I182 [is] one of the best of the 13 disclosed amino acid positions in Perkins for disrupting the interaction with the CR3 domain” and thus satisfying the disclosure in Perkins that, “[i]n 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.” *Id.* at 70, 73 (Ex. 1006, 16; Ex. 1002 ¶¶ 205, 210 (Dr. Rose opining that a POSA would

have been motivated to modify Perkins based on the VSV-G crystal structures in the RCSB PDB)).

Petitioner contends that a POSA would have had a reasonable expectation of success in making the I182E and I182D mutations because

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

Pet. 75; *see also* Ex. 1002 ¶ 215 (Dr. Rose opining that a POSA “would have appreciated that I182 is located in a different portion of the VSV-G crystal structure than the domains that were known to be involved in fusion” (citing Ex. 1018, 4 (FIG. 3)).

2. Patent Owner’s Contentions

Patent Owner contends that Petitioner advances

two theories for how a POSA would arrive at the claimed mutations: (1) that Perkins presents a “finite set” of possible mutations that are obvious to try; and (2) that the POSA could have used the RCSB PDB to arrive at the claimed mutations. Both of these theories fail.

Prelim. Resp. 31.

Patent Owner first contends that Petitioner’s characterization of Perkins disclosing a “finite set” of mutations is misleading. *Id.* at 32. Specifically, Patent Owner contends that Perkins discloses mutations at I182 among a list of 20 other possible locations for modifications in the VSV-G sequence, 13 of which are mutations at specific amino acid locations, each

of which can be changed to any of the 19 other natural amino acids. *Id.* Thus, according to Patent Owner, Perkins discloses 254 mutations, which when coupled together as “one or more” or “two or more” as disclosed in Perkins, becomes more than 42 quadrillion possible mutations, far from a “finite set” of mutations as alleged by Petitioner. *Id.* at 27, 32 (citing Ex. 1006, 17–18) (“Perkins Provisional discloses that ‘one, two, or more’ of the mutations can be made together”). Thus, according to Patent Owner, Perkins does not teach a finite list or limited class of mutations, but rather, Perkins fails to “provide[] any direction to a POSA regarding the choice of any particular mutation or combination of mutations that would work.” *Id.* at 33 (citing *Shire LLC v. Amneal Pharms., LLC*, 802 F.3d 1301, 1308 (Fed. Cir. 2015)). “At most, Perkins invites further experimentation concerning mutations to the VSV-G envelope protein with no guidance to adopt the mutations claimed in the patent.” *Id.*

Patent Owner contends that Petitioner’s analysis jumps directly to I182 without explanation of the motivation to do so. *Id.* Petitioner “does not even attempt to explain why a POSA would select a mutation at the 182nd position from the list of 12 other positions for a mutation, 6 positions for insertions, and one position for a deletion.” *Id.* Rather, “in arguing that a POSA would select an I182E or I182D mutation from the 19 possible mutations at position I182, [Petitioner] relies on conclusory statements that are guided by hindsight reasoning.” *Id.* at 34 (citing Pet. 66–70).

Patent Owner contends that Petitioner’s reliance on Perkins to further reduce the list of 19 possible mutations at position I182 to only 15 requires an improper picking-and-choosing approach. *Id.* (citing *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991)) (“It is impermissible, however, simply to

engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps."); *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014) (reversing finding of obviousness and criticizing expert for "rel[ying] on the [challenged] patent itself as her roadmap for putting what she referred to as pieces of a 'jigsaw puzzle' together.")).

Moreover, the extensive trial-and-error experimentation that a POSA would have to undertake to make and test all of the possible mutations that [Petitioner]'s argument contemplates merely confirms the non-obviousness of the claims. Applying [Petitioner]'s argument more broadly to the other possible mutations disclosed in the Perkins Provisional would lead to absurd results. Under [Petitioner]'s reasoning that Perkins itself would lead a POSA to make the claimed I182E and I182D mutations, the POSA would have also found essentially all 42 quadrillion possible mutations disclosed in the Perkins Provisional "obvious to try."

Prelim. Resp. 35–36.

Patent Owner further contends that Dr. Rose's testimony "parrots the language of the petition" and is conclusory and unsupported by evidence. *Id.* at 37–38. In particular, Patent Owner notes that Petitioner relies on two exhibits, Exhibits 2024 and 2027, to support its contention that a POSA would have "immediately recognized that I182 is nearby aspartic acid residues on the LDL-R that may be negatively charged." *Id.* at 38 (citing Pet. at 70). Patent Owner contends, however, that

a review of Exhibits 1024 and 1027 shows that they do not even mention aspartic acid, let alone "aspartic acid residues on the LDL-R that may be negatively charged." Exhibit 1024 provides a general description of the RCSB PDB and Ex. 1027 provides a general description of the UCSF Chimera. Thus, the only "evidence" supporting [Petitioner]'s contention that a POSA would have "immediately recognized that I182 is nearby aspartic

acid residues on the LDL-R that may be negatively charged”] is a conclusory statement from its expert. Such a statement is entitled to little weight, at most. [*Xerox Corp. v. Bytemark Inc.*], IPR2022-00624, Paper 9, at 15 (precedential); *see also* [*ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012)] (affirming JMOL of nonobviousness where defendant's expert offered only conclusory testimony).

Prelim. Resp. 39.

Patent Owner acknowledges that Petitioner

relies on the disclosure of Nikolic that “[t]wo basic residues of G (H8 from the TrD and K47 from PHD) are pointing toward two acidic residues which belong to the octahedral calcium cage of the CR domains (D69 and D73 on CR2; D108 and D112 on CR3 labeled I and II—Fig. 4a)” (Ex. 1018 at 7) for the proposition that “a POSA would have recognized that I182 is the closest out of the 13 disclosed amino acid positions in Perkins to an important aspartic acid residue in the CR3 domain,” but fails to explain why a POSA would consider those residues to be “important.” Moreover, [Petitioner] fails to explain why Perkins, which [Petitioner] admits cites and incorporates by reference Nikolic (Pet. at 69), did not take the disclosure of this “important acid residue” into consideration and expressly disclose a I182 mutation.

Prelim. Resp. 37 n.6. Indeed, according to Patent Owner, Petitioner

fails to reconcile its allegation that “[a] POSA would have had only two options out of the naturally occurring amino acids—glutamic acid (E) and aspartic acid (D)—to incorporate in lieu of isoleucine at position 182 and oppose an interaction with negatively charged residues through anionic repulsion” (Pet. at 71–72) with the reality that Perkins discloses a I182A mutation. Ex. 1005 at 21:28–30, 22:2–5, 22:23–24. The fact that Perkins discloses a I182A mutation, and not a I182D or I182E mutation, further evidences that [Petitioner]’s alleged motivation, “to incorporate a mutation which negated an interaction with the negatively charged residues in the LDL-R,” is purely based on improper hindsight reasoning.

Id. at 39 (citing *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) (“[T]he inventor’s own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art.”)).

3. Discussion

“When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 402 (2007). *KSR* thus suggests that an inference of obviousness may be supported where the number of options is “small or easily traversed.” *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

“Obviousness is a question of law based on underlying findings of fact.” *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009). A conclusion of obviousness is appropriate where the prior art “contain[s] detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.” *In re O’Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1988); *see also*, *In re Kubin*, 561 F.3d at 1359 (*KSR* “actually resurrects [the Federal Circuit]’s own wisdom in *In re O’Farrell*”). However, to render a claim obvious, prior art cannot be “vague” and must collectively, although not explicitly, guide an artisan of ordinary skill towards a particular solution. *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009). That is, when a field is “unreduced by direction of the prior art,”

and when prior art gives “no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful,” an invention is not obvious. *Bayer Schering*, 575 F.3d at 1347 (citing *In re O’Farrell*, 853 F.2d at 903).

Having considered the parties’ positions and evidence of record, summarized above, we are not persuaded that Perkins discloses a finite set or limited class of 19 mutations. Pet. 66. Rather, we agree with Patent Owner that Perkins discloses a large genus of mutant VSV-G polypeptides containing at least 254 species—“Perkins Provisional discloses mutations at I182 among a group of 20 other possible locations for modifications[,] . . . [13] of these 20 positions are specific amino acids that . . . can be changed to any of the 19 other natural amino acids”—each species combinable to create a vast number of species. Prelim. Resp. 32. Perkins does not indicate any preference among the 13 disclosed mutations, does not indicate any preference among the 19 other amino acids, and does not indicate any preference as to which mutations should be combined to successful effect. Ex. 1006, 17–18. Thus, while Perkins discloses that one or more mutations “inhibit the envelope protein’s ability to bind its native target, while preserving the envelope protein’s fusogenic properties,” beyond that, a POSA would have no direction for selecting the route to create the I182E or I182D mutations specified by the challenged claims among the various unpredictable alternatives suggested by Perkins. Ex. 1006 at 16; Ex. 1002 ¶ 193. We do not find this to be the easily traversed, small or finite number of alternatives that *KSR* suggested might support an inference of obviousness. *KSR*, 550 U.S. at 402.

There is no dispute that Perkins does not disclose the recited I182E or I182D mutations. Petitioner does not, and we do not, identify any teaching or suggestion in Perkins that would guide a POSA to make the specific I182E or I182D mutations. Indeed, as noted by Patent Owner, Petitioner

fails to reconcile its allegation that “[a] POSA would have had only two options out of the naturally occurring amino acids—glutamic acid (E) and aspartic acid (D)—to incorporate in lieu of isoleucine at position 182 and oppose an interaction with negatively charged residues through anionic repulsion” (Pet. at 71–72) with the reality that Perkins discloses a I182A mutation. Ex. 1005 at 21:28–30, 22:2–5, 22:23–24. The fact that Perkins discloses a I182A mutation, and not a I182D or I182E mutation, further evidences that [Petitioner]’s alleged motivation, “to incorporate a mutation which negated an interaction with the negatively charged residues in the LDL-R,” is purely based on improper hindsight reasoning.

Prelim. Resp. 39.

Petitioner attempts to fill that gap with reliance on RCSB PDB, Dr. Rose’s testimony (Ex. 1002 ¶¶ 195–219), and general knowledge of a person of ordinary skill in the art (Ex. 1022, 76–77; Ex. 1012, 120; Ex. 1023, 10). Pet. 64–76. As explained by Petitioner, RCSB PDB refers to the published crystal structures, known as “5OY9” and “5OYL” on the RCSB PDB, showing VSV-G bound to two distinct cysteine-rich domains, CR3 and CR2, of the LDL-R, respectively. *Id.* at 69–70 (citing Ex. 1025; Ex. 1026; Ex. 1002 ¶ 200). The RCSB PDB provides data for a POSA to produce and observe crystal structures, but does not itself contain any teaching or suggestion directing a POSA to create the I182E or I182D specified by the challenged claims. Rather, that suggestion is supplied by the bare testimony of Dr. Rose. Dr. Rose explains,

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 LDLR that may be negatively charged. (*See, e.g.*, Ex. 1024 at 569; Ex. 1027 at 1605.)

...

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.)

...

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 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.

Ex. 1002 ¶¶ 200, 205, 207.

We have considered Petitioner’s assertions and evidence of record, but are not persuaded. Perkins provides a list of many mutations and

combination thereof, but provides no direction as to which of the many possible choices is likely to be successful. Petitioner comes to the claimed I182E or I182D mutations by retracing the path of the inventor with hindsight accuracy supported only by the bare testimony of Dr. Rose, summarized above. This is particularly problematic in cases where, like here, expert testimony is offered not simply to provide a motivation to combine prior-art teachings, but rather to supply a limitation missing from the prior art. *See KSR*, 550 U.S. at 421 (stating that a “factfinder . . . must be cautious of arguments reliant upon ex post reasoning”); *Arendi S.A.R.L. v. Apple, Inc.*, 832 F.3d 1355, 1361–62 (Fed. Cir. 2016) (holding that reliance on common sense in an obviousness analysis is “typically invoked to provide a known motivation to combine, not to supply a missing claim limitation”) (emphasis omitted). Although doing so might be permissible when “the limitation in question [is] unusually simple and the technology particularly straightforward” (*id.* at 1362), we do not find that to be the case here, much less find sufficient evidentiary support for a determination that the navigation of RCSB PDB crystal structures to achieve the missing limitation would have been “*evidently and indisputably* within the common knowledge of those skilled in the art” (*id.* at 1365–66).

4. Conclusion

For the above reasons, we are not persuaded that Petitioner has sufficiently shown that the challenged claims would have been obvious over Perkins and RCSB PDB. Therefore, we are not persuaded that Petitioner has shown it is more likely than not that the challenged claims would have been obvious over the combination of Perkins and RCSB PDB.

E. Remaining Grounds

Petitioner additionally contends that claims 3–9 and 26–30 would have been obvious over the combination of Perkins and Hwang (Ground 2) and that claims 3–9 and 26–30 would have been obvious over the combination of Perkins, RCSB PDB and Hwang (Ground 3). As claims 3–9 and 26–30 depend from either claim 1 or claim 2, these proposed grounds of unpatentability rely on Perkins or the combination of Perkins and RCSB PDB rendering unpatentable claims 1 and 2. Therefore, because we are not persuaded that Petitioner has shown, more likely than not, that claims 1 and 2 would have been obvious over Perkins or the combination of Perkins and RCSB PDB, we decline to institute post-grant review of claims 3–9 and 26–30.

IV. CONCLUSION

Taking account of the information presented in the Petition, the Preliminary Response and the evidence of record, we determine that Petitioner has not met its burden under 35 U.S.C. § 324(a) and deny institution of post-grant review. Accordingly, the Petition is denied, and no trial is instituted.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied* as to all challenged claims, and no trial is instituted.

PGR2024-00008
Patent 11,767,366 B1

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