

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORTE BIOSCIENCES, INC.,
Petitioner,

v.

UNIVERSITY OF MASSACHUSETTS,
Patent Owner.

Case No. PGR2023-00014
Patent No. 11,278,505

PATENT OWNER'S SUR-REPLY

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I. Introduction

Petitioner's failure to address—much less dispute—key factual and legal points dooms its arguments.

The record establishes that cytokine pathway inhibition was well-developed for treating autoimmune diseases. As admitted by Petitioner's declarant, this was recognized as a class effect—not limited to individual inhibitors—based on proof-of-concept ("PoC") *in vitro* and animal studies. Petitioner has relied upon the same class effect to represent that the '505 patent's data "support[s] the therapeutic potential of anti-CD122... including in vitiligo...." EX2003, 1. The record further establishes that IL-15 was a "textbook" and well-studied cytokine pathway with more than 375 known inhibitors, multiple having proceeded to clinical development. Paper 19 ("POR"), 27, 63. Petitioner does not dispute that where—as here—"the invention was to use a group of compounds well known in the art... in a novel method of treating" and the genus of inhibitors used in the claimed method "is well understood in the art and not itself the invention but is instead a component of the claim, [such that] background knowledge may provide the necessary support for the claim." *Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629, 648 (E.D. Tex. 2017) ("*UroPep*"), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018).

The basis for institution that "evidence that there were well-known classes of compounds known to perform the function recited in the claim methods... [was] not

presented on the current record” (Paper 10 (“ID”), 20) is more than obviated by these undisputed facts and law. The unresolved failure of Petitioner’s declarants to consider the full specification—including the more than 300 incorporated references—and the POSA’s knowledge including the hundreds of known IL-15 pathway inhibitors ¹ further precludes establishing §112 unpatentability. Compounding its reliance on declarants who were not aware of and did not consider the POSA’s knowledge, Petitioner’s arguments resting on human testing and FDA approval (Paper 25, (“Reply”), 20-21) are contrary to law. *Infra*, §III.B.4.

Petitioner further fails to address the trial record on obviousness, ignoring key differences in *Harris* and *Xing* that contradicts any purported motivation to combine. Petitioner’s slim objective indicia reply is irreconcilable with its reliance on the patent’s model and data (reproduced in EX2046) to advertise its IL-15 pathway inhibitor (FB-102) in the context of a “LARGE UNMET NEED IN VITILIGO” in a market “valued at[]\$1.2 billion in 2018.” EX2004, 8, 26, 33; EX2045.

¹ Compare POR, 9-12 and EX2005, ¶¶68-79, 121-122, App’x A with Reply and EX2118, 168:11-16, 55:24-56:10, 60:19-22, 186:11-20.

II. Factual Record

A. State of the Art

1. Class Effect of Cytokine Inhibition and “textbook” IL-15 Cytokine

Contrary to Petitioner’s new arguments based on Dr. Plott (Reply, 8), the art reflects that IL-15/IL-15R inhibitors were recognized as a class based on their common property of blocking the IL-15 signaling pathway, regardless of specific blocking mechanism. EX2005, ¶¶79, 115-118, 122, 124, 127-128. Indeed, Petitioner does not dispute that IL-15 (1) was known to be a “textbook” cytokine with known cellular targets and biological effects (EX2002, 106; POR, 5); (2) functions primarily by *trans*-presentation; and (3) pathway inhibition was taught to be effective for multiple autoimmune diseases. POR, 6-8, 12-13; EX1011, 22; EX2013, 3; EX2017, abstract; EX2024, 17; EX2025, 2; EX2027, 4; EX2028, 9; EX2029, 4; EX2031, 23; EX2118, 53:22-54:9. Nor does Petitioner dispute that the art routinely relied on the “classic research paradigm” using a single cytokine pathway inhibitor to establish therapeutic inhibition of that pathway generally or the admission of its declarant, Dr. Abbas, that “it [was] common as of April 2017 [and today] to expect that species that would antagonize IL-15 signaling would be useful in diseases—autoimmune diseases that had been identified as having an IL-15 mechanism.” EX2007, 74:19-75:10; POR, 8-9, 12-14. Analogously, Dr. Plott recognized that chemically distinct JAK-inhibitors have a common class effect based on their

common inhibition of the downstream pathway most important for their efficacy.

EX2118, 41:9-43:25.

2. Hundreds of IL-15 Inhibitors Were Known

Petitioner's "trial and error" assertions (Reply, 9, 14) fail to account for and are contradicted by:

- (1) known techniques for rationally designing and identifying pathway inhibitors;
- (2) known beneficial therapeutic effects based on inhibiting IL-15 signaling in PoC models and/or human clinical data for multiple sclerosis, RA, lupus, diabetes, allergies, asthma, and GvHD; and
- (3) the expectation of common autoimmune therapeutic efficacy reported for novel inhibitors.

POR, 12-14; EX1011, 22; EX1018, 1; EX2005, ¶¶52-63, 80-83, 130; EX2013, 4, 25-26 (*in silico* methods identifying IL-15 inhibitors); EX2014, 5-6, 20-21 (same); EX2015, 8, 5 (same); EX2019, 3, 5-6; EX2024, 3-4, 14-15; EX2025, 2-3, 6; EX2026; EX2027, 4-6, 10-11; EX2028, 6, 11; EX2029, 4; *see also* EX1046, 231:20-25; EX2015, ¶[0003] ("This strategy has been proved lately by a number of biological assays. Reduction of IL-15-mediated biological responses, using soluble IL-15Ra receptor... antibodies inhibiting IL-2/IL-15R receptor... antibodies inhibiting IL-15...

or modified IL-15 molecule of competitive antagonist activity... always resulted in the alleviation of the disease symptoms.”); EX2028, 2:57-59 (“[POSA] can easily select the most appropriate [IL-15/IL-15R] Fc domain [] for autoimmunity.”); EX2118, 164:7-165:11, 178:7-17, 180:14-25, 182:3-11, 183:8-17.

Petitioner’s alleged “trial and error” also ignores that (1) the patent identifies (via expressly incorporated references) 20 exemplary compounds across nine inhibitor classes (POR, 9-11; EX1001, 2:49-52, 7:33-8:37) and (2) hundreds more were known in the art (POR, 11-12; EX2005, ¶¶68-69, 121-122 App’x A; EX2118, 53:22-54:9); *UroPep*, 276 F. Supp. 3d at 647-649. Nor does it account for—much less dispute—the patent’s disclosure that “[r]outine methods can be used to design an inhibitory nucleic acid that binds to the target sequence” (EX1001, 9:3-5) and examples of various types of inhibitory nucleic acids (EX1001, 13:18-20:13; POR, 11-12, n.12).

3. Vitiligo Is an Autoimmune Disease

Vitiligo is an autoimmune disease. POR, 14; EX1002, ¶49; EX1004, ¶37; *see also* EX2060. While there may be multiple possible triggers, the art taught that the resulting autoimmune disease is indistinguishable. *See* EX2053, 3 (chemically induced vitiligo “is indistinguishable from classical vitiligo”); EX2060; EX2118, 102:17-103:5; EX1046, 271:7-18.

Petitioner relies on Dr. Plott as affirmative testimony regarding vitiligo's causes. Reply, 16-17. But Dr. Plott testified he has no such opinions. EX2118, 94:18-95:25, 96:2-8. Nevertheless, Dr. Plott agreed with the depiction in EX2060, Figure 1 (reproduced below) showing that "vitiligo pathogenesis begins with altered melanocytes... [that] triggers autoimmunity...."

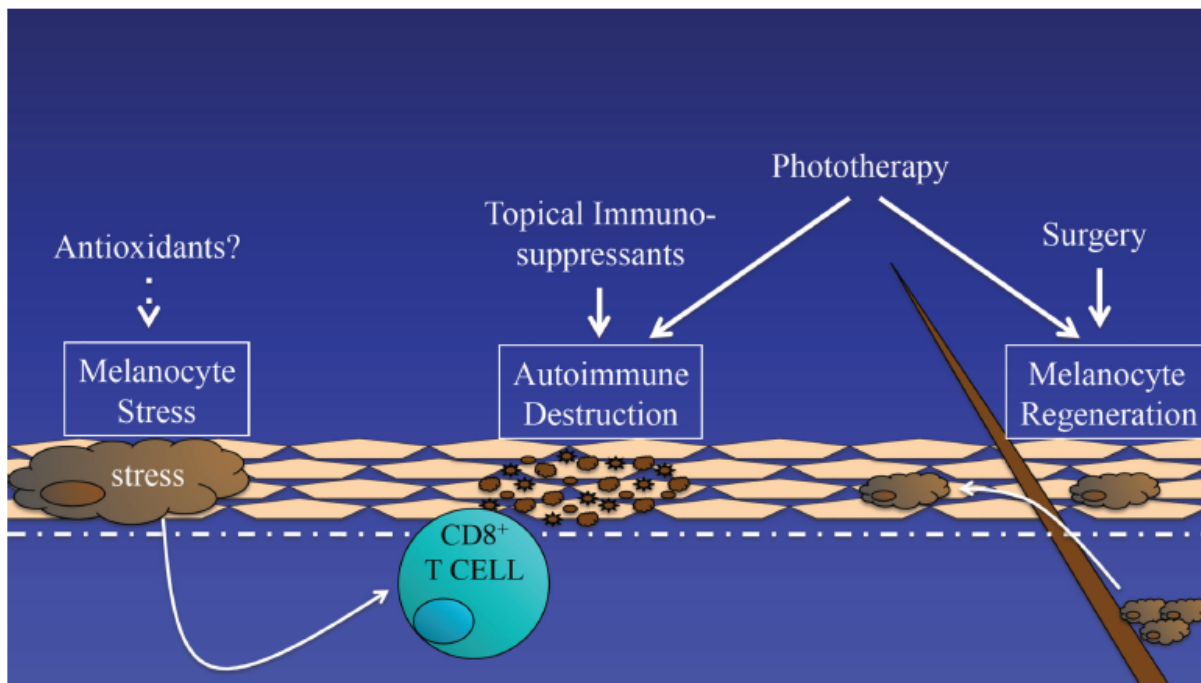


Fig. 1.

Vitiligo pathogenesis begins with altered melanocytes that exhibit an elevated cellular stress response. This triggers autoimmunity, which targets melanocytes for destruction, resulting in focal depigmentation. Repigmentation requires the growth and migration of melanocytes, typically from hair follicles. Thus, there are 3 goals to consider during the treatment of vitiligo: 1) reducing melanocyte stress, 2) suppressing autoimmune targeting of melanocytes, and 3) promoting melanocyte regeneration. Current treatments, including topical immunosuppressants, phototherapy, and surgical approaches, partially address these goals in overall non-targeted ways.

EX2060, 1-4, 14 (Fig. 1); EX2118, 104:24-105:10. That is, while there may be different triggering events, they ultimately lead to the same autoimmune pathogenesis. EX2060, 1 ("Vitiligo is caused by a dynamic interplay between

genetic and environmental risks that initiates an autoimmune attack on melanocytes in the skin.”).

B. Petitioner’s Declarants Did Not Address the POSA’s Perspective, Full Specification, or Art as a Whole

Petitioner does not dispute that a POSA had experience “researching cytokine signaling pathways” and was familiar with known inhibitors of IL-15 and IL-15R as described in the ’505 patent and recognized in the art. POR, 26-27. Drs. Plott and Abbas, however, failed to consider “the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010); *see also Kyocera Senco Indus. Tools v. Int’l Trade Comm’n*, 22 F.4th 1369, 1376-1377 (Fed. Cir. 2022) (excluding testimony when proffered expert did not qualify as a POSA). Indeed, neither considered the entirety of the specification’s incorporated references or the whole state of the art. POR, 30-32; EX2007, 6:2-17; EX2008, 5:18-22; EX2118, 55:24-56:10, 186:11-20. This “head-in-the-sand” approach is particularly problematic for §112 testimony, as declarants failing to consider the POSA’s perspectives are bound to find a disclosure insufficient.

1. Dr. Plott

Dr. Plott lacked bases to provide competent testimony. He admitted to having little to no experience with IL-15 signaling inhibitors, that he had not worked with

any nucleic acids that inhibit a particular cytokine, and that he was not familiar with types of nucleic acids that may be used for inhibiting gene sequences. EX2008, 16:14-17, 17:14-16. Dr. Plott also admitted to knowing very little about therapeutic use of IL-15 inhibitors beyond the two references relied upon to allege obviousness. EX2008, 19:23-20:8. He stated that he would have to consult specialized experts beyond his skill as a “medical practitioner” for specific relevant information regarding, *inter alia*, cytokine signaling pathways. EX2118, 8:24-9:4, 9:13-21, 11:1-3, 10:23-11:17, 12:6-14, 14:4-15:12, 15:21-16:3, 18:8-14, 22:3-14. Further, his experience studying vitiligo and immunology had not advanced since the 1980s, he believes treatment of vitiligo has changed “not very much” from 1990 to 2017, and his current clinical bio does not identify any vitiligo specialization or focus. EX2118, 22:24-23:10, 26:2-4, 26:20-25, 28:21-29:1.

Dr. Plott is also substantively wrong. He asserts that Patent Owner’s expert, Dr. Damsky, “never identifies any inhibitor of IL-15 or the IL-15 receptor for which he substantiates efficacy in humans.” EX1047, ¶15. But Dr. Plott mischaracterized a rheumatoid arthritis (RA) clinical trial (EX1049, 1) as a “failure” that “did not work in humans” even though there was “substantial improvement in disease activity” and *positive* “no significant effect” *safety* signals were reported. *Compare* EX1047, ¶27 *with* EX2118, 113:22-114:20. He then relied on the *absence* of data from a psoriasis clinical trial and willfully ignored statistically significant improvement in

pre-specified endpoints in coeliac disease to assert a “fail[ure] to translate efficacy in mouse models into efficacy in human disease.” *Compare* EX1047, ¶28 with EX2118, 116:5-16, 125:1-126:16, 128:19-129:8; EX1052, 2-3. His “evidence” of “no efficacy” included a single dose Phase I trial (not assessing efficacy) for leukemia (non-autoimmune disease) where the cells did not require IL-15 for proliferation. EX1012, 7; EX2118, 133:13-137:8. Contradicting his original premise, Dr. Plott ultimately admitted that POSAs knew IL-15 antibodies had shown human efficacy. EX2118, 130:15-24.

Significant portions of Dr. Plott’s testimony also lack evidentiary support and should be accorded no weight. EX1047, ¶¶10-15, 50-51, 53; *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (PTAB Aug. 24, 2022) (precedential). Large swaths are quotations, mischaracterizations, and uninformed interpretations of Dr. Damsky’s deposition²—improper opinion testimony entitled to no weight, seemingly included to circumvent Petitioner’s word count. EX1047, ¶¶55-67, 73; EX2118, 64:10-20, 67:7-22, 68:3-23, 69:1-16, 70:1-18, 72:2-20, 79:14-83:11, 94:18-95:4; Fed.R.Evid. 702. Indeed, Dr. Plott admitted he offered no opinion on

² *Compare* EX1047, ¶¶55 (citing EX1046, 94:7-8, 121:7-16, 158:16-23), 57 (citing EX1046, 232:1-235:7, 235:14-236:9) with EX2118, 63:22-64:5, 67:7-22, 69:1-24, 77:9-78:8, 79:22-80:4.

points central to the Reply, including JAK inhibitors and the causes of vitiligo. *E.g.* EX2118, 47:13-48:2, 72:2-20, 94:1-17, 95:7-97:2.

2. Dr. Abbas

Dr. Abbas offered no declaration in Reply. However, Petitioner's continued heavy reliance on Dr. Abbas (e.g., Reply, 3-5, 8, 12) is irreconcilable with his admissions, including that he was not aware of the number and type of IL-15 signaling antagonists. EX2007, 71:11-24, 81:21-82:12; *see also* POR, 30-31.

C. Forte Reliance

Petitioner does not dispute its reliance on the same *Harris* mouse model and data disclosed in the '505 patent (reproduced in EX2046) to expect efficacy of its different IL-15 antibody (FB-102) in human vitiligo. *Compare* POR, 33-25 with Reply, 21-22. In fact, confirming the "standard approach" of starting with "a scientific basis followed by rational design followed by proof of concept followed by clinical trials" described by Dr. Abbas (EX2007, 65:21-67:20), Petitioner relied on preclinical PoC data in multiple autoimmune conditions to expected therapeutic efficacy. POR, 33-35; EX2003, 1; EX2004, 5, 8, 26, 33; EX2009, 3-12; EX2045; EX2046; EX1007; EX1012. Petitioner's reliance on this data without knowing ChMBC7's structure (which is not reported in EX2046) is irreconcilable with its arguments that a POSA would not have understood the '505 patent to provide sufficient support for the claimed method of treating vitiligo.

III. Petitioner Failed to Establish Lack of Written Description or Nonenablement

Patent Owner presented significant evidence documenting a well-known class of compounds known to block IL-15 signaling, a classic research paradigm relied upon for expecting cytokine blockade to treat autoimmune diseases, and efficacy of IL-15 signaling inhibition in treating certain autoimmune diseases. *Supra*, §II.A. With this background knowledge, which was not considered in the Petition (Paper 2, (“Pet.”)) or ID (Paper 10), a POSA would have understood the ’505 patent to provide sufficient written description and enabling support for the claimed method of treating vitiligo with IL-15/IL-15R inhibitors. POR, 38-73.

Petitioner’s Reply maintains its head-in-the-sand approach, relying on an unqualified declarant—a combined lack of experience and failure to investigate—to narrowly focus on alleged differences in “type” of IL-15 signal inhibition, speculate about clinical development, and challenge the *Harris* mouse model. Petitioner’s challenges fall flat. Among other things, they fail to apply the appropriate legal analysis, ignore disclosures reflecting an understanding that inhibitors of IL-15 and IL-15R have class-wide efficacy for treating autoimmune conditions, and ignore Petitioner’s own reliance on identical information. Petitioner also wholly fails to address narrower claims 2-5. *Cf.* POR, 50-51, 73.

A. Petitioner Does Not Dispute or Apply Correct §112 Standards

Petitioner does not rebut Patent Owner’s arguments addressing the applicable legal standards for written description and enablement. Out of over thirty cases cited in the POR, Petitioner addresses only one—*United Therapeutics Corp. v. Liquidia Techs.*, 74 F.4th 1360 (Fed. Cir. 2023)—and only in passing. *Compare* POR, 39-71 *with* Reply, 15.³ Petitioner’s failure to dispute or apply this §112 precedent dooms its unpatentability arguments.

Petitioner, for example, ignores Patent Owner’s *Wands* analysis and never addresses—much less disputes—that the §112 inquiry is properly tied to the claimed novelty of using a known class of compounds to treat a disease not previously associated with those compounds or pathway. POR, 39-43, 52-57, 60-73. Like *UroPep*, here “the invention was to use a group of compounds well known in the art... in a novel method of treating” vitiligo. *UroPep*, 276 F. Supp. 3d at 648.

Petitioner instead continues to misrepresent that the “claims cover several massive genera” and argue that the patent’s disclosed working example “is not

³ Petitioner’s reference to “[b]inding precedent (including *Rochester* and *Amgen*),” addressed in the Institution Decision (Reply, 18) is an improperly incorporated and undeveloped argument not entitled to consideration. 37 C.F.R. §42.6(a)(3); *Apple Inc. v. Ameranth, Inc.*, CBM2015-00080, Paper 44 at 6-7 (PTAB Aug. 26, 2016).

representative” of “the claimed genera.” Reply, 1, 15-17. Because the prior art disclosed hundreds of IL-15/IL-15R inhibitors (§II.A.2., *supra*), §112 support for the novel treatment method does not turn on the size of the inhibitor genus disclosed in the patent. *UroPep*, 276 F. Supp. 3d at 649; *Merck Sharp & Dohme Corp. v. Genentech, Inc.*, PGR2021-00036, Paper 10 at 20 (PTAB July 24, 2021) (relevant inquiry is the challenged method claims and not the compounds themselves). Instead, given the undisputed “substantial knowledge in the field regarding the genus,” the disclosure in the ’505 patent provides requisite written description and enabling support for the claimed method. *UroPep*, 276 F. Supp. 3d at 649.

Petitioner does not dispute that the claimed method of treatment using a well-known class of cytokine inhibitors differs from claims to a novel class of antibodies or their uses, as in *Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023). POR, 54-56. To the extent Petitioner’s one word invocation of “*Amgen*” (Reply, 18) is considered, it fails to dispute the sufficiency of the ’505 patent’s disclosure in view of the Court’s explanation that:

it may suffice to give an example (or a few examples) if the specification also discloses some general quality running through the class that gives it a peculiar fitness for the particular purpose. In some cases, disclosing that general quality may reliably enable a person skilled in the art to make and use all of what is claimed, not merely a subset

and that a specification is not inadequate where

it leaves the skilled artist to engage in some measure of adaptation or testing.... [A] specification may call for a reasonable amount of experimentation to make and use a patented invention.

Amgen, 598 U.S. at 611-612 (internal citations and quotations omitted).⁴ Notably, the un rebutted evidence shows that the IL-15/IL-15R inhibitors disclosed in the specification and known in the art share the common “general quality” of inhibiting a pathway known to be relevant to and having “particular fitness for the particular purposes” of (*id.*) treating certain autoimmune diseases by blocking IL-15 signaling. *Supra* §II.A.1-2.

Regarding *United Therapeutics*, Petitioner’s arguments addressing the *Harris* mouse model are misdirected. *See* Reply, 15-17. First, Petitioner does not dispute that reliance on animal models is legally sufficient. *United Therapeutics*, 74 F. 4th at 1369; POR, 48. Second, the POR did not “invert[] the holding of *United Therapeutics*” (Reply, 15) that

It would be incorrect... to require a separate disclosure in the specification for each individual variant of the condition... in

⁴ ***Bold italic*** added herein.

order to satisfy... 35 U.S.C. §112, unless these variants are specified in the claims.

74 F.4th at 1371. Finally, Petitioner fails to address evidence documenting reliance on and linking the *Harris* mouse model to human vitiligo. *Supra*, §II.C; *infra*, §III.C.

As detailed in the POR and herein, the '505 patent claims meet the unrebutted and undisputedly applicable test of evaluating §112 by focusing on the claimed novel *method* (not on the genera of compounds used to implement that method), where those compounds represent a known class with “some general quality running through the class that gives it a peculiar fitness for the particular purpose.” *Amgen*, 598 U.S. at 611 (internal citations omitted).

B. Petitioner and Its Declarant Fail to Address the Known Classes of Inhibitors of IL-15/IL-15R

Petitioner ignores the state of the art by focusing instead on a few IL-15/IL-15R inhibitors, misrepresenting the specification (the entirety of which its declarants never considered), proffering an untimely and unsupported claim construction, and inferring failures where not reported. These misdirected arguments are irrelevant to §112 support for the claimed method of treatment employing a well-known class of inhibitors.

1. Petitioner Ignores the State of the Art

Petitioner contends that IL-15/IL-15R inhibitors were “not a recognized genus” (Reply, 11) and that the claims lack support because they allow for any level of IL-15

inhibition across any type of IL-15 receptor, which allegedly “implicate[s] different results” (Reply, 3-8). Petitioner ignores that by 2017 over 300 inhibitors of IL-15/IL-15R were known and expected to have therapeutic activity in blocking IL-15 signaling. *Id.* Thus, a POSA would have understood that IL-15/IL-15R inhibitors share a common trait—therapeutic activity from blocking IL-15 signal—regardless specific mechanism. EX1046, 161:14-162:4 (“[T]o the extent that something inhibited IL-15, I would expect that it is an IL-pathway inhibitor.”); §II.A.1-2, above. Regarding level of activity, Dr. Plott agrees that lower affinity drugs are used at higher doses to achieve the same effect, with dose adjustments being “routine.” EX2118, 113:1-9; EX1002, ¶110; Pet., 68.

Petitioner’s argument that “there was no expectation of class-wide efficacy” rests on Dr. Plott’s new testimony. Reply, 8 (citing EX1047, ¶¶10, 50). Not only does Dr. Plott ignore previously cited evidence and argument (e.g, POR, 12-13), he admits to not considering whether references he had in hand reflected an understanding that inhibitors of IL-15/IL-15R have such class-wide efficacy. For example, Dr. Plott ignored that references identifying novel IL-15/IL-15R inhibitors disclosed expected efficacy for treating IL-15 mediated autoimmune diseases without testing for disease-specific activity. EX2013, 6; EX2014, 2; EX2015, 8-9; EX2024, 4, 17; EX2024, 17; EX2028, 1, 9; EX2118, 177:22-178:5, 179:22-180:11, 181:10-21, 182:21-183:6. Petitioner’s argument is also contradicted by its

immunologist, Dr. Abbas, who admitted that “it [was] common as of April 2017 [and today] to expect that species that would antagonize IL-15 signaling would be useful in diseases—autoimmune diseases that had been identified as having an IL-15 mechanism.” EX2007, 74:19-75:10.

Rather than contradicting the expected class effect, Petitioner relies on allegedly “differential effects” based on inhibitor target and “unexpected” effects of a few aberrant inhibitors. Reply, 4-8; EX1047, ¶25 (“the lead IL-15 antibody blocked some forms of IL-15 signaling *but unexpectedly* enhanced others”), ¶26 (“*unexpectedly* increased the production of proinflammatory cytokines”), ¶29 (“*unexpectedly* potentiated IL-15”). Indeed, of the over 300 IL-15 inhibitors cited in Dr. Damsky’s Appendix A, Dr. Plott and Petitioner take issue with merely 15. *See* POR 11-12; EX2005, App’x A; EX1047, ¶¶29-30, 80-84; EX2118, 58:23-59:22 (no disagreement unless addressed in EX1047). This does not, however, undermine the voluminous evidence (including as described in the above paragraph) that common therapeutic effects were expected from commonly antagonizing IL-15 signaling. *E.g.*, EX2005, ¶¶52-63, 80-83; *supra* §II.A.1-2. Petitioner cannot establish unpatentability based on a handful of IL-15 inhibitors it claims to have “differential” or even no effect. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984) (“Even if some of the claimed [inhibitors] were inoperative, the claims are not necessarily invalid.”). The proper inquiry is

whether a POSA would have to unduly experiment to practice the claimed invention (*id.*); here, the record indicates a POSA would not and that Petitioner has not established otherwise. POR, §VIII; *supra* § II.A; EX2005, ¶¶52-63, 80-83.

2. Petitioner’s Challenges to the Specification Fail

Unable to rebut Patent Owner’s evidence that inhibitors of IL-15/IL-15R were well-known, Petitioner unpersuasively argues that the specification is insufficient for having a “narrow” working example and failing to disclose the structure or binding epitope of ChMBC7. Reply, 12-17. Petitioner’s arguments are misguided and fail to establish that the claimed method employing a well-known class lacks §112 support.

The ’505 patent provides extensive testing demonstrating that blocking the IL-15 pathway effectively treats vitiligo, which is sufficient to describe and enable that claimed method of treating vitiligo using a well-known class of inhibitors to inhibit a well-known pathway. EX1001, 30:53-37:17; EX2005, ¶¶101-106. There is no requirement or need to disclose the precise structure of ChMBC7, especially since IL-15 inhibitors were understood to share common therapeutic effects independent of their specific structure of mechanism of inhibition, i.e., binding target. *E.g.*, *Bayer Healthcare LLC v. Baxalta Inc.*, 989 F.3d 964, 981-82 (Fed. Cir. 2021); EX1046, 271:23-272:7; *supra* §II.A.1. Petitioner, tellingly, cites no contrary precedent. Notably, such information would also have been irrelevant to Dr. Plott, who would

not recognize structures of antibodies he uses and does not need to know their binding epitopes. EX2118, 30:5-14; 31:11-17, 31:24-32:10, 32:20-35:12.

Petitioner also argues that ChMBC7 is not representative of all potential inhibitors. Reply, 13. Petitioner ignores that “[i]t may suffice to give *an example*,” where, as here, there is “some general quality... running through the class that gives it a peculiar fitness for the particular purpose.” *Amgen*, 598 U.S. at 611 (internal citations omitted). And here the evidence shows that the “general quality” of IL-15/IL-15R inhibitors antagonizing the pathway were expected to have the common fitness for treating IL-15 mediated autoimmune diseases. §§II.A.1-2, II.C *supra*.

3. Petitioner’s Untimely “Downstream” Inhibition Argument Should Be Rejected

Petitioner raises untimely new claim construction arguments that the claims cover “downstream” inhibition, i.e., JAK inhibitors. *Compare* Reply, 9-11 with Pet., 56; *Boart Longyear Ltd., v. Australian Mud Company Party Ltd.*, IPR2019-01129, Paper 26, 20 (PTAB Nov. 20, 2020) (rejecting Petitioner’s claim construction argument made first in Reply as “new and untimely because it could have and should have been raised in the Petition”). Petitioner’s new assertions are inconsistent with the specification, prosecution history, and Petitioner’s own obviousness theory, none of which are addressed by Petitioner. *Cf.* Reply, 9-11.

As an initial matter, it is unclear which claim term Petitioner is now construing. But asserting that use of JAK inhibitors are within the claim scope is inconsistent with the specification (not addressed by Petitioner) describing “Inhibitors of IL-15 and the IL-15 Receptor” (EX1001, 7:34-8:5) and *separately* disclosing JAK inhibitors. EX1001, 8:6-22. Notably, Petitioner and its declarant knew of—but selectively ignored—testimony of Dr. Damsky that administering a therapeutically effective amount of a JAK inhibitor would *not* satisfy claim 1. EX1045, 159:20-160:3; EX2118, 77:9-78:8.

4. Petitioner’s Improper Requirement for Human Clinical Efficacy

Petitioner’s reliance on allegedly “abandoned” clinical trials and the absence of FDA approved IL-15/IL-15R inhibitors (Reply, 19-21) is not only irrelevant to §112 support but misrepresents the evidence. *See also* EX2118, 140:16-141:5 (if not FDA approved, a putative treatment “has to at least meet a milestone that the investigators would say, you know, this is worthwhile moving forward”).

First, that human clinical testing will ultimately be required for any individual inhibitor to confirm safety and efficacy is relevant for FDA approval but not for §112. *United Therapeutics*, 74 F.4th at 1369.

Second, Petitioner manufactures failures where none are reported. Its basis for characterizing Hu-Mikβ1 as a “failure” is a lack of additional reported trials, not

absence of efficacy. Reply, 21; EX1047, ¶37; *see also* EX2118, 149:13-29, 150:10-151:12.

Third, alleged (but unconfirmed) absence of clinical development does not reflect “failure.” *Cf.* Reply, 21 (citing EX1047, ¶¶39-41). Similarly, that one prolific group sought to develop new inhibitors does not mean that prior inhibitors lacked efficacy. *Cf.* Reply, 21 (citing EX1047, ¶¶39-41, EX2013, 4:1-8, EX2014, 4:9-15, EX2015, ¶[0022], EX2025, 4:34-5:2). To the contrary, that group recognized the “[p]ositive results of phase II clinical trials....” EX2025, 4:21-24.

At bottom, Petitioner’s arguments rest on improper metrics. Petitioner’s discrete outliers also do not obviate the POSA’s documented expectation that IL-15/IL-15R inhibitors were therapeutically effective for IL-15 mediated diseases. *See* §§II.A.1-2, above.

C. The *Harris* Mice Are Representative of Vitiligo

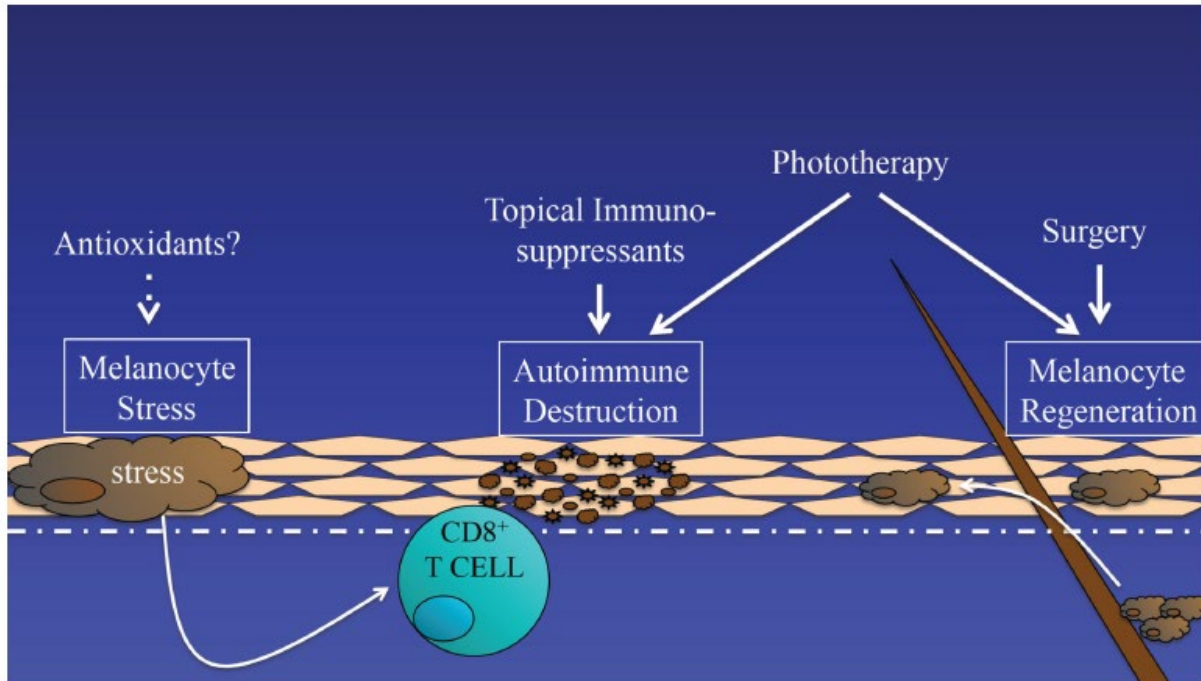
Petitioner argues that the “Harris model is too narrow a subset to represent the disease [vitiligo] as a whole.” Reply, 15-17. This argument fails for several reasons.

First, as established in the POR, reliance on preclinical PoC models to support expected human treatment is reflected in the art and Petitioner’s own practice. POR, 15; EX2005, ¶¶84-89. Petitioner also has not disputed that the *Harris* model was the primary vitiligo model as of 2017. *Compare* POR, 15 *with* Reply, 15-17; *see also* §II.C *supra*.

Second, any requirement for human testing is contrary to precedent that—unlike FDA approval—reliance on animal models is more than sufficient for patentability. *United Therapeutics*, 74 F.4th at 1369.

Third, Petitioner’s speculation that different disease triggers might affect efficacy of IL-15 treatment fails to support its §112 burden. Reply, 17 (citing EX1047, ¶48)⁵; *Alcon*, 745 F.3d at 1190 (speculation does nothing to establish “that any claimed embodiments would be inoperable and that a person of ordinary skill in the art would have been unable to practice the asserted claims without resorting to any experimentation, let alone undue experimentation”). Petitioner also conflates triggering *causes* of vitiligo with the autoimmune disease itself. Reply, 15-17. While there may be multiple possible triggers, the art taught that the result is the same autoimmune disease:

⁵ Dr. Plott disclaimed that EX1047, ¶48 provides any affirmative opinions. *E.g.*, EX2118, 96:10-97:2. Moreover, his assertion that “inhibiting CD8+T cells depends not only on treating a key mechanism but also depends on the ability to treat the different root causes” (EX1047, ¶48) appears to rely on EX1057, which does not support the assertion and instead states that the primary mechanistic causes of vitiligo “likely overlap” and ultimately all lead to skin depigmentation. EX1057, 17.



EX2060, 1-4, 14 (Fig. 1); *supra* §III.A.3. Petitioner’s passing references to “segmental” vitiligo (Reply, 17) also go nowhere. *E.g.*, EX2053, 3 (segmental vitiligo “is 10 times less common than other variants of vitiligo”); *United Therapeutics*, 74 F.4th at 1370-71.

D. Dr. Damsky’s Testimony Should Be Credited Over Dr. Plott

Petitioner’s Reply declarant, Dr. Plott, lacks expertise in cytokine signaling. He admitted to having little to no experience with inhibitors of IL-15 signaling, little knowledge of therapeutic uses of IL-15 inhibitors, and limited recent experience studying vitiligo. *See supra* §II.B.1. Fundamentally, he failed to consider the ’505 patent specification or art as a whole and applied the wrong standards to the limited evidence he did consider (*supra* §II.B.1) including improperly relying heavily on

human clinical efficacy and safety as standards for patentability. *See e.g.*, EX1047, ¶¶24, 27-28, 31. But whether any IL-15/IL-15R inhibitor had shown efficacy in humans (they had) or approved for clinical use (Reply, 19) is not the proper inquiry. *Supra* §III.B.4.

In contrast, Patent Owner's declarant, Dr. Damsky, provided the requisite analysis based on the '505 patent's disclosure that an inhibitor of IL-15R (ChMBC7) effectively treats a patient's vitiligo lesion and remains durable after treatment is stopped. Combined with the general knowledge in the art, a POSA would have recognized that targeting IL-15 signaling was "a strategy to clear autoreactive memory cells from the tissue, resulting in a long-lasting, durable response to treatment." EX1001, 6:16-24; EX2005, ¶¶106, 153.

Instead of showing that classes of IL-15/IL-15R inhibitors were unknown, Petitioner nitpicks and mischaracterizes Dr. Damsky's testimony. EX2118, 186:11-20. For example, Petitioner misleadingly relies on Dr. Damsky's testimony that "assays were inadequate to identify conclusively whether implicated molecules were encompassed by the claims" based on poor hypotheticals that failed to specify conditions. Reply, 11-12. When assays have specific conditions and data, Dr. Damsky explains that a POSA would "have been able to conclusively determine whether a compound is an inhibitor of IL-15 or the IL-15 receptor...." EX1046, 270:2-19. In fact, the '505 patent describes cytokine and downstream IFN γ

production assays for determining whether the tested IL-15R inhibitor effectively blocks IL-15 signaling.⁶ EX1001, 4:16-24, 33:48-34:44. Petitioner's attacks on Dr. Damsky premised on distinguishing clinical trials for "anti-IL-15 antibodies vs. anti-CD122 antibod[ies]" ignores that both were in clinical trials that were completed or initiated. Reply, 19; EX1016, 6; EX2118, 129:9-132:6.

Unable to marshal facts or law to demonstrate unpatentability, Petitioner resorts to unfounded *ad hominem* attacks on Dr. Damsky. Reply, 25-27. Dr. Damsky was qualified as a POSA by the time of invention: he received his Ph.D. in Cell & Molecular Biology in 2011 and M.D. in 2013, and was working as a Chief Resident in Dermatology at Yale, where he had been practicing as a medical resident since 2013 and began treating patients with vitiligo even earlier as a medical student. EX2005, ¶¶2-6; EX2006, 1; EX1046, 116:16-19, 117:1-9. Dr. Damsky's Ph.D. training focused on intracellular signaling pathways and the effects of alerting signaling to these pathways, including the role of cytokine signaling. EX2005, ¶6. As of the critical date, Dr. Damsky thus exceeded the educational requirements of a POSA with two qualifying degrees and at least 3-5 years of experience in treating

⁶ Petitioner ignored evidence of record confirming that such assays were routine. EX2013, 14-19; EX2014, 11-15; EX2015, 9-10; EX2024, 14-15; EX2118, 160:1-5, 178:7-183:17.

autoimmune diseases (via residency beginning in 2013) *and* researching cytokine signaling pathways relevant to treating autoimmune diseases (via at least Ph.D. work before 2011). *See* EX1046, 267:17-268:16; *contra* EX2118, 22:20-23:10, 26:3-4, 26:20-25. Petitioner’s unsubstantiated attorney argument that Dr. Damsky is somehow biased (Reply, 26-27) is contradicted by his signed declaration affirming he is an independent expert (EX2005, ¶1), his CV which reports his research with Incyte (EX2006, 3), and his testimony confirming he did not consult with any of the parties or inventors regarding this case (EX1046, 131:20-132:24). Instead, along with Petitioner’s reliance Dr. Damsky’s publication (EX1021), Petitioner only reinforces that Dr. Damsky (unlike Drs. Plott and Abbas) is a reliable expert active in the research field.

IV. Petitioner Fails to Establish that Claims 1-5 Would Have Been Obvious Over *Xing* and *Harris*

A. Petitioner Fails to Establish a *Prima Facie* Case

At institution, the Board found that Petitioner failed to demonstrate that *Xing* and *Harris* render the claimed invention obvious. ID, 31-34. Petitioner fails to provide any evidence to address the Board’s concerns or otherwise show how the Board erred in its analysis. Reply, 22-23. Instead, Petitioner points to the same unsupported conclusory assertion that “[a]dministering TM- β 1 to Harris mice was thus reasonably expected to treat vitiligo lesions and durably reverse them.” Reply, 23.

Petitioner further fails to address *Xing*'s own statements that blocking IL-15 signaling did not reverse disease. Nor does Petitioner address the Board's concerns or Dr. Damsky's explanation of *Xing*'s feed-forward loop leading to increased IL-15 production that would dissuade use of TM- β 1. ID, 33; EX2005, ¶200. Given these uncontroverted facts, Petitioner fails to show that the challenged claims are obvious.

B. Petitioner Fails to Counter Objective Indicia of Nonobviousness

Petitioner's response to Patent Owner's evidence of unexpected results, long-felt need, commercial value, and copying rests on unsupported attorney argument "carries no weight." *Sandoz Inc. v. AbbVie Biotech. Ltd.*, IPR2017-01823, Paper 16 at 15-16 (PTAB Feb. 9, 2018); *Apple Inc. v. Qualcomm Inc.*, IPR2019-00112, Paper 7 at 10 (PTAB Apr. 11, 2019). Tellingly, Petitioner's declarant did not address Patent Owner's objective indicia in Reply. Dr. Plott's admission, however, that the treatment of vitiligo has changed "not very much" from 1990 to 2017 (EX2118, 26:2-4) reinforces the long-felt need.

Regarding unexpected results, Petitioner offers no new evidence but argues that the unrebutted evidence of durable repigmentation "is not commensurate in scope with the claims" because "[t]he claims *do not* recite durable repigmentation." Reply, 24 (Petitioner's emphasis). But there is no requirement for unexpected results to be claimed in order to be commensurate in scope. *See Purdue Pharma L.P. v.*

Endo Pharms. Inc., 438 F.3d 1123, 1136-37 (Fed. Cir. 2006). Its argument against the *Harris* mice fail for the reasons previously addressed. §III.C *supra*.

V. Conclusion

For these reasons and those detailed in the POR, Petitioner has failed to prove that any challenged claim is unpatentable.

Respectfully submitted,

Dated: February 28, 2024

/Mark J. Feldstein/

Mark J. Feldstein

Reg. No. 46,693

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I, Mark J. Feldstein, certify that **PATENT OWNER'S SUR-REPLY** contains 5,551 words, excluding those portions identified in 37 C.F.R. § 42.24(c), as measured by the word-processing system used to prepare this paper.

Dated: February 28, 2024

/Mark J. Feldstein/

Mark J. Feldstein

Reg. No. 46,693

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Sur-Reply** was served electronically via email on February 28, 2024, in its entirety on the following:

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Dated: February 28, 2024

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