

PGR2024-00008
U.S. Patent No. 11,767,366

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KELONIA THERAPEUTICS, INC,
Petitioner,
v.

INTERIUS BIOTHERAPEUTICS, INC.,
Patent Owner

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

Case No. PGR2024-00008

PATENT OWNER'S PRELIMINARY RESPONSE

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Exhibit No.	Description of Document
2001	U.S. Patent Application Publication No. 2021/0106632 A1

Pursuant to 35 U.S.C. § 323 and 37 C.F.R. § 42.207, Patent Owner Interius Biotherapeutics, Inc. (“Interius”) submits this Patent Owner Preliminary Response to Kelonia Therapeutics, Inc.’s (“Kelonia”) Petition challenging claims 1-30 of U.S. Patent 11,767,366 (“the ’366 patent”). The Board should deny Kelonia’s Petition because Kelonia has not met its burden of establishing that there is a reasonable likelihood it would prevail with respect to at least one challenged claim.

As an initial matter, Kelonia relies on the same or substantially the same prior art that was before the Examiner during prosecution. Kelonia’s arguments supporting institution despite this overlap simply allege that the Examiner made a mistake by not agreeing with Kelonia’s view of the prior art. This is insufficient on its face, and the Board should exercise its discretion and deny this petition under § 325(d).

Kelonia’s arguments on the merits fare no better. Kelonia mischaracterizes the law regarding anticipation, and ignores the Federal Circuit’s precedent regarding when a disclosed genus anticipates a species—and when it does not. Under a proper reading of the law, Kelonia cannot prove that any claim of the ’366 patent is anticipated.

Kelonia’s obviousness arguments similarly fail because Kelonia makes no attempt to establish a motivation to arrive at the claims with a reasonable expectation of success. Kelonia has not shown that a person of ordinary skill in the art (“POSA”)

would have been motivated to (1) choose the claimed I182 mutation from the extensive disclosure of Perkins, (2) choose to make the specifically claimed mutations to I182, and (3) choose to further modify the protein with other mutations. Only through the benefit of hindsight can Kelonia draw these conclusions, and therefore they should be rejected.

Kelonia's petition fails to establish that there is a reasonable likelihood that Kelonia would prevail with respect to any challenged claim. Therefore, the Board should deny the petition.

I. TECHNOLOGY BACKGROUND

The inventions of the '366 patent relate to therapies to treat various types of cancer, including B-cell malignancies, such as B-cell lymphomas, B-cell leukemias, and plasma cell dyscrasias. B-cell lymphomas represent 80-85% of non-Hodgkin's lymphomas (NHL), and clinically they range from indolent to aggressive.

In particular, the inventions relate to CAR T-cell and CAR NK-cell therapies. CAR T-cell therapy is a type of treatment in which a patient's T cells (a type of immune system cell) are transformed into cells that attack cancer cells. In traditional *ex-vivo* CAR T-cell therapy, the CAR T-cells are formed outside a patient's body in a laboratory. In this process, genes for the chimeric antigen receptor or CAR are inserted into T-cells taken from the patient's blood to form millions of CAR T-cells. CAR is a special receptor that binds to a certain protein on the patient's cancer cells.

The CAR T-cells are then introduced back into the patient by infusion. CAR NK-cell therapies are similar except that NK, or natural killer, cells have an intrinsic cytotoxic quality that is then enhanced with the CAR genes.

However, patients receiving currently approved *ex-vivo* autologous CAR T-cell therapies require lymphodepleting chemotherapy prior to receiving a CAR T-cell infusion to prevent the patient's immune system from rejecting the treatment. Lymphodepleting chemotherapy involves toxic levels of fludarabine and cyclophosphamide prior to treatment that depletes the patient's existing immune cells, including their T-cells.

Interius has developed a novel product to produce CAR T-cells and/or CAR NK-cells *in vivo*, which avoids the use lymphodepleting chemotherapy. Additionally, the novel product avoids the necessity of having to produce a patient-specific product for each patient treated, which is in contrast to existing, approved *ex-vivo* CAR T-cell therapies. The invention of the '366 patent can be used to produce an off-the-shelf product that can be mass produced, similarly to any other biologic or gene therapy, since it does not require isolating immune cells from the patient prior to producing the drug product, i.e, the CAR T-cells and/or CAR NK-cells.

This is accomplished by administering a non-replicating, self-inactivating (SIN) lentiviral vector (LV) delivering a transgene for a CAR to the patient's T-cells

or NK-cells such that the CAR T-cell or CAR NK-cell is produced *in vivo*. The lentiviral vector is designed to generate CAR T-cells and CAR NK-cells *in vivo* following a single intravenous administration of the viral vector. However, if the lentivirus were to be administered without modifications it will not specifically infect the proper cell type and/or will have off-target effects.

To overcome the non-specific or non-desired infectious properties of a lentivirus, the Patentee has produced a pseudotyped lentivirus that utilizes the fusogenic properties of the glycoprotein of Vesicular Stomatitis Virus (“VSV-G”) in combination with a targeting agent, both of which are expressed on the surface of the virus. The combination allows the LV to specifically infect the patient’s T-Cells or NK-cells and produce the CAR T-cells or CAR NK-cells *in vivo*. However, the wild-type VSV-G protein, if used to target the LV, would bind to the Low Density Lipoprotein Receptor (LDL-R), which is ubiquitously expressed on many cell types, causing off-target effects and reducing the amount of VSV-G that is able to act as a targeting agent. Therefore, to overcome the non-specific issues related to the wild-type VSV-G protein, Patentee has invented a mutated VSV-G protein that retains its fusogenic properties while abrogating its binding to LDL-R. Thus, Patentee’s claimed VSV-G variant protein retains its fusogenic properties, but avoids infecting cells that are not specifically targeted by the targeting agent.

This invention, therefore, enables, in effect, a single treatment with a viral vector that results in the “manufacture” of autologous CAR T-cells and CAR NK-cells inside the patient without a requirement for lymphodepletion and the associated risks. As an off-the-shelf product, the products utilizing the present patented invention have the potential to meet a serious unmet medical need by providing a safer, more accessible, and cost-effective treatment option for cancer patients, including lymphoma patients relative to approved *ex vivo* CAR T-cell products.

II. THE '366 PATENT

The '366 patent, titled “Pseudotyped Viral Particles, Compositions Comprising The Same, And Uses Thereof,” issued from U.S. Application Ser. No. 18,066,420 (“the '420 application”) filed on December 15, 2022. The '420 application claims priority to U.S. Provisional Application Nos. 63/289,888 filed December 15, 2021; 63/289,977 filed December 15, 2021; 63/266,044 filed December 27, 2021; and 63/267,039 filed January 21, 2022.

As described above, the '366 patent relates to mutations of the VSV-G polypeptide, which is known to bind to a cell's LDL-R. Ex. 1001 at 1:28-32, 2:1-4. VSV-G is a protein that is made up of a 16 amino acid signal peptide followed by a 495 amino acid portion known as the ectodomain. *Id.* at 17:31-48; col. 121. The claims of the '366 patent are directed to VSV-G polypeptides that have specific mutations to the genetic sequencing of the ectodomain, namely mutations of the

amino acid at position 182. In the native VSV-G, the amino acid at position 182 is isoleucine or “I.” The claims of ’366 patent are directed to variations of this sequence where the I at position 182 is mutated to either aspartic acid (“D”), a mutation known as I182D, or to glutamic acid (“E”), a mutation known as I182E. *Id.* at 17:31-48, 145:10-18. The ’366 patent discloses that these I182D and I182E mutations improve the binding characteristics of the VSV-G polypeptide. *Id.* at 17:22-31.

III. EXPERT TESTIMONY

Kelonia alleges that its positions are supported by the testimony of Dr. John Rose, but Dr. Rose’s declaration merely parrots the exact statements that appear in the petition, without additional support or explanation. As such, the alleged expert testimony set forth in Ex. 1002 should be disregarded. *Compare, e.g.,* Paper 1, Petition for Post-Grant Review of U.S. Patent No. 11,767,366 (“Pet.”) at 65-72 *with* Ex. 1002 (Rose Decl.), ¶¶ 190-207. As the Board has stressed, conclusory and unsupported expert testimony is entitled to little weight. *Xerox Corp. v. Bytemark Inc.*, IPR2022-00624, Paper 9, at 15 (P.T.A.B. August 24, 2022) (precedential). Dr. Rose’s statements do not provide additional explanation that would assist the Board with its analysis and, therefore provide only the precise type of conclusory testimony that the Board has cautioned against.

IV. CLAIM CONSTRUCTION

Interius 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.

V. 35 U.S.C. § 325(d) SUPPORTS DENIAL OF THE PETITION BECAUSE THE EXAMINER CONSIDERED THE SAME AND SUBSTANTIALLY THE SAME PRIOR ART

Perkins¹, Hwang², and the subject matter of RCSB PDB on which Kelonia relies, i.e., the crystal structures of VSV-G bound to two regions of the LDL-R, were all before the Patent Examiner, and the application was allowed over those references. The Petition offers no evidence of error in that decision. The Petition should be denied on this basis alone.

In determining whether to institute proceedings, the Board may “reject the petition [where] the same or substantially the same prior art or arguments

¹ As used herein, “Perkins” refers to Published International Patent Application No. WO/2022/183072, which is Exhibit 1005.

² As used herein, “Hwang” refers to 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), which is Exhibit 1007.

previously were presented to the Office.” 35 U.S.C. § 325(d). The Board has articulated several nonexclusive factors that guide its application of § 325(d).

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8, at 17-18 (P.T.A.B. Dec. 15, 2017) (precedential). These factors have been

consolidated into two questions: (1) whether “the same or substantially the same art or arguments previously were presented to the Office”; and if so, (2) whether the “petitioner has demonstrated a material error by the Office.” *Advanced*

Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH, IPR2019-01469,

Paper 6, at 10 (P.T.A.B. Feb. 13, 2020) (precedential). Here, these factors strongly

favor discretionary denial. Kelonia’s petition relies on references (Perkins,

Hwang, and the crystal structures available in RCSB PDB) that the Patent Office

considered during prosecution, and Kelonia has not established that the Examiner

materially erred in issuing the ’366 patent. Discretionary denial is therefore

appropriate.

A. The Asserted Art Is Either the Same or Substantially the Same as the Prior Art Before the Examiner

Perkins, Hwang, and the crystal structures are the same as, or substantially the same as, references provided to the Examiner during prosecution. The

Advanced Bionics and *Becton, Dickinson* factors weigh against institution where the petitioner’s asserted references are the same as, or are materially

indistinguishable from, those previously before the Examiner. *See Exa Bio-Rad*

Labs., Inc. v. 10X Genomics, Inc., IPR2019-00566, Paper 21, at 7-8 (P.T.A.B. July 22, 2019) (finding that *Becton* factors (a) and (b) favored discretionary denial where two of the petitioner’s asserted references were before the Examiner and the third reference had no “material differences” from those before the Examiner); *see also Husky Injection Molding Sys., Ltd. v. Plastipak Packaging, Inc.*, IPR2020-00438, Paper 23, at 12 (P.T.A.B. July 29, 2020) (finding that the “first part of the *Advanced Bionics* framework”—*i.e.*, *Becton* factors (a), (b), and (d)—was satisfied where the reference in question “previously was presented to the Office during the prosecution”).

Here, there is virtually complete overlap between the art asserted in the petition and the art considered by the Examiner.

1. Perkins and Hwang Were Before the Examiner

There is no dispute that Perkins and Hwang were presented to the Office and before the Examiner during prosecution. *See* Pet. at 84. Kelonia’s assertion that “the Examiner was not aware of *Perkins*” is therefore unfounded. Interius submitted an Information Disclosure Statement (“IDS”) listing both Perkins and Hwang on January 30, 2023. *See* Ex. 1004 at 270, 272. The Examiner signed the IDS on June 17, 2023 and indicated that each reference had been considered. *Id.* at 1494, 1496; *see also* Ex. 1004 at 1498 (“All references considered except where lined through.”) (capitalization removed).

Therefore, the Examiner considered the exact references on which Kelonia relies for Grounds 1 and 2 and the primary reference on which Kelonia relies for Grounds 3 and 4, when allowing the '366 patent to issue. As a result, there can be no dispute that the first *Advanced Bionics* factor is satisfied with respect to Perkins and Hwang. *See Advanced Bionics*, IPR2019-01469, Paper 6, at 7-8; *see Biocon Pharma Ltd. v. Novartis Pharms. Corp.*, IPR2020-01263, Paper 12, at 9 (P.T.A.B. Feb. 16, 2021); *see Roku, Inc. v. Universal Elecs., Inc.*, IPR2019-01619, Paper 17, at 7 (P.T.A.B. May 25, 2021).

2. The Relevant Portions of the RCSB PDB Are Disclosed In the '366 Specification and Were Before the Examiner

The only other reference cited in the Grounds raised in the Petition is what Kelonia refers to as the Research Collaboratory for Structural Bioinformatics Protein Databank or RCSB PDB. Pet. at 3. The RCSB PDB is a digital resource that includes over 113,000 three-dimensional protein structures. *See Ex. 1024* at 1. Kelonia relies on two of these structures—a structure showing VSV-G bound to a portion of the lipoprotein receptor known as CR3 and a structure showing the VSV-G bound to another portion of the lipoprotein receptor known as the CR2 domain of LDL-R. Pet. at 69. In the RCSB PDB, these structures are identified as accession codes “5OY9” and “5OYL,” respectively. *Ex. 1018* at 11. Kelonia explains that the two structures were submitted to the database based on a 2018 study that was published by Nikolic et al., which is Exhibit 1018. Pet. at 11 n. 2.

Kelonia also notes that Nikolic et al, Exhibit 1018, disclosed that “[t]he atomic coordinates and structure factors have been deposited in the Protein Data Bank (accession code 5OYL and 5OY9).” Pet. at 69 n. 14.

According to Kelonia, “[a] POSA would have been motivated to modify *Perkins* based on the VSV-G crystal structures in the RCSB PDB . . . to incorporate a mutation which negated an interaction with the negatively charged residues in the LDL-R.” Pet. at 70. These “VSV-G crystal structures,” however, were considered by the Examiner. In fact, the specification of the ’366 patent actually refers to these specific structures in the Protein Databank, which it refers to by their “pdb” accession codes: “[u]sing a published crystal structures of VSV-G bound to CR2 and CR3 of the LDL-R (pdb 5OYL and 5OY9)” and references Figure 1. Ex. 1001 at 104:48-49. The specification describes Figure 1:

FIG. 1A and FIG. 1B illustrate crystal structures of VSV-G bound to LDL-R. FIG. 1A illustrates the crystal structure of VSV-G bound to CR3 of the LDL-R. FIG. 1B illustrates the crystal structure of VSV-G bound to CR2 of the LDL-R.

Ex. 1001 at 5:8-12. Thus, the Examiner was aware that the crystal structures of VSV-G bound to the CR3 and CR2 domains of LDL-R were known in the prior art as depicted in Figures 1A and 1B, and publicly found in the Protein Databank at accession codes 5OYL and 5OY9.

Moreover, Kelonia fails to acknowledge that Interius submitted Nikolic (Ex. 1018)—the study that Kelonia admits disclosed the protein structure—to the Patent Office in an IDS and that the Examiner considered it (*see* Ex. 1004 at 1497). Accordingly, the Examiner considered art that was substantially the same as RCSB PDB during prosecution.

That the Examiner did not reject the claims based on Kelonia’s references does not mean that they were not considered. To the contrary, the Board has held that submission through an IDS, with an indication that the references were considered, is sufficient. *See, e.g., Nespresso USA, Inc. v. K-Fee Sys. GmbH*, No. IPR2021-01222, Paper 9, at 11 (P.T.A.B. Jan. 18, 2022); *Biocon*, IPR2020-01263, Paper 12, at 9; *Cultec, Inc. v. Stormtech LLC*, No. IPR2017-00777, Paper 7, at 10 (P.T.A.B. Aug. 22, 2017) (informative). As discussed above, Kelonia submitted an IDS containing Perkins, Hwang, and Nikolic, and the Examiner signed the IDS with the notation that “all references [were] considered except where lined through.” Ex. 1003 at 1498 (capitalization removed). No references were lined through. *See id.* Kelonia’s argument that the Examiner did not “substantively consider” the prior art finds no basis in the record other than the fact that the Examiner did not reject the claims based on the arguments Kelonia raises here. Pet. at 84.

Thus, the Examiner considered the same or the substantially the same art as all of the references Kelonia relies upon for the Grounds in its Petition, satisfying the first prong of the *Advanced Bionics* analysis.

B. Kelonia Has Failed to Identify Any Material Error by the Examiner

Because the art in the Petition is substantially the same as that before the Examiner, Kelonia must “demonstrate[] a material error by the Office.” *Advanced Bionics*, IPR2019-01469, Paper 6, at 10. Kelonia has made no such showing here. As the Board has explained, a material error cannot be established “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments.” *Id.* at 9. At most, Kelonia claims error where it disagrees with the Examiner’s conclusion, which is insufficient to establish material error.

Kelonia speculates that the Examiner was not aware of Perkins because he did not refer to it as “the closest prior art” in the Notice of Allowance. Pet. at 14. But, Kelonia ignores that the reference the Examiner identified as the closest prior art (Kim) explicitly discloses the VSV-G protein with a substitution of the amino acid at residue 162. *See* Ex. 2001 (U.S. Pat. App. Pub. No. 2021/0106632 A1) at Abstract (“The present invention relates to a recombinant plasma membrane-based vesicle . . . comprising a VSV-G mutated protein in which histidine, the 162nd amino acid, has been substituted with arginine. . .”). Unlike in *Hum Indus.*, the Examiner did not identify a critical feature missing from the prior art that was, in

fact, present in a cited reference. That the Examiner cited Kim as the “closest prior art” reflects, at most, a reasonable disagreement concerning what reference would meet that standard. In no way does it suggest that the Examiner did not review and understand Perkins. Rather, a more reasonable conclusion is that the Examiner reviewed the art that was submitted and decided that a rejection over Perkins was unnecessary. The identification of Kim as the closest prior art is not a material error, and does not rise to the level of requiring this Board to reconsider the Examiner’s decision.

Kelonia mistakenly relies on *Hum Indus. Tech., Inc. v. Amsted Rail Co., Inc.*, IPR2023-00539, Paper 10 (P.T.A.B. July 26, 2023). In *Hum Indus.* the Board found that Petitioner established a material error where it identified a specific disclosure in the prior art that the Examiner obviously missed. The Petitioner demonstrated “the prior art relied upon [in the Petition] teaches the very limitation found by the examiner to be missing from the prior art.” *Id.* at 52. Unlike the Petitioner in *Hum Indus.*, Kelonia does not, and indeed cannot, point to a disclosure in the cited prior art that the Examiner misconstrued or ignored.

Finally, Kelonia does not offer any “additional evidence [or] facts [that] warrant reconsideration of the prior art or arguments.” *Becton*, IPR2017-01586, Paper 8, at 18. Kelonia attempts to supplement the references and arguments that were already before the Examiner with a declaration from a putative expert. *See*

Ex. 1002. But “the mere introduction of declaration testimony alone does not strongly support reconsideration of the prior art and arguments”—at best, an expert declaration might “slightly weigh[] against denying institution.” *Hisense Visual Tech. Co., Ltd. v. LG Elecs. Inc.*, IPR2020-01164, Paper 15, at 20 (P.T.A.B. Jan. 7, 2021). Here, moreover, the cited declaration fails to offer even that slight support. As discussed above (in Section III), the declaration merely repeats the arguments in the Petition and is entitled to little weight (at most).

As a result, each of the *Advanced Bionics/Becton, Dickinson* factors counsels against institution, and the Board should deny the petition pursuant to § 325(d).

VI. GROUND 1: KELONIA HAS NOT SHOWN THAT ANY CHALLENGED CLAIM IS ANTICIPATED

Should the Board reach the asserted grounds of invalidity, Kelonia has failed to show that there is a reasonable likelihood that any challenged claim is anticipated. Kelonia’s arguments are based on faulty interpretations of both the law regarding prior art disclosures under 35 U.S.C. § 102(d) and the law regarding anticipation of a species claim by a disclosed genus.

A. The Entirety of Perkins is Not Prior Art

1. Kelonia Misconstrues 35 U.S.C. § 102(d)

Perkins is a published international patent application based on an international application that was filed on February 25, 2022, which claims priority

to a provisional application, filed on February 26, 2021. Kelonia treats all of the disclosures of Perkins as entitled to the priority date of the provisional application. But in the year between the two filing dates, the Perkins applicant made additional developments, which are reflected in the published patent application including disclosures not present in the provisional application. Therefore, the entire published application is *not* entitled to the priority date of the provisional.

Section 102(d) provides, in relevant part,

For purposes of determining whether a patent or application for patent is prior art to a claimed invention under subsection (a)(2), such patent or application shall be considered to have been effectively filed, ***with respect to any subject matter described in the patent or application...*** or (2) if the patent or application for patent is entitled to claim a right of priority under section 119, 365(a), 365(b), 386(a), or 386(b), or to claim the benefit of an earlier filing date under section 120, 121, 365(c), or 386(c) based upon 1 or more prior filed applications for patent, ***as of the filing date of the earliest such application that describes the subject matter.***

35 U.S.C. § 102(d) (emphasis added). While pursuant to § 102(d) patents and applications may constitute prior art as of their earliest priority date listed on their face (*see Penumbra, Inc. v. Rapidpulse, Inc.*, No. IPR2021-01466, Paper 34, at 32 (P.T.A.B. Mar. 10, 2023) (precedential)), this does not mean that all disclosures in a

later application are automatically prior art entitled to that date. As clearly stated in the statute, and as the Board has consistently held, 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.

For example, in an appeal of a final rejection, the Board held that the asserted prior art reference, a published patent application, was not prior art to the claims at issue “because Glass was filed after the present application and, although Glass claims the benefit of Glass Provisional, Glass Provisional *does not describe the subject matter* of paragraphs 26, 37, or 45 of Glass, as applied to the disputed limitations of claim 1.” *Ex Parte O’Connor*, Appeal 2020-000483, 2021 WL 2889747, at *6 (P.T.A.B. July 8, 2021) (emphasis added). Similarly, in denying institution of post-grant review, the Board held that an asserted published patent application was not prior art to the challenged patent because “the disclosures in *Meine II* are *only* effective as prior art for subject matter *also* described in the ’953 provisional application.” *Ironridge, Inc. v. Pegasus Solar, Inc.*, PGR2022-00024, Paper 9, at 30 (P.T.A.B. Aug. 10, 2022) (original emphasis); *see also Forescout Techs., Inc. v. Fortinet, Inc.*, No. IPR2021-01328, Paper 12, at 9-10 (P.T.A.B. Jan. 27, 2022) (denying institution of IPR based on patent improperly claiming priority to provisional); *Ex Parte Hu*, Appeal 2020-006026, 2021 WL 5822584, at *4 (P.T.A.B. Dec. 6, 2021) (reversing rejection based on published patent application

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claiming priority to provisional); *Ex Parte Bhunia*, Appeal 2021-002223, 2022 WL 2902453, at *6 (P.T.A.B. July 21, 2022) (same); *Ex Parte Hwang*, Appeal 2019-004258, 2020 WL 6257228, at *3 (P.T.A.B. Oct. 21, 2020) (same); *Ex Parte Graham III*, Appeal 2022-002536, 2023 WL 2682932, at *6 (P.T.A.B. Mar. 20, 2023) (same); *Ex Parte Kim*, Appeal 2021-004939, 2022 WL 3573044, at *4 (P.T.A.B. Aug. 17, 2022) (same).

Indeed, this requirement make sense. The statute preserves the rights of the first inventor to file a patent application, but only to the extent that first filer described the subject matter at issue. Any different interpretation would give patent applicants the ability to effectively claim large swaths of information with early generic disclosures, and only later—after further development or after seeing their competitors’ activities—disclose to the public their actual invention. Such is the situation here—the Perkin’s Provisional discloses an enormous genus of possible mutations of the VSV-G protein (as explained in detail below), but only after further development in the field was the Perkins applicant able to identify the mutations that are the subject of that application. The Perkins applicant should not be able to prevent competitors from making developments in the science during that intervening time that they did not contemplate in the initial application. The premise of the patent system—that a patent applicant must *disclose* an invention in exchange for the right to exclude—similarly applies to prior art. If the *disclosure* was not

made before the priority date, that information cannot act as prior art to invalidate another patent.

2. Perkins is Only Prior Art to the Extent the Perkins Provisional “Describes the Subject Matter” Relied Upon

The effective filing date of the ’366 patent is December 15, 2021, and Kelonia does not challenge that priority date. Pet. at 4. Perkins did not publish until September 1, 2022. Accordingly, because Perkins was published after the effective filing date of the ’366 patent, it cannot be prior art under 35 U.S.C. § 102(a)(1). 35 U.S.C. § 102(a)(1). Perkins claims priority to U.S. Provisional Application No. 63/154,639 (Ex. 1006) (the “Perkins Provisional”), filed on February 26, 2021, and for purpose of this Preliminary Response, Interius does not challenge the sufficiency of that priority claim. Therefore, based on the Board’s current interpretation of 35 U.S.C. § 102(d), Perkins *could* be prior art to the ’366 patent based on its priority claim to the Perkins provisional application. *Penumbra*, Paper 34, at 32. 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 Kelonia relies.

Here, Kelonia heavily relies on the disclosure in Perkins of an I182 mutation among only four specific mutations in the amino acid sequence. For example, in its Ground 1, Kelonia asserts that “Perkins in fact disclosed a mutated VSV-envelope protein comprising a mutation at **four amino acid positions**, including ‘a I182

mutation.” Pet. at 33; *see also* 39 (“*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.’”); 65 (“*Perkins* also disclosed a mutated VSV-envelope protein comprising ‘a I182 mutation’ **out of four mutations**”) (emphasis added). In support of each of these allegations, Kelonia cites to *Perkins* at 22:2-3 and to the *Perkins* Provisional at 17-18. *Id.* at 33, 39, 65, 73. But this disclosure of I182 in a group of four amino acid positions does not appear in the *Perkins* Provisional. While Kelonia *cites* to both *Perkins* and the *Perkins* Provisional to support its claims, the specific disclosures on which Kelonia bases its arguments are materially different in these two references:

Perkins (Ex. 1005 at 22:2-3) (emphasis added)	Perkins Provisional (Ex. 1006 at 17-18) (emphasis added)
In some embodiments, the mutated VSV-G envelope protein comprises a N180 mutation, a I182 mutation, a T352 mutation, and a E353 mutation.	In some embodiments, the mutated VSV-G envelope protein includes a mutation at H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182 , M184, Y209, I347, T350, T352, E353, R354 [hereinafter, “Mutation Set 1”], 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, [hereinafter,

	<p>“Insertion Set 1”] and/or a deletion of residues 1-8. In certain embodiments, the VSV-G envelope protein includes two or more mutations selected from a mutation at one or more of [Mutation Set 1], [Insertion Set 1], and a deletion of residues 1-8. In other embodiments, the VSV-G envelope protein includes three or more mutations selected from a mutation at one or more of [Mutation Set 1], [Insertion Set 1], and a deletion of residues 1-8. In other embodiments, the mutated VSV-G envelope protein comprises a H8A, K47A, K47Q, Y209A, R354A, and/or R354Q mutation. In still other embodiments, the VSV-G envelope protein includes one 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, [hereinafter, “Mutation Set 2”], [Insertion Set 1] 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 [Mutation Set 2], [Insertion Set 1], and a deletion of residues 1-8. In some embodiments, a mutated VSV-G envelope protein is selected from one or more</p>
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	of an H8A, K47A, K47Q, Y209A, R354A, and R354Q mutation.
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While Perkins discloses an embodiment where a mutation at position 182 is *required*, as are mutations at three other positions, the Perkins Provisional, in contrast, includes a *possible* mutation at I182, among at least 12 other possible mutation positions, another 6 insertions, and a deletion. Contrary to Kelonia's representations, the Perkins Provisional does not disclose a mutation at position 182 as one of four mutations to the VSV-G envelope protein. The provisional application is lacking the disclosure upon which Kelonia relies in Perkins.

Under § 102(d), Perkins can only be prior art for the subject matter disclosed in the Perkins Provisional, which does not include the "four mutations" on which Kelonia relies. Instead, Perkins can only be prior art to the '366 patent for the broad disclosure of possible VSV-G mutations as disclosed in the Perkins Provisional. *See, e.g., Ex Parte O'Connor*, 2021 WL 2889747, at *6.

B. Perkins Does Not Anticipate Any Challenged Claim

1. Kelonia Misapplies the Law Regarding When Disclosure of a Genus Can Anticipate a Species Claim

Kelonia presents no argument that the species claimed in claim 1 of the '366 patent is explicitly disclosed in Perkins. To the contrary, at most Perkins discloses a genus that would include the claimed species. The 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.*” *Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.*, 50 F.4th 147, 152 (Fed. Cir. 2022) (internal quotations omitted) (emphasis added). In contrast, 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. *See, e.g., In re Gleave*, 560 F.3d 1331, 1337-38 (Fed. Cir. 2009). Kelonia heavily relies on *Perricone v. Medicis Pharm. Corp.*, which falls into the latter category. 432 F.3d 1368, 1376 (Fed. Cir. 2005). There, the question was whether a disclosure of ascorbyl palmitate among a list of fourteen possible ingredients, some of which were categories of ingredients (e.g., “sunscreens”), anticipated a claim specifically directed to the use of ascorbyl palmitate. *Id.* at 1376-77. The Federal Circuit held that the explicit disclosure of ascorbyl palmitate, even among a list of at least fourteen possible ingredients, was anticipatory. *Id.* at 1378.

Notably, the Federal Circuit in *Perricone* distinguished the facts of that case—where the claimed species was explicitly named—from genus cases:

In this case, the prior art does not merely disclose a genus of skin benefit ingredients without disclosing the particular claimed ingredient. Rather Pereira specifically discloses ascorbyl palmitate. That 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. at 1377. The Federal Circuit further confirmed this distinction in *In re Gleave*. There, the prior art reference explicitly listed more than 1400 specific oligonucleotides. *In re Gleave*, 560 F.3d at 1333. Several of these listed species fell within the claimed genus of an “oligodeoxynucleotide is of sufficient length to act as an antisense inhibitor of human IGFBP–2 and human IGFBP–5.” *Id.* The Federal Circuit stated that “[f]or the purposes of whether they are anticipatory, lists and genera are often treated differently under our case law” and contrasted the situation in *Perricone* to traditional genus cases such as *Atofina*, where the prior art discloses a genus that encompasses the claimed species. *Id.* at 1337; *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999-1000 (Fed. Cir. 2006) (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”).

Here, there is no dispute that neither Perkins nor the Perkins Provisional explicitly discloses an anticipatory species. While I182 is identified as one location for a potential mutation, the claimed I182E and I182D mutations are never mentioned. Kelonia’s arguments rely on the Perkins’ disclosure of a genus of

potential mutations, of which I182E and I182D are undisclosed species, and therefore, Kelonia must show that a POSA would “at once envisage” the claimed mutations. *Mylan Pharms.*, 50 F.4th at 152. As explained below, Kelonia cannot make that showing.

2. The Broad Genus Disclosed by the Perkins Provisional Does Not Anticipate the Challenged Claims

Kelonia fails to show that the prior art disclosure of Perkins anticipates the claims of the '366 patent because it cannot show that a POSA would “at once envisage” an I182E or I182D from the disclosures in the Perkins Provisional. *Mylan*, 50 F.4th at 152 (emphasis added).

As explained above, only the disclosures of the Perkins Provisional are properly considered prior art to the '366 patent. And the Perkins Provisional does not contain any disclosure of an I182E or I182D mutation.

In 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, e.g.:

In still other embodiments, the VSV-G envelope protein includes one or more mutations selected from a mutation at ***one or more*** of N9 [1], Q10 [2], K50 [3], A51 [4], S183 [5], S179 [6], N180 [7], **I182 [8]**, M184 [9], I347 [10], T350 [11], T352 [12], and E353 [13], an insertion of TT between N9 and Q10 [14], an insertion of GGS

between H8 and N9 [15], an insertion of GGS between N9 and Q10 [16], an insertion of TT between N208 and Y209 [17], an insertion of GGS between P46 and K47 [18], an insertion of GGS between N208 and Y209 [19], and a deletion of residues 1-8 [20].

See Ex. 1006, Perkins Provisional, at 17-18 (emphasis added). The 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. As Kelonia 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:

Listed Mutation Site	Possible mutations
N9	19
Q10	19
K50	19
A51	19
S183	19
S179	19
N180	19
I182	19

M184	19
I347	19
T350	19
T352	19
E353	19
an insertion of TT between N9 and Q10	1
an insertion of GGS between H8 and N9	1
an insertion of GGS between N9 and Q10	1
an insertion of TT between N208 and Y209	1
an insertion of GGS between P46 and K47	1
an insertion of GGS between N208 and Y209	1
and a deletion of residues 1-8	1
Total:	254

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.³

³ Indeed, even if the entirety of Perkins is determined to be prior art, the narrowest genus disclosed by it that encompasses a I182 mutation is a mutated VSV-G envelope that includes mutations at four amino acid positions including the I182 position. Ex. 1005 at 22:23-24. Setting aside that this embodiment requires *all*

The Federal Circuit has held that disclosures of much smaller genera do not anticipate a claimed species. For example, in *Mylan* the panel affirmed the Board's finding of no anticipation of a claimed sitagliptin phosphate salt in a 1:1 ratio where the prior art disclosed sitagliptin in a list totaling 957 possible salts. *Mylan*, 50 F.4th at 153-54. The panel explained that the disclosure of 957 possible salts "is a far cry from the 20 compounds 'envisaged' by the narrow genus in *Petering*." *Id.* at 154; *see also Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006) (holding that claim to riluzole was not anticipated by prior art disclosure of formula I where "riluzole is just one of hundreds of compounds included in formula I"); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1377 (Fed. Cir. 2006) (indicating that a disclosure of 21 compounds including MATTPCA and six different possible salts of those compounds including bisulfates would not anticipate the claimed bisulfate of MATTPCA).

Accordingly, a POSA could not possibly envisage the claimed mutations from the disclosure in the Perkins Provisional of a genus containing over 42 quadrillion

four of the identified mutations and assuming that Perkins identifies I182 as one of four *possible* mutations, even this narrower class still totals 19^4 or 130,321 possible sequences.

members, or even the disclosure of the narrower class in Perkins of 130,00 members.

Perkins, therefore, cannot anticipate the claimed I182E or I182D mutations.

VII. GROUND 2: KELONIA HAS NOT SHOWN THAT CLAIMS 3-9 AND 26-30 ARE RENDERED OBVIOUS BY PERKINS IN VIEW OF HWANG

Kelonia's Ground 2 is based on the presumption that Perkins discloses both the claimed I182E or I182D mutations. Kelonia fails to acknowledge that neither Perkins application makes such a disclosure and makes no attempt to argue that a POSA would have specifically chosen I182E or I182D to combine with Hwang. As a result, Kelonia has failed to make a sufficient obviousness claim for Ground 2.

To establish the obviousness of claims 3-9 and 26-30, Kelonia must show (1) a POSA would have been motivated to select an I182E or I182D mutation from the broad disclosures of possible mutations in the Perkins Provisional, and (2) a POSA would have been motivated to combine those specific mutations with the mutations in Hwang. Kelonia has not even attempted to show that a POSA would have been motivated to select a polypeptide containing a I182E or I182D mutation from the class of over 42 quadrillion members as a starting point for arriving at the claimed protein.⁴ *See, e.g., In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) (reversing Board's

⁴ It is undisputed that Hwang does not disclose or suggest any mutation at the I182 position. Therefore, Hwang cannot remedy the insufficiencies of Perkins.

finding of obviousness where claimed species was encompassed by prior art genus because there was no suggestion to select claimed species); *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992) (reversing Board’s finding of obviousness and rejecting Solicitor’s argument that “regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it); *Knauf Insulation, Inc. v. Rockwool Int’l A/S*, 788 F. App’x 728, 733 (Fed. Cir. 2019) (“It is not enough, even after *KSR*, to support a determination of obviousness that a reference includes a broad generic disclosure and a common utility to that in the claims and other prior art references—there must be some reason to select a species from the genus.”) (citing *In re Jones*, 958 F.2d at 350-51); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006) (affirming finding of nonobviousness of claimed olanzapine and rejecting defendants’ argument “that the district court erred by erecting a threshold requirement that defendants establish a teaching or incentive to treat the closest prior art [ethyl olanzapine] as a lead compound.”) (internal quotations omitted).

Kelonia’s obviousness argument in Ground 2, however, completely skips the first part of this analysis. Instead, Kelonia’s argument improperly starts with a VSV-G protein with a I182E or I182D mutation and only explains its theory regarding the further modifications that a POSA would have to make to arrive at the challenged claims. In light of the expansive disclosure of the Perkins Provisional,

Kelonia's argument is lacking because there is no motivation for a POSA to specifically choose one of the two claimed I182 mutations from a genus of 42 quadrillion. Therefore, Kelonia has not met its burden of establishing any challenged claim is "more likely than not" obvious in light of the combination of Perkins and Hwang.

VIII. GROUNDS 3 & 4: KELONIA HAS NOT SHOWN THAT ANY CHALLENGED CLAIM IS OBVIOUS OVER PERKINS IN VIEW OF THE RCSB PDB

Kelonia fails to meet its burden of showing at least one claim is more likely than not invalid under Grounds 3 & 4 because it fails to establish that a POSA would have been motivated to choose the claimed I182E or I182D mutations from the broad disclosures in the Perkins Provisional. Kelonia seems to advance 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.

A. A POSA Would Not Have Been Motivated to Choose the Claimed I182E or I182D Mutations from the Disclosures in Perkins

Kelonia argues that "[b]ased on any of these disclosures in *Perkins* of mutation at I182 among a finite set, it would have been obvious for a POSA to make a I182 mutation to Perkins' VSV-G envelope protein." Pet. at 65. Kelonia goes on to argue 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.” Pet. at 66. This characterization, however, is misleading. As explained above, the Perkins Provisional discloses mutations at I182 among a group of 20 other possible locations for modifications in the VSV-G sequence. Ex. 1006, Perkins Provisional, at 17-18. Thirteen of these 20 positions are specific amino acids that—as Kelonia admits (Pet. at 66)—can be changed to any of the 19 other natural amino acids. Ex. 1006, Perkins Provisional, at 17-18. And the Perkins Provisional discloses that “one, two, or more” of the mutations can be made together, which results in more than 42 quadrillion possible combinations. *Id.* Therefore, Kelonia’s representation that the mutations disclosed in the Perkins Provisional are a “finite set” is plainly wrong.⁵

Kelonia’s reliance on *Valeant* is ill-placed. There, the Federal Circuit found it would have been obvious to try pH values within the claimed range of 3.0 to 4.0, which the Court found to represent at most 100 possible values. *Valeant Pharms. Int’l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 34 (Fed. Cir. 2020). This case is more akin to *Shire LLC v. Amneal Pharmaceuticals, LLC*, 802 F.3d 1301, 1308

⁵ Indeed, even the much narrower class disclosed by Perkins of over 130,000 possible combinations could not be considered a “finite set.”

(Fed. Cir. 2015). In *Shire*, the Federal Circuit held that methods of using amphetamine derivatives to treat ADHD were not obvious over the prior art, where the primary prior art reference disclosed categories of compounds that could be combined to arrive at the claimed combination. *Id.* The Federal Circuit held that the prior art in *Shire* “provides no direction as to which of many possible choices is likely to be successful,” and therefore, did not make the claimed species “obvious to try.” *Id.* (internal quotations omitted).

Like the prior art in *Shire*, neither Perkins nor the Perkins Provisional provides any direction to a POSA regarding the choice of any particular mutation or combination of mutations that would work. Kelonia does not, and indeed cannot, point to any teaching in Perkins that would elevate the selection of any particular mutation, and the disclosure of more than 42 quadrillion possibilities cannot be a “finite set” that would be obvious to try. 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. Such an invitation does not render patentee’s solution to this problem obvious.

As an initial matter, Kelonia 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. Here again, Kelonia’s arguments jump directly to I182 without explanation of the motivation to

do so. Therefore, Kelonia's obviousness argument is incomplete. *See, e.g., In re Baird*, 16 F.3d at 383.

Moreover, in arguing that a POSA would select an I182E or I182D mutation from the 19 possible mutations at position I182, Kelonia relies on conclusory statements that are guided by hindsight reasoning. Pet. at 66-70. For example, Kelonia argues that Perkins' definition of a "conservative substitution" would cause a POSA to rule out substituting leucine or valine for isoleucine based on a patent application (Ex. 1023) published in 1997. Pet. at 67. Then Kelonia argues that a POSA would exclude proline because of a 2007 article (Ex. 1015) and rule out cysteine based on a 2006 article (Ex. 1014). Pet. at 68. This picking-and-choosing approach is a classic example of hindsight reasoning that should be rejected. *See, e.g., 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 "reli[ing] on the [challenged] patent itself as her roadmap for putting what she referred to as pieces of a 'jigsaw puzzle' together.").

Finally, after eliminating just four of the nineteen amino acids, Kelonia simply concludes that because there would be only 15 amino acids left to choose from, “it would have at least been obvious for a POSA to make ‘a I182E mutation as compared to SEQ ID NO:2.’” Pet. at 68. Kelonia’s arguments are nothing more than working backwards from the claimed invention by relying on conclusory expert testimony based on improper hindsight reasoning, which is prohibited in an obviousness analysis. “[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.” *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017); *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). Kelonia has not pointed to any suggestion in Perkins that would lead a POSA to make the claimed I182E or I182D mutations.

Moreover, the extensive trial-and-error experimentation that a POSA would have to undertake to make and test all of the possible mutations that Kelonia’s argument contemplates merely confirms the non-obviousness of the claims. Applying Kelonia’s argument more broadly to the other possible mutations disclosed in the Perkins Provisional would lead to absurd results. Under Kelonia’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.” Thus, the Board should reject Kelonia’s improper, hindsight-driven attempts to narrow the analysis to only the claimed mutations.

B. A POSA Would Not Have Been Motivated to Make the Claimed I182E or I182D Mutations Based on a Combination of Perkins and RCSB PDB

Kelonia’s second theory of obviousness fares no better. Apparently realizing the flaws in relying on Perkins and the Perkins Provisional alone, Kelonia goes on to argue that a “POSA would also have had a good reason to focus on *Perkins*’ express disclosure of a I182 mutation.” Pet. at 72. According to Kelonia, “a POSA could have easily checked the 13 amino acid positions disclosed in *Perkins* for making a mutation” based on the published structures of the VSV-G bound to the LDL-R. *Id.* Kelonia then claims 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” 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. Kelonia concludes that a “POSA would thus have concluded that I182 was as one of the best of the 13 disclosed amino acid positions in *Perkins*

for disrupting the interaction with the CR3 domain” and thus satisfying the statement 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.

Kelonia strings together this daisy chain of “logic” relying principally on the declaration of Dr. Rose, which simply parrots the language of the petition.⁶

Kelonia’s obviousness argument is thus a series of conclusory statements from its

⁶ Kelonia 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, Kelonia fails to explain why Perkins, which Kelonia 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.

expert based on hindsight reasoning. And the Board has stated that conclusory and unsupported expert testimony is entitled to little weight. *Xerox*, IPR2022-00624, Paper 9, at 15 (precedential); *see also ActiveVideo Network*, 694 F.3d at 1327 (affirming JMOL of nonobviousness where defendant's expert offered only conclusory testimony).

Moreover, in arguing that a POSA would have been motivated to select an I182E or I182D mutation from the other 17 possible mutations at position 182 based on the RCSB PDB, Kelonia again relies on hindsight reasoning and conclusory statements. Pet. at 70-76. For example, Kelonia's obviousness argument is basically that a POSA would have (i) "immediately recognized that I182 is nearby aspartic acid residues on the LDL-R that may be negatively charged," (ii) "would have been motivated to incorporate a mutation which negated an interaction with the negatively charged residues in the LDL-R," (iii) would have understood 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," and (iv) would have understand that the he 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 70-71. In support of step (i),

Kelonia cites Ex. 1024 at 569 and Ex. 1027 at 1605, as well as Dr. Rose's

Declaration at paragraphs 201-204. Pet. at 70. But 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 step (i) of Kelonia's obviousness argument is a conclusory statement from its expert. Such a statement is entitled to little weight, at most. *Xerox*, IPR2022-00624, Paper 9, at 15 (precedential); *see also ActiveVideo Network*, 694 F.3d at 1327 (affirming JMOL of nonobviousness where defendant's expert offered only conclusory testimony).

Moreover, Kelonia 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 Kelonia'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. *See, e.g., Millennium Pharms.*, 862 F.3d at 1367.

In sum, each of Kelonia's obviousness grounds fail. Kelonia fails to establish that a POSA would be motivated to make a mutation at position 182 over any of the other numerous positions disclosed in the Perkins Provisional and fails to establish that, even if a POSA were motivated to make a mutation at position 182, a POSA would be motivated to substitute aspartic acid or glutamic acid for the isoleucine or at that position. Kelonia's arguments rely purely on conclusory expert testimony based on improper hindsight reasoning, and therefore, should be rejected.

IX. THE PETITION SHOULD BE DENIED AS DEFICIENT UNDER 37 C.F.R. § 42.22

Petitioner is required to provide "[a] full statement of the reasons for the relief requested, including a detailed explanation of the significance of the evidence including material facts, and the governing law, rules, and precedent." 37 C.F.R. § 42.22(a)(2). Kelonia has failed to do so here. Specifically, Kelonia has failed to provide a detailed explanation—or even acknowledge the existence of—the difference between the disclosures of Perkins and the disclosures of the Perkins Provisional. As explained above, these differences are significant. As a result, Kelonia's Petition is fatally flawed and should be denied.

Kelonia relies on the disclosure in Perkins (Ex. 1005 at 22:2-3) of mutations at four positions in the amino acid sequence including the I182 position for every ground of the Petition. *See, e.g.,* Pet. at 33 ("*Perkins* in fact disclosed a mutated

VSV-envelope protein comprising a mutation at *four amino acid positions*, including ‘a I182 mutation.’”) (Ground I) (emphasis added); Pet. at 53-54 (citing Ex. 1005 at 22:2-3) (Ground II); Pet. at 65 (“*Perkins* also disclosed a mutated VSV-envelope protein comprising ‘a I182 mutation’ out of *four mutations*.”) (Ground III); Pet. 82 (referring back to Ground 3) (Ground 4) (emphasis added). But, Kelonia fails to acknowledge that this embodiment was not disclosed until *after* the effective filing date of the ’366 patent. In fact, Kelonia’s petition at best misconstrues the disclosures in the Perkins Provisional, as it includes a citation to the Perkins Provisional for the representation that the prior art disclosed I182 in a list of just four mutations. *See id.* at 33, 54, 65 (citing “Ex. 1006 at 17-18”). But, as detailed above in Section VI.A.2, a careful review of pages 17 and 18 of the Perkins Provisional shows that there is no such disclosure. Far from disclosing mutations at only four possible positions, in every embodiment in the Perkins Provisional that includes an I182 mutation, the I182 mutation is one of *twenty* or more possible mutations or changes to the VSV-G envelope protein. *See* Ex. 1006 at 17-18 (“In still other embodiments, the VSV-G envelope protein includes one or more mutations selected from a mutation at one or more of N9 [1], Q10 [2], K50 [3], A51 [4], S183 [5], S179 [6], N180 [7], I182 [8], M184 [9], I347 [10], T350 [11], T352 [12], and E353 [13], an insertion of TT between N9 and Q10 [14], an insertion of GGS between H8 and N9 [15], an insertion of GGS between N9 and Q10 [16], an insertion of TT between

N208 and Y209 [17], an insertion of GGS between P46 and K47 [18], an insertion of GGS between N208 and Y209 [19], and a deletion of residues 1-8 [20].”).

Because, under 35 U.S.C. § 102(d), the disclosure of a provisional application can be determinative of the scope of the prior art disclosure, the Board has found that petitions that fail to clearly explain how a provisional application supports the petitioner’s ground are deficient under 37 C.F.R. § 42.22(a)(2). For example, in *Schlumberger*, the Petitioner asserted that a published international patent application claiming priority to two provisional applications filed before the effective filing date of the challenged patent was prior art. *Schlumberger Tech. Corp. v. DynaEnergetics Europe GmbH*, PGR2021-00089, Paper 13, at 32 (P.T.A.B. Dec. 14, 2021). The *Schlumberger* Petition made several assertions regarding the disclosure of the international application and provided a citation to the provisional applications for each assertion. *Id.* at 41-42. The Board found that the citation to the provisional applications without explanation was inadequate. *Id.* at 42 (“[W]e determine that Petitioner cites to several aspects of Sokolove ’009 without adequate explanation as to how the subject matter relied upon in Sokolove ’009 is described in Sokolove Provisional ’999 or Sokolove Provisional ’591.”). Additionally, the Board found that the Petitioner’s expert’s testimony was not persuasive because it also did not provide an explanation of how the provisional applications disclosed the assertion regarding the prior art disclosure—“the deficiencies in the Petition persist

in [the expert's] declaration.” *Id.* at 47. Accordingly, the Board held that “Petitioner ha[d] not adequately identified the grounds and evidence that support the grounds with the required particularity” and denied the petition. *Id.* at 49.

As in *Schlumberger*, Kelonia’s petition fails to adequately explain how the Perkins Provisional discloses the subject matter on which Kelonia relies. *Compare Schlumberger*, PGR2021-00089, Paper 13, at 42 (“[prior art assertion] (Ex. 1005, [29], [25]-[26], [32]-[33], [35]; see also EX1006, 19-20, 22; EX1007, 22-23; EX1003, ¶¶ 134-138)”) ⁷ to Pet. at 32-33 (“[prior art assertion] (*See, e.g.,* Ex. 1005 at 20:29-21:14, Ex. 1006 at 17-18; Ex. 1002 at ¶ 79).” Additionally, as in *Schlumberger*, Dr. Rose’s expert declaration also fails to provide an explanation to cure the defects in the Petition. *See, e.g.,* Ex. 1002 at ¶ 79 (“*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.)”). Therefore, as it did in *Schlumberger*, the Board should find that Kelonia’s petition is wholly deficient under 37 C.F.R. § 42.22(a)(2) and deny the petition.

⁷ In *Schlumberger*, the published international patent application was Ex. 1005, the provisional applications were Exhibits 1006 and 1007, and the expert declaration was Ex. 1003. PGR2021-00089, Paper 13, at 5 n. 1, 6.

X. CONCLUSION

In light of the above, Kelonia has not shown that there is a reasonable likelihood that at least one challenged claim is unpatentable, and Kelonia's petition should be denied.

PGR2024-00008
U.S. Patent No. 11,767,366

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing PATENT OWNER'S PRELIMINARY RESPONSE complies with the type-volume limits of 37 C.F.R. § 42.24(b)(1) because it contains 10,051 words according to the word-processing system used to prepare this Response, excluding the words in the Table of Contents, Table of Authorities, List of Exhibits, Certification Under §42.24(d), and Certificate of Service, as set forth in 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.6(e)(4), the undersigned certifies that a true and correct copy of PATENT OWNER'S PRELIMINARY RESPONSE together with all exhibits identified in the above Table of Exhibits, were provided via email, to the Petitioner by serving the correspondence email addresses of records as follows:

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