

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

PETITIONER'S REQUEST FOR REHEARING

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I. INTRODUCTION

Petitioner respectfully requests rehearing pursuant to 37 C.F.R. § 42.71(d) of the Board’s Decision (Paper 11, “Decision” or “Dec.”) denying post-grant review of claims 1-30 of the U.S. Patent No. 11,767,366 (“the ’366 patent”). Respectfully, Petitioner’s request should be granted and review instituted because the Decision misapprehended or overlooked Petitioner’s arguments and evidence establishing that *Perkins* in view of other prior art (e.g., *RCSB PDB*) renders obvious the challenged claims.¹

Rehearing is warranted because the Decision discounted Petitioner’s undisputed evidence in incorrectly finding that *Perkins*’ disclosures do not provide an “easily traversed, small or finite number of alternatives that *KSR* suggested might support an inference of obviousness.” (Decision, 35.) This error stems from the Decision’s overlooking or misapprehension of Petitioner’s evidence with respect to why a POSA would have routinely and rationally narrowed *Perkins*’ limited list of 13 disclosed mutations down to I182. (*See, e.g.*, Petition, 20-22, 72-74; Ex. 1002 at ¶¶ 52-55, 208-213.) Once a POSA narrows *Perkins*’ list of mutations down to I182,

¹ Although the Decision is also incorrect with respect to Grounds 1 and 2, Petitioner’s rehearing focuses on Grounds 3 and 4 for the sake of efficiency. (Decision, 8 (listing grounds).)

then it is undisputed that there are only 19 options for making a mutation at I182, including the claimed I182E and I182D mutations. A mere nineteen (19) options clearly constitutes a “small or finite number of alternatives” and renders the claim obvious under Federal Circuit precedent.

The Decision completely overlooked this critical aspect of the obviousness inquiry as it focused on the wrong question, namely: whether it would have been obvious for a POSA to select I182E and I182D out of 254 options in *Perkins*. (Decision at 35). Petitioner submits that the proper legal question to ask, in the first instance, is whether a POSA would have narrowed down the 254 options contemplated by *Perkins* to a much smaller subset in view of the prior art. Dr. Rose’s undisputed evidence shows that POSA would have been motivated to select I182 as the mutation based on express disclosures in *Perkins*, coupled with the details of the crystal structure deposited in the *RCSB PDB*, leaving only 19 options. The Decision did not engage in that analysis, and that is an abuse of discretion.

Even if the Decision focused on the correct question, it legally erred in discounting Dr. Rose’s testimony that a POSA would have selected the claimed species (“I182E” and “I182D”) based on a POSA’s knowledge (and common sense) regarding the advantages of the E and D mutations. The Decision, in an abuse of discretion, overlooked Dr. Rose’s testimony entirely because it believed that *Perkins* or *RCSB PDB* alone needed to provide the requisite motivation (Decision, 35-38)

when it is black-letter law that the motivation “does not have to be found explicitly in the prior art references sought to be combined, but rather ‘may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.’” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362 (Fed. Cir. 2007) (internal citation omitted).

For at least the above reasons and those set forth below, Petitioner respectfully requests rehearing and institution of post grant review.

II. LEGAL STANDARD

A rehearing from a denial of institution is reviewed for an abuse of discretion. *See* 37 C.F.R. § 42.71(c). An abuse of discretion occurs when a “decision [i]s based on an erroneous conclusion of law or clearly erroneous factual findings, or . . . a clear error of judgment.” *Apple Inc. v. DSS Technology Management, Inc.*, IPR2015-00369, Paper No. 14 at 3 (August 12, 2015) (citing *PPG Indus. Inc. v. Celanese Polymer Specialties Co.*, 840 F.2d 1565, 1567 (Fed. Cir. 1988)). The “request must specifically identify all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, a reply, or a sur-reply.” 37 C.F.R. § 42.71(d).

III. ARGUMENT

A. The Decision Overlooked Evidence Establishing That a POSA Would Have Selected the I182 Mutation in *Perkins*

Perkins discloses a limited list of 13 positions for making an amino acid mutation, which includes I182 as an expressly recited option. (Petition, 72 (citing Ex. 1005 at 21:16-27 (disclosing a mutation at “N9, Q10, K50, A51, S183, S179, N180, **I182**, M184, I347, T350, T352, and E353” (emphasis added); Ex. 1006 at 17-18).) As explained in the Petition and Dr. Rose’s declaration, a POSA would have had good reason to focus on *Perkins*’ I182 mutation from this list. (*Id.*, (citing Ex. 1002, ¶ 208).) Specifically, *Perkins* expressly desired mutations to VSV-G that “inhibit binding of VSV-G to the low-density lipoprotein receptor (‘LDL-R’), while preserving the VSV-G protein’s fusogenic function.” (See, e.g., Ex. 1005 at 19:29-20:2, 20:29-21:14, 21:16-27; Ex. 1006 at 16; 1002 at ¶ 205.) And, as Dr. Rose testified, it is apparent from looking at the crystal structure of VSV-G (as deposited in *RCSB PDB*) that I182 is one of the best of the 13 disclosed options in *Perkins* for achieving *Perkins*’ express objective of inhibiting binding of VSV-G to LDL-R receptor. (Ex. 1002 at ¶¶ 208-213.)

For example, Dr. Rose testified 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 of the LDL-R known to be involved in the coordination of calcium. (Ex. 1002 at ¶ 209.) With citation to specific evidence from *RCSB PDB*, Dr. Rose

testified that I182 was the only amino acid out of the 13 disclosed amino acid positions in *Perkins* that could additionally interact with a second negatively charged amino acid in the CR3 domain. (*Id.* (Appendix B (Images 1 and 3)).) Dr. Rose further opined that, once considered in its known structural context, a POSA would have concluded that I182 was “one of the best of the 13 disclosed options in *Perkins* for disrupting the interaction with the CR3 domain of the LDL-R.” (Ex. 1002 at ¶ 210.) Dr. Rose then performs a similar analysis on the CR2 domain of the LDL-R, and in working through his specific findings, explains why a POSA, once again, would have landed on I182 out of the 13 disclosed positions in *Perkins*. (*See* Ex. 1002 at ¶¶ 211-212; Appendix B (Images 2 and 4).) As such, the 13 disclosed positions in *Perkins* are not equal options that a POSA would have rotely explored, and focusing on I182 was a reasonable choice for a POSA to implement *Perkins*’ desire of inhibiting binding of VSV-G to LDL-R. (Petition, 73-74 (citing Ex. 1002 at ¶¶ 208-213.)

In the context of obviousness, such testimony is perfectly acceptable “to narrow the genus” disclosed in *Perkins* to I182. *Pfizer*, 480 F.3d at 1362-63 (finding the claim obvious based on expert testimony (and other evidence) establishing that there was “ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate.”); *see Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1379

(Fed. Cir. 2014) (“because prior art references ‘provide[d] ample motivation to narrow the [a previously patented] genus of ... pharmaceutically-acceptable anions to a few,’ . . . we concluded that the species at issue in this case was unpatentable.”) (citing *Pfizer*, 480 F.3d at 1363, 1366). Once *Perkins*’ list is narrowed to I182, the claim is obvious because it is undisputed that the I182 mutation is a small genus of only 19 options, including the claimed I182E and I182D mutations. Such a small genus necessarily renders the claim obvious. *Abbvie*, 764 F.3d at 1379 (holding that in the obviousness context, “species are unpatentable when prior art disclosures describe the genus containing those species such that a person of ordinary skill in the art would be able to envision every member of the class.”) (citing *In re Petering*, 49 CCPA 993, 301 F.2d 676, 681–82 (1962).)

The Decision, however, overlooked Dr. Rose’s testimony by focusing on whether *Perkins* or *RCSB PDB* “contain any teaching or suggestion directing a POSA to create the I182E or I182D specified by the claims.” (Decision, 36.) But whether a POSA would have selected the “E” or “D” mutation for I182 is a *second* step that is not reached until, *first*, considering whether a POSA would have selected the position of I182 out of the 13 listed positions for making a mutation in *Perkins*. The Decision altogether skipped this first step, or at a minimum conflated both steps, thereby engaging in an erroneous obviousness analysis, which is an abuse of discretion. If a POSA first narrows the position of making a mutation to I182, he or

she is only left with 19 options, which includes the “E” and “D” mutations. Even without the additional evidence (*e.g.*, Dr. Rose’s testimony on why a POSA would have selected the “E” and “D” mutations once I182 is the chosen location), such a limited set of 19 options renders the claims obvious because it is a limited finite set of alternatives.²

To the extent the Decision required *RCSB PDB* or *Perkins* to have an explicit teaching as to why a POSA would have selected I182 (*see* Decision, 35-37), that is legal error because a “suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather ‘may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.’” *Pfizer*, 480 F.3d at 1362. Here, *Perkins* expressly identified I182 in a limited list of positions for making a mutation. *RCSB PDB* provided three-dimensional (“3D”) context for where that position was located in relation to the LDL-R, which was discussed by *Perkins*. It is legally acceptable for Petitioner to rely on the testimony of Dr. Rose, and the images taken from his

² As further explained in Section III.B below, the Decision misapprehended Petitioner’s evidence regarding why a POSA would have selected the “E” and “D” mutations for I182.

analysis of *RCSB PDB*, to explain why a POSA would have selected a I182 mutation from *Perkins*' 13 disclosed amino acid positions.

The Patent Owner's Preliminary Response does not show error in Dr. Rose's testimony regarding a POSA's reasons to select the I182 mutation. For example, Patent Owner's argument that Petitioner "fails to explain why a POSA would consider" the acidic residues that belong to an octahedral calcium cage of the CR domains "to be 'important'" is incorrect. (Prelim. Resp. 37 n. 6.) Dr. Rose at ¶ 213 of his declaration expressly explains that:

[a] person of ordinary skill in the art in my opinion would have been interested in amino acids such as I182 that interact with the octahedral calcium cage of the LDL-R CR domains. For instance, a person of ordinary skill in the art was aware that '[t]he LDL-R gene family consists of trans-membrane receptors that . . . require Ca^{2+} for ligand binding.' (See, e.g., Ex. 1018 at 4.) Nikolic *et al.* reported that "the presence of Ca^{2+} was mandatory for the correct folding of the proteins." (See, e.g., *id.* at 5.) As the calcium cage appears to mediate binding, a person of ordinary skill in the art would have looked to residues in close proximity. (See, e.g., *id.* at 9.)

The Petition also cites this paragraph of Dr. Rose's Declaration to explain why a POSA would have chosen I182 in context. (See Petition, 74 ("Accordingly, the

RCSB PDB provided ample reason for a POSA to focus on *Perkins*' disclosure of a I182 mutation, and to the make a I182E mutation based on the location of I182 in the crystal structures and the limited options to effectively accomplish *Perkins*' stated goal of inhibiting LDL-R binding. (Ex. 1002 at ¶¶ 208-213).")

Furthermore, contrary to the Decision's analysis, there is evidentiary support "for a determination that the navigation of RCSB PDB crystal structures . . . would have been '*evidently and indisputably* within the common knowledge of those skilled in the art.'" (Decision, 38.) For example, Petitioner cited background references on *RCSB PDB* (Ex. 1024 (Zardecki) and the visualization software, Chimera (Ex. 1027 (Pettersen))), used by Dr. Rose. Dr. Rose also disclosed numerous structural papers on VSV-G. (*See, e.g.*, Ex. 1013-1015, 1018.) At least these references evidence the common use of crystal structures and navigation software by a POSA as of the relevant timeframe. Dr. Rose further explained how the use of such software and crystal structures was within the common knowledge of a POSA. (*See, e.g.*, Ex. 1002 at ¶¶ 52-55, ¶¶ 198-200.) To the extent the Board was not fully convinced about a POSA's knowledge or Dr. Rose's reasons for why a POSA would have been immediately drawn to I182, trial should have been instituted to allow the record to be fully developed on these issues.

Any suggestion that Dr. Rose’s testimony is merely “retracting the path of the inventor with hindsight accuracy” (Decision, 38) is incorrect.³ *Perkins* itself sets out the path for Dr. Rose (and a POSA) by expressly stating that it desires mutations to VSV-G that “inhibit binding of VSV-G to the low-density lipoprotein receptor (‘LDL-R’), while preserving the VSV-G protein’s fusogenic function.” (See, e.g., Ex. 1005 at 19:29-20:2, 20:29-21:14, 21:16-27; Ex. 1006 at 16; 1002 at ¶ 205.) Dr. Rose consulted the limited list of disclosed amino acid positions in *Perkins*, and then—as any POSA would do—looked to the known prior art crystal structure of VSV-G deposited in *RCSB PDB* to understand which of *Perkins* disclosed mutations would best achieve the stated objective in *Perkins*. (Ex. 1002 at ¶¶ 52-55, 198-201, 208-213). Dr. Rose explained how a POSA, starting from the limited list of positions disclosed in *Perkins*, would have rationally selected I182 to ablate an interaction between VSV-G and LDL-R. (See Ex. 1002 at ¶¶ 208-213; Appendix B.)

Dr. Rose’s reasoning is not found in the ’366 patent and thus cannot be labeled as mere “hindsight” reconstruction of the claims or the inventor’s path. The ’366

³ To be sure, the Decision’s comment regarding Dr. Rose retracting the inventor’s path was not made with reference to the selection of position I182 itself, before modification to I182D or I182E, as the Decision did not expressly address that evidence. Petitioner, however, explains why there is no hindsight at play here.

patent provides a mere two paragraphs which note that the crystal structures of VSV-G were consulted and two putative positions in VSV-G were identified with side chains oriented towards the binding interface on LDL-R. (*See* Ex. 1001 at 104:47-64.) Associated images at FIG. 1 illustrate I182 without providing context as to all of the nearby residues or any distances involved. Residue I182 is vaguely reported to “contact several residues in both CR2 and CR3.” (*See id.* at 104:59-64.)

By contrast, Dr. Rose explains how a POSA would have selected I182 starting from *Perkins*’ disclosure and objective, and analyzes the disclosed positions. (*See* Ex. 1002 at ¶¶ 208-213.) Dr. Rose discusses specific nearby amino acid residues and specific distances, along with potential interactions. (*Id.*) Dr. Rose explains why a POSA would have naturally arrived at position I182 in view of his combined findings for both CR2 and CR3 (which involve separate analyses). (*Id.*) The ’366 patent does not provide anywhere near this level of detail, nor explain how the prior art crystal structure would have specifically lead someone to select position I182.

B. The Decision Overlooked Evidence Regarding Reasons to Select the “E” and “D” Mutations for I182

The Decision rejected Petitioner’s reasons for why a POSA would have selected the “E” and “D” mutations to I182 because it found that that *Perkins* discloses a I182A mutation and not a I182D or I182E mutation. (Decision, 36.) According to the Decision, this shows that Petitioner engaged in “improper hindsight

reasoning.” (*Id.*) But the Decision fails to appreciate that the ’366 patent also discloses a I182A mutation as its specific alternative embodiment to a I182D or I182E mutation. (*See, e.g.*, Ex. 1001, 104:59-64 (disclosing I182A, I182D, and I182E).) The fact that *Perkins* disclosed making a mutation at position I182 before the earliest priority date of the ’366 patent, and proposed making an obvious mutation of I182A, does not suggest that making another mutation of I182D or I182E would not have also been obvious.

The Decision cites to Patent Owner’s argument suggesting that Petitioner only cited to Exhibits 1024 and 1027 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.” (Decision, 32.) This argument is misleading. Exhibits 1024 and 1027 are background references that provide the database entry for the 3D crystal structure of *RCSB PDB* and the paper describing the visualization software to view the crystal structure (Chimera). As explained by Petitioner and Dr. Rose, it is the crystal structure itself—a 3D prior art structure—that provides context for the location of I182 and the nearby calcium cage aspartic acid residues that Dr. Rose testified would have been important to a POSA, with reference to cited evidence in Nikolic (Ex. 1018). (*See* Ex. 1002, ¶¶ 208-213.) It is unclear what the Decision would have expected Petitioner to additionally cite, when the conclusion is drawn from the contents of the 3D prior art crystal structure in *RCSB PDB*.

Additionally, Patent Owner's argument ignores that Dr. Rose elsewhere explained that a POSA "would have understood that aspartic acid is negatively charged at pH 6, which is the optimal pH condition for fusion of the VSV-G protein to occur." (See Ex. 1002 at ¶ 206 (citing Ex. 1012 at 120; Ex. 1022 at 76-77).)

Dr. Rose in his declaration provides images of the 3D crystal structure (*i.e.*, evidence supporting his opinions) from *RCSB PDB* that show the nearby aspartic acid residues that interact with position I182. (See Ex. 1002 at ¶¶ 200-213; Appendix B). Dr. Rose did not supply any missing element from the prior art to narrow down *Perkins'* list to I182. *Perkins* expressly disclosed I182, and the *RCSB PDB* crystal structure provides context as to why position I182 would have been considered one of the most desirable locations for a POSA seeking to achieve *Perkins'* stated goal of ablating LDL-R interactions. (See Ex. 1002 at ¶¶ 208-213). Once a POSA had selected position I182, a mutation to I182D or 182E is among a genus of only 19 options which, as discussed above, is obvious under Federal Circuit precedent. In any event, a POSA by that point would have arrived at I182D or I182E through "common sense," as explained by Dr. Rose. (Ex. 1002 at ¶¶ 206-207; *see also* Petition at 71-72.)

Dr. Rose's testimony is the lens by which the amino acid positions disclosed in *Perkins* would have been appreciated by a POSA in view of their known prior art locations. That is precisely—and properly—what Petitioner uses Dr. Rose's

testimony for, and not, as alleged by the Decision, to provide threadbare assertions to supply a missing prior art element. Dr. Rose's declaration provides substantive analysis with evidence specifically demonstrating what a POSA would have appreciated from the prior art 3D crystal structure of VSV-G. Respectfully, the Decision dismissed this testimony altogether in an abuse of discretion.

IV. CONCLUSION

For the reasons explained above, Petitioner's rehearing request should be granted and post grant review instituted.

Respectfully submitted,

Dated: June 17, 2024

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CERTIFICATE OF SERVICE

I hereby certify that on June 17, 2024, I caused a true and correct copy of the foregoing Petitioner's Request for Rehearing to be served by email at the following email addresses of record:

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