

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORTE BIOSCIENCES, INC.,
Petitioner,

v.

UNIVERSITY OF MASSACHUSETTS,
Patent Owner.

Patent No. 11,278,505

REPLY DECLARATION OF DR. R. TODD PLOTT

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I, R. Todd Plott, declare as follows:

I. QUALIFICATIONS

1. I have been retained by Counsel on behalf of Forte Biosciences, Inc. My opinions are based on my skills, knowledge, training, education, and experience in matters of this nature, and my examination of the materials utilized in preparing this declaration.

2. I am a Board-certified Dermatologist serving as the Chief Medical Officer for Epiphany Dermatology.

3. I received my Doctorate of Medicine at the University of Texas Galveston in 1989, Dermatology residency at University of Arkansas and Dermatology research fellowship at the National Institutes of Health.

4. I spent 16 years in various positions in the pharmaceutical industry developing dermatology drugs and the last 13 years as a general-practice dermatologist.

5. One of the papers that I have authored pertains to the surgical treatment of vitiligo.

6. I treat a wide variety of skin diseases, including vitiligo in my dermatology practice.

7. One of the awards that I have received was first-place in a national research competition for my research in vitiligo.

8. A copy of my *Curriculum Vitae*, submitted as EX1005, contains further details on my education, experience, publications, and other qualifications to render an expert opinion in this matter.

II. SCOPE OF WORK AND SUMMARY

9. I previously submitted testimony in this case. I have been asked to review and respond to the declaration of Dr. William Damsky (EX2005), which was submitted after my testimony. I have been asked to address Dr. Damsky's testimony regarding whether a person of ordinary skill in the art as of April 2017 (the invention date evaluated by Dr. Damsky), expected class wide therapeutic activity from inhibitors of IL-15 or the IL-15 receptor, including newly discovered inhibitors.¹ In connection with this analysis, I have relied on my specialized

¹ I note that Dr. Damsky uniformly addressed April 2017 as the date of "invention" for purposes of his opinions. EX2005, ¶¶94, 111, 141; *see also* EX1046, 12:7-9 (Dr. Damsky admitting that 2017 is the critical date in this case). Dr. Damsky also testified in his declaration that the understanding of a POSA had not changed from 2017 to the present (presumably Oct. 2023 when he signed his declaration) regarding his opinion that IL-15 signaling inhibitors share common therapeutic utility based on their common mechanisms of inhibiting cytokine signaling. EX2005, ¶110.

education, knowledge, training and experience. Forte pays \$1,075 per hour for my services. No part of my compensation is dependent on my opinions or on the outcome of this proceeding.

10. Dr. Damsky's opinion that a person of ordinary skill in the art as of April 2017 expected common therapeutic activity from inhibitors of IL-15 or the IL-15 receptor, including newly discovered inhibitors, is incorrect. Dr. Damsky's own deposition testimony illustrates that cytokine signaling, including IL-15 signaling and inhibition thereof, was complex and unpredictable. As illustrated by the same references cited by Dr. Damsky, the effects of a given molecule varied widely depending on its target (e.g., IL-15 vs. IL-15R α vs. IL-15R β vs. IL-15R γ), the variety of IL-15 receptor(s) implicated, the location (i.e., epitope) where the molecule interacts with a given target, and the nature of the specific molecule being used. Indeed, molecules shown to block the interaction of IL-15 with iterations of the IL-15 receptor, and even shown in vitro to inhibit IL-15-induced proliferation of T cells, lacked the hoped-for efficacy in vivo (and in some cases achieved the opposite of the hoped-for effects). Moreover, molecules that appeared to show efficacy in animal studies lacked demonstrated efficacy in humans. Dr. Damsky's chosen exhibits fail to support his opinions that efficacy was accepted as a class wide property of inhibitors of IL-15 or the IL-15 receptor.

11. Moreover, Dr. Damsky's sweeping opinions in his declaration about class wide efficacy are unsupported and even contradicted by the references he cites. They also are rebutted by what he said candidly before he was hired to testify here. In 2021, more than four years *after* the critical date, he admitted that the "proof of concept study" evaluating IL-15 blockade in patients with vitiligo was taking place and he had his "finger crossed" that it is going to work. EX1046, 232:1-235:7. In other words, he was wishing for luck because no one knew whether the IL-15 blockade using the tested antibody really would work for patients with vitiligo. Dr. Damsky elaborated with a conditional that "if" the IL-15 blockade "were able to turn off that memory response," then "maybe" you're looking at a long-lasting treatment for vitiligo. EX1046, 235:14-236:9. Dr. Damsky noted in his declaration that the anti-CD122 antibody developed by Villarís is called Auremolimab. EX2005, ¶106 n.3. In other words, years after the critical date, attempting to determine whether a particular molecule (e.g., an anti-CD122 antibody) is effective for treating vitiligo was an uncertain and burdensome trial-and-error process. *See, e.g.*, EX1048, 14 (Dr. Harris stating plainly in 2020: "this type of research takes a lot of time and resources").

12. Aside from Dr. Damsky's failure to accurately assess the prior art or account for the unpredictability in this particular field at the time, the specification of the '505 patent still amounts to nothing more than a proverbial black box, as I

will explain in detail below. The specification does not tell a person of ordinary skill in the art what specific type of inhibition was employed (other than a code name and a receptor target) or provide any basis other than an invitation to search using trial and error for inhibitors of IL-15 or the IL-15 receptor that may or may not provide the same results. Moreover, the Harris mice mimicked symptoms of vitiligo using a simplified model of causation (eliminating the native immune system and replacing it with melanocyte-targeting CD8⁺ T Cells) that was not representative of natural or spontaneous vitiligo. Accordingly, I disagree with Dr. Damsky that the '505 patent's experiments, which exclusively used the minimally characterized ChMBC7 antibody in the Harris mouse model, indicated there was class wide efficacy for inhibitors of IL-15 or the IL-15 receptor even in the Harris mouse model, much less in natural or spontaneous vitiligo.

III. LEVEL OF SKILL IN THE ART

13. From my perspective as a medical practitioner who treats vitiligo, a person of ordinary skill in the art (POSA) of the '505 patent in April 2017 likely would have had a relevant advanced degree and would have worked together in a team with other qualified individuals with expertise in medicine, immunology, molecular biology, cell biology, microbiology, pathology, biochemistry, peptide chemistry, or related fields. A POSA likely would have had several (i.e., 3-5) years of experience in treating autoimmune diseases or researching cytokine signaling

pathways relevant to treating autoimmune diseases. A POSA also could have worked in consultation with a pharmaceutical scientist familiar with formulating drugs for administration.

IV. INHIBITORS OF IL-15 OR THE IL-15 RECEPTOR WERE NOT RECOGNIZED TO HAVE CLASS WIDE EFFICACY FOR TREATING AUTOIMMUNE CONDITIONS.

14. Dr. Damsky argues that “the efficacy of blocking IL-15 signaling for treating certain autoimmune conditions was well established” by April 2017. EX2005, ¶65. He also argues that “the existing knowledge of inhibitors of IL-15 and the IL-15 receptor was advanced by 2017[.]” EX2005, ¶83. Having considered Dr. Damsky’s testimony and the materials he relied upon regarding the use of an IL-15 or IL-15 receptor inhibitor for treating an autoimmune disease, Dr. Damsky is wrong. His opinions create a completely false impression that the prior art taught there was a class wide efficacy for inhibitors of IL-15 or the IL-15 receptor. But it is my considered opinion that a person of ordinary skill in the art did not expect common therapeutic activity from all inhibitors of IL-15 or the IL-15 receptor, including newly discovered inhibitors, and their effects were instead unpredictable. Dr. Damsky’s conclusion of class wide efficacy is simply not supported by the prior art literature at the time. In fact, the prior art literature supports the opposite conclusion. That is, the literature reports instances of failure and unpredictability.

15. Dr. Damsky's opinions are undermined by at least three critical problems. First, he mischaracterizes the references he cites. Second, he takes statements from the references out of context and ignores the portions of the same references that contradict his opinions by teaching variability, unpredictability, and failure. Third, he never identifies any inhibitor of IL-15 or the IL-15 receptor for which he substantiates efficacy in humans. Examples of such errors in Dr. Damsky's testimony are discussed in greater detail below.

A. Dr. Damsky Mischaracterizes Waldmann 2006 and Erroneously Confuses a CD122 Antibody With an IL-15 Antibody

16. Dr. Damsky's representations about the prior art are factually inaccurate. For example, Dr. Damsky argues that Waldmann 2006 states that ““therapeutic strategies that inhibit the actions of IL-15 might prove to be of value in the treatment of such T-cell-mediated autoimmune inflammatory diseases,’ **including RA where a humanized antibody (Mik β 1) specific for IL-15R β (CD122) was in Phase I/II clinical trials.**” EX2005, ¶65 (EX1016, 6; EX1018, Abstract).² This is incorrect. Dr. Damsky is confusing an anti-IL-15 antibody with Mik β 1, a CD122 antibody. Waldmann 2006 does not report that Mik β 1 had been in phase I/II clinical trials for rheumatoid arthritis.

² All bold emphasis in quotes added unless otherwise indicated.

17. Dr. Damsky mischaracterizes Waldmann 2006 as identifying Mik β 1, a humanized antibody specific for IL-15R β (CD122), as already being in Phase I/II clinical trials for rheumatoid arthritis (RA). Waldmann 2006 relies on Villadsen 2003 for the proposition that an “antibody specific for IL-15,” in other words, an anti-IL-15 antibody, “has been effectively used in mouse models of autoimmune diseases, including psoriasis.” EX1016, 600. Waldmann 2006 then states that “such an antibody” (i.e., an anti-IL-15 antibody) “has shown efficacy in a Phase I/II clinical trial involving patients with rheumatoid arthritis.” EX1016, 600 (citing EX1049). Waldmann 2006 is citing Baslund 2005, which concerns an anti-IL-15 antibody, not Mik β 1. This is an important point because he is confusing an antibody to IL-15 with an antibody to the IL-15 receptor. Later, Waldmann 2006 states that Waldmann’s research group tried a humanized IL-2/15R β -specific antibody (Mik β 1) to block trans-presentation of IL-15 to see if it showed efficacy in a phase I clinical trial in patients with T-cell large granular lymphocytic leukemia. EX1016, 600. Waldman 2013, discussed below, explains that this attempt failed to show efficacy. Nowhere does Waldmann 2006 state that Mik β 1, a CD122 antibody, already had been in Phase I/II clinical trials for RA. While Dr. Damsky trumpets the promise of Mik β 1 in 2006, he mischaracterizes the reference and fails to inform the Board that this antibody failed to show efficacy. These types of errors are littered throughout his declaration.

18. Dr. Damsky's conflation of a CD122 antibody with an IL-15-specific antibody is not a harmless mistake, as molecules interacting with these different targets were known to have highly disparate effects. For example, Dr. Harris, an inventor of the '505 patent, admitted during a talk he gave in Dr. Damsky's presence in February 2021 that inhibition of IL-15 was very different than inhibition of its receptors. Among other things, Dr. Harris admitted that it is very difficult to saturate IL-15 with antibody to block the signaling because IL-15 is very highly expressed throughout all tissues of the body. EX1046, 52:1-23, 63:23-65:13; EX1040, 2. Dr. Harris reiterated in a public blog post in January the year before that inhibiting the receptor is not representative of inhibiting the cytokine, with the latter being a worse strategy, less effective, less long-lasting, and less safe in his opinion. EX1048, 3. Accordingly, for at least these reasons, any particular form of CD122 inhibition (Mik β 1 inhibition of IL-15R β) is not necessarily representative of any particular form of IL-15 inhibition.

B. Dr. Damsky Selectively Ignores Reports of Variability, Unpredictability, and Failure of IL-15 Inhibitors.

19. The very references Dr. Damsky cites demonstrate that inhibition of IL-15 signaling using different inhibitors had differential effects rather than class wide efficacy. Dr. Damsky selects out a small subsection of optimistic sounding soundbites but ignores the content actually reported in those references, which report that many candidates failed to show efficacy. Indeed, his sweeping

generalizations are not actually supported by the prior art references he cited. For example, Dr. Damsky quotes Waldmann 2006's statement that there was speculation in 2006 that some inhibitors of IL-15 "might" someday in the future prove to have value in treatment of T-cell-mediated autoimmune inflammatory diseases. EX2005, ¶65 (EX1016, 6). But Waldmann 2006 is not reporting that class wide efficacy had been demonstrated. Dr. Damsky fails to acknowledge that Dr. Waldmann's later paper explained that their investigations failed to show efficacy. Indeed, Dr. Damsky's own cited literature confirms that there was wide variability, unpredictability, and failure rather than class wide efficacy. This is just one of many instances in which Dr. Damsky picks sentences out of context without considering that the prior art as a whole actually contradicts rather than supports his assertion of a class wide efficacy.

i. Dr. Damsky Ignores That One IL-15 Antibody Is Not Representative of Other IL-15 Inhibitors.

20. The very references Dr. Damsky cites demonstrate that inhibition of IL-15 signaling using different inhibitors had differential effects rather than class wide efficacy. For example, Villadsen (cited in Waldmann 2006 and relied upon by Dr. Damsky) tested the anti-IL-15 monoclonal antibody called 146B7, which Villadsen identifies as the same Amgen antibody also called HuMax-IL-15. EX1018, 1571 (Conflict of interest), 1572 (right column) and 1574 (right column): (mAb 146B7 or 404E4 specific for IL-15), Abstract. In both instances that

Waldmann 2006 referred to an anti-IL-15 antibody for potential use in psoriasis or RA, Waldmann 2006 is referring to HuMax-IL-15. EX1049 (Baslund), Abstract. Villadsen confirms that there was no class wide efficacy for anti-IL-15 antibodies.

21. Villadsen explained that the particular anti-IL-15 mAb (called 146B7, HuMax-IL-15) that was tested in the mouse model for psoriasis operated in a specific manner. It permitted IL-15 to bind to its receptor (IL-15R α) while “potently interfere[ing] with the assembly of the IL-15 receptor α , β , γ complex” to “block[] IL-15-induced T cell proliferation and monocyte TNF- α release in vitro.” EX1018, Abstract. The 146B7 mAb thus recognized receptor-bound IL-15, whereas other anti-IL-15 antibodies (e.g., mAb 404E4) did not. EX1018, 1575 (left column). Villadsen teaches that these two antibodies likely recognize different epitopes of IL-15, with the 404E4 antibody likely recognizing an epitope of IL-15 that is required for it to interact with IL-15R α . In other words, Villadsen illustrates that there are multiple different mechanisms of inhibiting IL-15 cytokine signaling that are encompassed by inhibition of IL-15 or the IL-15 receptor.

22. Villadsen also thereby illustrates that even molecules that share the same target (in this case IL-15) have different effects that vary both with the location (i.e., epitope) where the molecule interacts with the target, the variety of receptor, and the nature of the molecule being used. EX1046, 207:11-14 (Dr. Damsky admitting that whether or not antibodies prevent binding or not depends

on the epitope where the antibodies bind), 203:3-10 (Dr. Damsky admitting that whether a monoclonal CD122 antibody inhibits IL-15 depends on the antibody), 207:15-21 (“There may be examples where it doesn’t block signaling.”).

23. Indeed, Villadsen reported that inhibition of IL-15-induced proliferation of T cells was “noticeably” different for the 146B7 anti-IL-15 mAb than for the 404E4 anti-IL-15 mAb. EX1018, 1576-77. Though both of the two IL-15-specific antibodies inhibited IL-15 induced T-cell proliferation *in vitro* “via different modes of action,” the “classical inhibitory antibody” 404E4 “showed to be the least effective” despite the two anti-IL-15 antibodies having comparable binding affinities. EX1018, 1579. Villadsen concluded that the 146B7 antibody interferes with IL-15 binding to the γ -chain and thereby prevents assembly of the α , β , γ receptor components to block both IL-15 induced T-cell proliferation **and TNF- α production**. EX1018, 1576 (right column), 1579 (left column). In contrast, 404E4 mAb would have to “be used at very high concentrations to be effective” because of its very different mode of action. EX1018, 1579. Though each anti-IL-15 antibody was an inhibitor of IL-15 or a variety of the IL-15 receptor under at least some circumstances, and indeed bind the very same target molecule (IL-15), they employed different mechanisms for inhibiting cytokine signaling and therefore yielded differential effects, contrary to Dr. Damsky’s assertions of class wide efficacy.

ii. Dr. Damsky Selectively Ignores Reports of Failed Inhibitors of IL-15 or the IL-15 Receptor.

24. Thirteen years after Villadsen, and more than a decade after Waldmann 2006, the efficacy of blocking IL-15 signaling using HuMax-IL-15 (146B7) for human autoimmune diseases still was not well established at the critical date. To the contrary, some of the very exhibits that Dr. Damsky relies upon to argue that some inhibitors of IL-15 or the IL-15 receptor **might** treat autoimmune diseases teach specifically that clinical trials of HuMax-IL-15 achieved the opposite of the intended effect when administered to humans. *See, e.g.,* EX2013, 2:10-18; EX2014, 2:12-20; EX2015, ¶[0003]; EX2025, 2:10-18.

25. Dr. Damsky's references describe the HuMax-IL-15 or AMG-714 anti-IL-5 antibody trials as "[t]he most advanced and promising, from the medical application point of view" trials "aimed at the inhibition of the IL-15 activity by ant[i]-IL-15 human antibodies." EX2013, 2:10-18; EX2014, 2:12-20; EX2015, ¶[0003]; EX2025, 2:10-18. But these references also raise a "matter of serious concern," specifically "the effect of 'reverse signaling.'" EX2013, 2:10-18; EX2014, 2:12-20; EX2015, ¶[0003]; EX2025, 2:10-18. Dr. Damsky's references explain that reverse signaling occurs when the HuMax-IL-15 antibody binds to IL-15 and forms a complex with it, because this complex "can itself induce a cell response." EX2013, 2:10-18; EX2014, 2:12-20; EX2015, ¶[0003]; EX2025, 2:10-18. Dr. Damsky's references explain that the reverse signaling induced by this anti-

IL-15 antibody is “thus limiting the therapeutic effectiveness of this antibody directed toward IL-15 neutralization[.]” EX2013, 2:10-18; EX2014, 2:12-20; EX2015, ¶[0003]; EX2025, 2:10-18; EX2078, 267 (“the reverse signaling through membrane IL-15 considerably increased the production of several proinflammatory cytokines by monocytes including IL-6, IL-8 and TNF α , thereby indicating the relevance of this process to the complex immunomodulatory function of these cells.”). In other words, the lead IL-15 antibody blocked some forms of IL-15 signaling but unexpectedly enhanced others.

26. Though Villadsen taught that the HuMax-IL-15 anti-IL-15 antibody effectively inhibited in vitro IL-15-signaling in *cis* as well as in *trans* (EX1018, 1579), this IL-15 inhibition unexpectedly increased the production of pro-inflammatory cytokines in humans. This was the opposite of the hoped-for result. After more than a decade of research following Villadsen and Waldmann 2006, the hoped-for therapeutic efficacy of HuMax-IL-15-mediated inhibition of IL-15 based on in vitro studies and animal models had not been fully validated in human disease. This was still true at the critical date.

27. Indeed, HuMax-IL-15 had not been shown to be efficacious for treating autoimmune disease in humans by reducing T cells numbers before the critical date, and still has not been approved for treatment of any autoimmune disease as of today. Baslund 2005, the reference cited in Waldmann 2006 for the

proposition that an anti-IL-15 antibody “has shown efficacy in a Phase I/II clinical trial involving patients with rheumatoid arthritis,” (EX1016, 600) teaches that there were “**no significant effects** on T lymphocyte subset and natural killer cell number.” EX1049, Abstract. The failure of this IL-15 inhibitor to significantly decrease T cells in vivo was observed despite **in vitro studies** that had demonstrated that HuMax-IL-15 suppressed proliferation and induced apoptosis in an IL-15-dependent cell line and neutralized several biologic effects of IL-15 in synovial tissue. EX1049, Abstract. In other words, though HuMax-IL-15 was well tolerated clinically and inhibited IL-15 in vitro, it did not work in humans.

28. ClinicalTrials.Gov indicates that a trial for AMG714 in rheumatoid arthritis was begun in 2002 but had been abandoned without published results in 2007. EX1050. Clinical trials for AMG714 in psoriasis were begun in 2007 but had been abandoned without published results in 2010. EX1051. Two clinical trials for AMG714 in coeliac disease ended when AMG714 failed to demonstrate efficacy as compared to placebo. EX1052; EX1053. Accordingly, a person of ordinary skill in the art would have been aware by April 2017 that IL-15 inhibition using an anti-IL-15 antibody had failed to translate efficacy in mouse models into efficacy in human disease for psoriasis and RA. Not only was there no recognized class wide efficacy for inhibitors of IL-15 and the IL-15 receptor, but the most promising

antibody had not achieved the potential aims that Waldmann 2006 had hoped might be achieved.

29. HuMax-IL-15 was not the only inhibitor of IL-15 or the IL-15 receptor that worked in vitro or in animal models but not in vivo. In 2011, Finch et al. published “Identification of a potent anti-IL-15 antibody with opposing mechanisms of action in vitro and in vivo” in volume 162 of the periodical publication called British Journal of Pharmacology (“Finch,” EX1054). Finch characterized a monoclonal antibody that is specific for human IL-15, which they called DISC0280. EX1054, Abstract. Finch demonstrated that DISC0280 was an IL-15 inhibitor using direct binding assay of IL-15 with IL-15R α to show that it bound to IL-15 and blocked it from binding to IL-15R α . EX1054, Abstract. Finch also demonstrated that DISC0280 inhibited IL-15 signaling, using an in vitro assay to measure its inhibition of IL-15-induced proliferation of IL-15R-heterotrimeric- and IL-15R-heterodimeric-expressing T cells. EX1054, Abstract. But injecting DISC0280 into mice unexpectedly potentiated IL-15 because, though the DISC0280 bound the IL-15 and prevented it from binding IL-15R α , the antibody replaced the IL-15R α as a platform for trans-presenting the IL-15 to the signaling IL-15 receptors β and γ . EX1054, Abstract.

30. Finch also explains that administering soluble IL-15R α similarly functions as an agonist for IL-15 by serving as a platform for trans presentation.

EX1054, Abstract. Dr. Damsky repeatedly identified the soluble IL-15 receptor alpha chain as an inhibitor within the scope of the claims. E.g., EX2005, ¶71 (citing EX2017), Appendix A at pg. 41-42. In other words, DISC0280 and soluble IL-15R α are two examples of compounds (in addition to HuMax-IL-15) that are both inhibitors of IL-15 or the IL-15 receptor, inhibit some IL-15-signaling, but also enhance some IL-15-signaling in vivo. Though Dr. Damsky cited exhibits teaching as much in his declaration, he didn't recall during his deposition that soluble IL-15R α was both an inhibitor and an agonist of IL-15 signaling or that IL-15 antibodies that inhibit IL-15 signaling in vitro can act as agonists in vivo. EX1046, 256:15-258:4, 258:9-16; *but see* EX2005, ¶163 (in vivo half-life and efficacy of IL-15 improve by generating IL-15/IL-15R alpha conjugates); EX2079, 1, 5-6, 8.

31. Dr. Damsky argues that targeting the IL-15 cytokine signaling pathway “always resulted in the alleviation of the disease symptoms.” EX2005, ¶82 (quoting EX2025, 1-2). But Dr. Damsky takes this reference and this statement out of context. As just explained, the tested compounds alleviated disease symptoms in the specific animal models employed, and thus seemed to be effective in those models, “but none of them has been approved for clinical use so far.” EX2013, 1:31-2:18; EX2014, 1:30-2-20; EX2015, ¶[0003]; EX2025, 1:31-2:18; *see also* EX2013, 3:32-37; EX2014, 4:4-8; EX2015, ¶[0018]; EX2025, 3:33-4:2

(“These peptides are supposed to bind the receptor IL-15R α subunit, which should result in the inhibition of T cells proliferation, diminished TNF- α induction, as well as expression of IL-8 and IL-6. To date the efficacy of these new compounds has not been proved in clinical studies.”). That remained true in 2017. Dr. Damsky’s testimony thus selectively ignores reports of failed inhibitors of IL-15 or the IL-15 receptor.

iii. Dr. Damsky Selectively Ignores Reports That Anti-CD122 Antibodies That Inhibit the IL-15 Receptor Failed Repeatedly to Show Efficacy in Humans.

32. IL-15 specific inhibitors were not the only inhibitors whose effects were known to be variable and unpredictable. Waldmann 2006 stated an intention to initiate clinical trials of the CD122 antibody Mik β 1 in “an effort to **test the hypothesis** that IL-15 has a role in the pathogenesis of certain autoimmune diseases.” EX1016, 600. However, a review of ClinicalTrials.Gov confirms that the only clinical trial of Mik β 1 was the phase I study that Waldmann 2006 reported had already been completed.

33. From the perspective of a clinician in 2017 (more than a decade after Waldman 2006 was published), it was clear that Waldmann’s hopes had not validated a hypothesis that Mik β 1 blockade of IL-15 signaling was effective. Indeed, Waldmann 2013 affirmed that they observed “no efficacy” when using Mik β 1 mAb to blockade trans IL-15, and abandoned Mik β 1 in the hope that a

humanized antibody would work. EX1012, 477. As I explain in further detail below, that hope too remained unvalidated as of April 2017.

34. Dr. Damsky argues that “it was recognized that inhibiting IL-15 signaling would have beneficial therapeutic effects based on proof-of-concept (PoC) models.” EX2005, ¶80 (citing EX1012 for proposition that one CD122 inhibitor (Hu-Mik β 1) had entered Phase I clinical trials for leukemia; also citing EX1018, 2 for proposition that IL-15 signaling played a pivotal role in disease pathogenesis of RA and that there may be “therapeutic potential” in “other inflammatory diseases, like psoriasis”). But Dr. Damsky ignores the teachings of the publications he cites, which explain that inhibiting IL-15 failed to treat these diseases in humans.

35. In 2013, Waldmann et al. discussed the Phase 1 trial of “IL-15 *trans* presentation blockade using humanized Mik-Beta-1 mAb” to blockade “in patients with T-cell large granular lymphocytic leukemia” (T-LGL). EX1012, Title. Waldmann 2013 explained that this anti-CD122 antibody “did not block IL-15 action in cells that expressed the heterotrimeric IL-15 receptor in *cis*.” EX1012, Abstract; *see also* EX1012, 479 & Fig. 2 (Hu-Mik β 1 was **unable** to inhibit proliferation of cells expressing the trimeric IL-15 receptor whereas anti-IL-15 antibody did inhibit IL-15-mediated proliferation in these cells).

36. Even though Hu-Mik β 1 had been shown in vitro to specifically inhibit IL-2- and IL-15-dependent proliferation of 32D β and Kit 225 cell, Waldmann 2013 reported that “no major clinical responses were observed” when the antibody was administered to patients. EX1012, 477-79 & Figs. 1-2, Abstract. Waldmann had previously observed “no efficacy” when using Mik β 1 mAb to blockade trans IL-15 in T-LGL, but hoped that the humanized antibody would achieve better results by increasing the “very short in vivo survival” (i.e., half-life) of the antibody and by fixing complement and manifesting Ab-dependent cellular cytotoxicity with human mononuclear cells. EX1012, 477. Despite addressing these issues, Hu-Mik β 1-mediated blockade of CD122, yielded no efficacy (other than a transient increase in neutrophils). EX1012, 482 (“Although Hu-Mik β 1 demonstrated Ab-dependent cellular cytotoxicity in vitro, in the present study, this characteristic was not sufficient to yield a meaningful reduction in the number of circulating leukemic cells.”).

37. Concluding that Hu-Mik β 1-mediated CD122 blockade was “not sufficient to yield a meaningful reduction” in leukemic cells, Waldmann 2013 hypothesized that the agent “might” find more favorable targets in autoimmune diseases that result from disorders of IL-15 expression and action. EX1012, 482. Waldmann thus initiated phase I clinical trials of Hu-Mik β 1 in patients with HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and CD8⁺

T-cell, NKG2D-related celiac disease. EX1012, 483. But Waldmann 2013 did not purport to demonstrate, and did not demonstrate, that Hu-Mik β 1 was therapeutically effective in treating any autoimmune disease. Indeed, ClinicalTrials.Gov reports that clinical trials of Hu-Mik β 1 were abandoned once these three Phase I trials were completed. EX1055. In other words, Hu-Mik β 1's ability to blockade CD122 and thereby block IL-15 action still has not been shown to translate into an effective therapy for humans for any autoimmune disease.

C. Dr. Damsky Never Identifies Any Inhibitor of IL-15 or the IL-15 Receptor For Which He Substantiates Efficacy in Humans.

38. Dr. Damsky argues that there was a “scientific basis for the development of rationale approaches for the IL-15-targeted treatment of autoimmune diseases” already in 2004. EX2005, ¶64 (quoting EX1022, 3). As I explained above, this rational approach had been attempted before the critical date for more than a decade without success. That the approach may be rational (e.g., worthy of investigation) does not mean that class wide results were expected.

39. Dr. Damsky argues that “newly identified inhibitors of IL-15 signaling were understood to have the similar or improved therapeutic effects already established in PoC models based on their common property of inhibiting IL-15 signaling and without the need for specific testing.” EX2005, ¶¶81-82 (citing EX2024). Another way of saying this is that the molecules identified in EX2024 were shown to be inhibitors of IL-15 or the IL-15 receptor using in vitro

assays, but were never demonstrated therein to show in vivo efficacy for treating any autoimmune disease even in animal models, much less in human disease.

EX2024, 28:15-29:7. Efficacy was not assumed.

40. In vivo success in human autoimmune diseases turned out to be much more complicated and unpredictable than in vitro assays or animal model studies, and success in the former did not make successful treatment of the actual disease in human predictable. The Warsaw Medical University authors of EX2013-EX2015 and EX2025 sought to create new generations of inhibitors of IL-15 and the IL-15 receptor exactly because the earlier generations, despite effectively inhibiting IL-15 or the IL-15 receptor, had not been shown in the clinic to be effective for treating the human autoimmune diseases despite more than a decade of attempts. They thus sought to develop small molecules that could inhibit **both** angiogenesis and IL-15-induced proliferation in the hope that this different type of inhibitors of IL-15 or the IL-15 receptor might have therapeutic efficacy:

A need to design a new drug based on a small synthetic molecule inspired the authors of the present invention to **alter the concept** of the treatment of the IL-15 overexpression related diseases. This approach relates to the inhibition of the IL-15 biological activity by a compound selectively binding to IL-15R α receptor. According to the current state of knowledge and our own unpublished results, the strategy, while implemented, should **reduce the pro-inflammatory cascade** as well as **angiogenesis caused by the pro-inflammatory cytokine IL-15**.

The effect of additive synergism is likely to be a so far unrecognized mechanism of biologicals inhibiting IL-15 biological activity.

EX2013, 4:1-8; EX2014, 4:9-15; EX2015, ¶[0022]; EX2025, 4:34-5:2 These molecules thus provide another example of inhibitors of IL-15 or the IL-15 receptor that have very differential effects than other inhibitors of IL-15 or the IL-15 receptor, contradicting Dr. Damsky's assumption of class wide efficacy.

41. As Dr. Damsky points out, though, these references provide no in vivo results for any of their inhibitors even in animal models, much less in actual autoimmune disease. EX1046, 243:4-12, 249:5-10, 252:6-25, 253:1-8, 256:1-9. Their only tests used PBMCs, which Dr. Damsky testified might or might not be reliably predictive of their effect on CD8+ T cells. EX1046, 243:11-244:11; *see also* EX1046, 248:15-249:1 (proliferation assay using CD8+ NKG2D+ T cells instead of PBMCs might suggest it is an inhibitor of IL-15). A person of ordinary skill in the art after April 2017 was thus left with trial-and-error to attempt to know which inhibitors of IL-15 or the IL-15 receptor might be efficacious.

42. In additional circumspect statements, Dr. Damsky acknowledges that the references merely "suggest[]" that IL-15 inhibition "**could** have a therapeutic **potential**." EX2005, ¶82 (quoting EX2019, 2:1-6; citing EX2028, 1:18-29; EX2029, [0009]); *see also* EX2005, ¶¶53 (admitting that "just because a particular gene is overexpressed" does "**not mean** that inhibiting it will result in

improvement of the disease”), 64 (arguing that “the IL-15 signaling mechanisms and **potential clinical utility** as a therapeutic target have been extensively studied” (citing EX2010, 1, 10-13 (2001 reference); EX1022, 1 (2004 reference))).

Ultimately, the references at best teach that there was interest in identifying inhibitors of IL-15 or the IL-15 receptor to potentially treat autoimmune diseases but that their ability to actually address autoimmune disease was highly variable and unpredictable. At the end of the day, prior art as a whole undermines, rather than supports, Dr. Damsky’s general assertion of class wide efficacy.

V. THE ’505 PATENT’S DESCRIPTION OF CHMBC7 IS ESSENTIALLY A BLACK BOX THAT MAKES REPRESENTATION OF THE GENUS IMPOSSIBLE.

43. Dr. Damsky cannot dispute that the ’505 patent provides just a single, minimally characterized example to support their claims. Indeed, he has admitted that the only experiments in the ’505 patent in which an inhibitor of IL-15 or the IL-15 receptor is administered always used a single CD122 antibody identified by the codename ChMBC7, and that the ’505 patent does not tell us the primary sequence or secondary structure of the antibody or the epitope of CD122 to which it binds. EX1046, 224:18-225:12 (patents always and only used ChMBC7 codenamed antibody in the ’505 patent), 225:25-226:8 (patent does not tell the sequence for ChMBC7), 230:3-5 (secondary structure), 230:6-13 (no disclosure of

what epitope ChMBC7 binds). Dr. Damsky never identified any prior art literature providing the missing information.

44. The most Dr. Damsky could say is that he thinks it may have been established sometime **after** the April 2017 critical date that ChMBC7 binds to the same epitope as the TM- β 1 antibody that was previously employed in the Xing reference. EX1046, 230:6-231:10. Dr. Damsky thus thinks these two antibodies would have the same effect in the Harris mice as was observed in the patent. Dr. Damsky also relies on a 2009 study by Yokoyama of the effects of TM- β 1 *trans* blockade of IL-15 signaling on autoimmune intestinal damage. EX2005, ¶65 (citing EX2012 (Yokoyama)). Of course, even if it had been known at the critical date that the antibody codenamed ChMBC7 was targeting the same CD122 epitope as the antibody used in Xing and Yokoyama, this at best just suggests the TM- β 1 antibody would eliminate the CD8⁺ T cells from the skin of the Harris mice, just as it did in the skin of the mice in Xing.

45. The effects of TM- β 1 inhibition of CD122 in the Harris mice was predictable because the Harris mice presented a simplified model of cause and effect. The mice had been irradiated to eliminate their natural immune system, which had been replaced by melanocyte-targeting (PMEL) CD8⁺ T cells. EX1006, 1870. Dr. Damsky admitted during his deposition that these CD8⁺ T cells are not T regulatory cells. EX1046, 169:25-170:8 Accordingly, the Harris mice model

permits exploring CD122 inhibition (which implicates both IL-2 and IL-15 signaling) without accounting for the T regulatory cells in actual patients. But the predictability of the effects of TM- β 1 inhibition in Harris mice resulted from the simplified etiology in the Harris mice.

46. Because Xing disclosed that TM- β 1 eliminated the CD8+ T cell from the skin of the mice that Harris disclosed were the sole and exclusive source of melanocyte destruction in those mice, durable repigmentation of the Harris mice was the predictable result of using this particular antibody in those particular mice soon after depigmentation lesions arose. As Dr. Damsky explained during his deposition, it was known that the body naturally repigmented vitiligo lesions (drawing from a reservoir of melanocyte stem cells in the bulge of the hair follicle to repopulate the interfollicular epithelium with mature melanocytes) once the cause(s) of melanocyte destruction (e.g., CD8+ T cells or oxidative damage) were eliminated. EX1046, 121:17-125:6 (Repigmentation comes when melanocyte stems cells proliferate and mature, and mature melanocytes migrate from bulge of hair follicle into the intrafollicular epidermis), 125:8-12 (Dr. Damsky could not name any treatment that repigments vitiligo skin without making use of the melanocyte stem cell reservoir), 126:23-128:2 (ruxolitinib approved for vitiligo; the working model for every treatment is that depigmentation occurs based on repopulation of the melanocytes from the natural reservoir); EX1048, 6 (Dr. Harris

confirming that UVB treatment—which was available before the critical date—“can prevent spread of vitiligo and reverse it even if it’s stable”); EX1056, 3 (Dr. Desai confirming in recorded conversation with Dr. Damsky that “[t]here are things we can do to make it better” and “the earlier we can treat the patient, the better”). Although it was obvious to use a mouse CD122 antibody (e.g., TM-β1) that was known to deplete CD8⁺ T cells in order to deplete CD8⁺ T cells in the Harris mouse model to permit the body to naturally reverse the depigmentation lesions caused by the CD8⁺ T cells, a person of ordinary skill in the art would not have assumed the results from this particular mouse model would be representative of the results in natural or spontaneous vitiligo in human patients, for which the etiology was much more complicated.

47. As Dr. Damsky admitted, vitiligo can arise from a variety of distinct causes, including a breakdown of the body’s defenses against oxidative stress (the oxidation resulting in melanocyte destruction). EX1046, 139:24-141:9 & 142:19-25 (“I was aware of that hypothesis, yes”), 143:18-144:3 (vitiligo caused by breakdown of oxidation-preventing enzymes). Indeed, the literature explained that there were multiple causes of vitiligo, with no singularly true mechanism behind the disease, and its pathogenesis remained elusive. EX1057, Abstract (“Vitiligo is a commonly encountered pigmentary disorder...however, the pathogenesis of vitiligo remains elusive.... Although the exact pathogenesis of vitiligo is uncertain,

each of these theories likely plays a role.”), 153 (““What causes vitiligo?’ remains ambiguous. The lay population generally accepts the concept of ‘the autoimmune destruction of pigment-producing cells called melanocytes’ as an answer; however, this assertion is not wholly correct. The exact pathogenesis is unknown and complex, involving the interplay of multiple factors, many of which are not elucidated.”), 153 (“Although research has made many aspects of the pathogenesis of vitiligo clearer, to date, nothing has been unequivocally established as the singularly true mechanism behind the disease.”), 169 (“The pathogenesis of vitiligo remains to be elucidated.... In this review, we have discussed these major theories.”).

48. For example, extensive research supported that chemicals produced by the body in response to stress or that the breakdown of enzymes designed to protect the body from oxidative damage were causing vitiligo in at least some patients. EX1057, 157-160 (neural causes of segmental vitiligo), 162 (non-segmental or general vitiligo characterized by increased CD8/CD4 ratio and increased IL-2 receptor expression on T cells and increased macrophage abundance and other immune mediators, including potentially IFN- γ , TNF- α , IL-10, IL-17, IL-1, IL-6), 163 (“The immune system is complex, involving cell-mediated and humoral mechanisms—both of which appear to play some role in ultimately eliciting vitiligo.”), 163-167 (“important evidence for oxidative stress as

a cause of vitiligo”), 167-169 (“Melanocytorrhagy...a relatively new approach to explaining the pathogenesis of vitiligo”). Even if CD8+ T cells play a key role in melanocyte destruction for all types of vitiligo, efficacy of inhibiting CD8+ T cells depends not only on treating a key mechanism but also depends on the ability to treat the different root causes.

49. Dr. Damsky’s familiarity with the full, complex etiology of vitiligo was admittedly limited during his deposition, though he was less skeptical about the complex causes of vitiligo outside the context of litigation. EX1046, 138:6-144:3 (Dr. Damsky demonstrating limited familiarity with neural-, melanocytorrhagy-, or oxidative stress-induced vitiligo), 223:2-25 (claim encompasses all types of vitiligo, including segmental, chemically-induced, oxidative stress-induced), 117:18-22 (Dr. Damsky did not recall treating segmental vitiligo before the critical date), 118:2-119:17 (Dr. Damsky did not recall treating chemically-induced vitiligo before the critical date); EX1056, 4 (Dr. Seemal Desai discussing oxidative-stress-induced vitiligo with Dr. Damsky: “That continued oxidative stress and that CD8 T-cell-mediated damage for persistent depigmented patches is a challenge.”); EX1046, 224:1-7 (Dr. Damsky confirming he gave DermView presentations for the Dermatology Times with Dr. Seemal Desai). Dr. Damsky’s failure to account for the complex etiologies of natural and spontaneous

vitiligo further undermine his assertions that there was an accepted class wide efficacy.

50. A person of ordinary skill in the art in April 2017 would not conclude based on experiments in the Harris mice that one could reliably extrapolate the results of ChMBC7 inhibition therein to vitiligo treatment using all CD122 antibodies, all CD122 inhibitors, all IL-15R inhibitors, or all IL-15 inhibitors. As I discussed above, different molecules that can inhibit IL-15 operate differently depending on the specific molecule used, its target, where it binds that target, and which types of IL-15 signaling and other cytokine signaling it inhibits or enhances.

51. Moreover, more was needed than merely identification of the epitope. The '505 patent never discloses how strong the inhibition was. Dr. Damsky testified that the claims are so broad as to encompass the use of a molecule that inhibits IL-15 signaling by as little as 1%. EX1046, 245:8-246:21. The '505 patent provides no direction as to what level of inhibition was required, leaving the person of ordinary skill in the art with no direction and a task that amounts to unguided trial and error.

52. The '505 patent also never discloses what type of inhibition (*cis* only, *trans* only, or both; dimeric; IL-2 only, IL-15 only, both; etc.) was induced by ChMBC7. It is undisputed that some CD122 antibodies are non-blocking and that even different blocking CD122 antibodies provide variable effects. EX1011, 2:35-

48, 2:61-3:2, 9:27-38; *see also* EX1012, 481-82. A person of ordinary skill in the art was left only to investigate through trial and error what other molecules might be represented by ChMBC7, if any.

53. The specification of the '505 patent is essentially a black box (so far as which aspects of IL-15 signaling it inhibits and how it operates), leaving the reader to guess through trial and error which molecules might operate similarly to ChMBC7 and which do not. Dr. Damsky attempts to sidestep this problem by incredibly assuming that all inhibitors of IL-15 or the IL-15 receptor operate exactly the same and have the exact same effects. But this is clearly not true, as demonstrated by my discussion above, and by Dr. Damsky's own deposition testimony (discussed in further detail below).

VI. DR. DAMSKY'S DEPOSITION REVEALS GREAT COMPLEXITY AND UNPREDICTABLE EFFECTS OF INHIBITING IL-15 OR THE IL-15 RECEPTOR.

54. Contrary to Dr. Damsky's declaration testimony, there was no acceptance by persons of ordinary skill in the art as of April 2017 of a well-known class of inhibitors of IL-15 or the IL-15 receptor recognized to have class wide efficacy. Instead, IL-15 was part of a "complex network" of interconnected cytokine mediators, and its role in the "complex immunomodulatory function of these cells" was understood to have significant areas of unpredictability. *See, e.g.*, EX2015, ¶[0020] ("immune mediators" present a "complex network"); EX2025,

4:5-24 (similar); EX2078, 267 (“the reverse signaling through membrane IL-15 considerably increased the production of several proinflammatory cytokines by monocytes including IL-6, IL-8 and TNF α , thereby indicating the relevance of this process to the complex immunomodulatory function of these cells.”). In addition to the literature he cites, Dr. Damsky’s deposition testimony also contradicts his sweeping and unsupported assertions of class wide efficacy.

55. Indeed, Dr. Damsky testified repeatedly during his deposition that the subject matter was “complicated.” EX1046, 94:7-8 (“it is more complicated than that”), 121:7-16 (“I think it is complicated because we don’t fully understand the mechanism why MBEH is doing what it does...I think it’s complicated.”), 158:16-23 (whether the prior art JAK inhibitor tofacitinib is an inhibitor of IL-15 within the meaning of claim 1 “is really complicated”), 118:25-119:5 (regarding the mechanism of chemical vitiligo, “I wouldn’t say that the mechanism is known to be that simple”), 209:1-12 (blocking IL-15 from α , “It is not as simple as that” because some IL-15 dissociates from the IL-15R α on the cell membrane and becomes accessible in solution).

56. Dr. Damsky admitted during his deposition that he could not recognize from the structure of a compound whether it is an inhibitor of IL-15 or the IL-15 receptor. EX1046, 236:12-17. He wasn’t confident whether a pharmaceutical scientist would be able to tell. EX1046, 236:18-24. As I explain

below, he counted mere reagents as inhibitors of IL-15 or the IL-15 receptor in his Appendix.

57. Moreover, Dr. Damsky demonstrated that it was complex and unpredictable to determine even whether a known compound was an inhibitor of IL-15 or the IL-15 receptor. Even having established that a compound was an inhibitor of IL-15 or the IL-15 receptor, Dr. Damsky could do no more in 2021 (years after the critical date) than cross his fingers that this compound would treat vitiligo in humans, hope that the inhibitor would turn off the memory response, and maybe achieve long-lasting treatment. EX1046, 232:1-235:7, 235:14-236:9.

A. Dr. Damsky Admits Inhibition of IL-15 Signaling Encompasses Multiple Different Types of Inhibition That Operate Differently With Differential Effects.

58. Dr. Damsky admitted during his deposition that there are multiple versions of the IL-15 receptor and many different types of inhibition encompassed by inhibitors of IL-15 or the IL-15 receptor. EX1046, 162:12-163:25, 165:11-16 (claims encompass all iterations of the IL-15 receptor, including (1) heterodimeric IL-15 receptor comprises $\beta\gamma$ receptors on a single cell; (2) heterotrimeric *cis* IL-15 receptor comprises $\alpha\beta\gamma$ on a single cell; (3) heterotrimeric *trans* IL-15 receptor comprises $\beta\gamma$ on a single cell and α supplied by an adjacent cell; (4) heterotrimeric *trans* IL-15 receptor comprises $\beta\gamma$ on a single cell and soluble α floating in solution), 170:25-173:2 (claims include any inhibitors of α , β (shared by IL-2 and

IL-15), or γ (shared by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21)), 173:3-22 (claims not restricted to any antibody or peptide), 174:13-175:1 (claims include any inhibitory nucleic acids that target α , β , or γ), 176:3-11 (claim 1 does not require that the nucleic acids target α , β , or γ).

59. Dr. Damsky also admitted during his deposition that these different receptors operate differently. For example, CD122 (β) can initiate JAK1/STAT1 signaling when a cytokine binds to it whereas CD132 (γ) can initiate JAK3/STAT5 signaling when a cytokine binds to it. EX1046, 58:5-60:13, 63:2-9, 91:25-93:10. Accordingly, inhibition of CD122 thus has the potential to inhibit JAK1/STAT1 signaling whereas inhibition of CD132 has the potential to inhibit JAK3/STAT5 signaling. In contrast, IL-15R α generally does not initiate JAK signaling; its predominant function is instead to present IL-15 to the beta and gamma receptors. EX1046, 60:14-20, 166:3-8. Each form of inhibition of each different subunit thus operates differently from the others.

60. Dr. Damsky testified during his deposition that it was possible for an inhibitor to prevent IL-15R α from binding to β without interfering with binding to γ so that γ signaling (JAK3) occurs but β signaling (JAK1) does not. EX1046, 212:17-213:3, 214:7-15. Some inhibitors of IL-15 or the IL-15 receptor may do the opposite (blocking γ signaling (JAK3) but allowing β signaling (JAK1)). EX1046,

214:17-215:4. Dr. Damsky did not know whether blocking just one but not the other signaling pathway would impair T cell survival. EX1046, 216:18-217:3.

61. Similarly, Dr. Damsky testified that there were many different types of inhibition of IL-15 or the IL-15 receptor encompassed by the claims. EX1046, 219:24-222:8. Based on Dr. Damsky's list, the interaction could be differentially blocked depending on whether one:

- Blocks alpha from interacting with beta
- Blocks alpha from interacting with gamma
- Blocks the interaction of beta and gamma
- Blocks IL-15 from interacting with alpha
- Blocks IL-15 from interacting with beta
- Blocks IL-15 from interacting with gamma
- Blocks IL-15 from interacting with both beta and gamma
- Blocks IL-15 from interacting with alpha, beta, and gamma
- Reduces IL-15 expression using a nucleotide inhibitor
- Reduce alpha expression using a nucleotide inhibitor
- Reduces beta expression using a nucleotide inhibitor
- Reduces gamma expression using a nucleotide inhibitor

62. Because six different cytokines signal through CD132 (γ), inhibiting CD132 not only can inhibit some IL-15 signaling but also can inhibit

immunostimulatory signaling (including JAK3 signaling) induced by other cytokines, including IL-4, and cause severe immunodeficiency called SCID. EX1046, 96:18-97:8 (gamma shared by six cytokines), 95:21-24 (IL-4 is an immunostimulatory cytokine), 97:22-98:1 (IL-4 binds gamma and probably initiates JAK3), 98:2-7 (blocking binding to gamma can inhibit JAK3 signaling induced by IL-4), 222:9-25 (absence of CD132 shared by the six cytokines causes severe immunodeficiency), 99:17-100:2 (defining SCID). Accordingly, CD122 inhibition is not representative of CD132 inhibition.

B. Dr. Damsky Admitted That Identifying Inhibitors of IL-15 or the IL-15 Receptor Was Complicated and Unpredictable.

63. Dr. Damsky initially testified that if something inhibits the binding of IL-15 to IL-15R α , it would qualify as an IL-15 pathway inhibitor and as an inhibitor of IL-15 or the IL-15 receptor. EX1046, 189:4-19. But later Dr. Damsky testified that whether something that blocks the association of IL-15 with IL-15 α is an inhibitor within the scope of claim 1 “would depend on the specific compound.” EX1046, 192:6-15. Though binding assays could be used to demonstrate what type of binding and blocking was occurring, Dr. Damsky admitted during his deposition that these assays were merely suggestive that the compound was an inhibitor of IL-15 or the IL-15 receptor within the scope of the claims, not conclusive. EX1046, 193:18-195:18 (“sometimes there is just a one-off example that doesn’t reflect”);

189:20-191:13 (if it is binding, one possibility is that it's inhibiting), 191:15-192:4 (generally it would suggest that it is an inhibitor but it is not definitive).

64. Dr. Damsky testified that an in vitro IL-15 induced proliferation assay could be used to provide further evidence that the compound is an inhibitor within the scope of claims, but again this would just be highly suggestive and wouldn't confirm conclusively that it is an IL-15 inhibitor. EX1046, 195:20-196:22, 181:8-186:6. Dr. Damsky testified that additional data could be obtained by performing phosphorylation studies or looking at other known biological effects of IL-15. EX1046, 198:21-199:21. But Dr. Damsky eventually admitted that there is no "absolute standard" for identifying an inhibitor within the scope of the claims, that people would have to approach the question in a variety of directions, and that he could not name anything specific to do to conclusively determine whether a molecule is within or without the scope of the claims. EX1046, 197:12-198:19, 200:1-8.

65. Moreover, Dr. Damsky admitted that inhibitors of downstream signaling of IL-15 that also inhibit other cytokine signals can still be IL-15 inhibitors. EX1046, 161:14-162:4. IL-2, IL-15, and interferon- γ are all upstream molecules to the JAK/STAT pathway that can signal through them. EX1046, 93:11-23, 95:1-20. Accordingly, JAK1/3 inhibitors such as tofacitinib inhibit signaling of each of IL-2, IL-15, and IFN- γ .

66. Dr. Damsky also admitted during his deposition that an inhibitor of IL-15 is anything that inhibits a biological effect of IL-15 or its receptor. EX1046, 156:9-17. He testified that JAK signaling is a biological effect of IL-15 and he could not categorically rule out that ruxolitinib or tofacitinib are inhibitors of IL-15. EX1046, 156:19-21 (JAK is a biological effect of IL-15), 157:18-21 (not ruling out ruxolitinib is an inhibitor of IL-15), 158:1-159:6 (ruxolitinib inhibits JAK1 downstream of IL-15 just like beta inhibition), 159:7-14 (whether or not tofacitinib is an inhibitor of IL-15 would depend on the context).

67. Dr. Damsky testified that tofacitinib inhibits JAK1 and JAK3 downstream of IL-15, the same JAK/STAT pathways inhibited by inhibiting β and γ , and that whether or not tofacitinib is an inhibitor of IL-15 “is really complicated” and will depend on context such as the dose (i.e., sometimes the same compound is an inhibitor of IL-15 and sometimes it is not). EX1046, 158:12-160:20. Notably, JAK inhibitors such as tofacitinib and ruxolitinib had been administered to treat vitiligo patients before April 2017. EX1032; EX1033. Dr. Damsky’s inability to definitely rule out whether the claims encompass known prior art vitiligo treatments such as JAK inhibitors underscores the unpredictable and vague nature of the claimed genus.

68. On the other extreme, Dr. Damsky also appears to include within the scope of the claim the use of molecules whose predominant mode of action is not

through any direct action on IL-15 or the IL-15 receptors. For example, the '505 patent sweeps in compounds that inhibit microbial activity, IL-2, IL-17, Bcl-xL, or MDM2. EX1001, 7:40-45 (citing EX2015 for cefazolin and Ushio 2008, EX2016, for Y-320), 7:60-64 (citing EX2022 for Ro26-4550, SP4206, ABT-737, Nutlin-2, and compound 3); EX1046, 259:7-261:19 (ABT-737 and Nutlin-2 inhibit Bcl-xL and MDM2, respectively, neither of which are directly a component of the IL-15 or IL-2 receptors); EX2022, 36 (Ro26-4550 inhibits IL-2:IL-2R α interaction), 41 (SP4206 and compound 3 are IL-2 antagonists), 46-47 (ABT-737 and Nutlin-2 inhibit Bcl-xL and MDM2).

69. Dr. Damsky repeatedly identified cefazolin as an “inhibitor of IL-15-induced cellular responses” but omitted Y-320 from his list of IL-15 inhibitors. EX2005, ¶¶71 (citing EX2015 for cefazolin but omitting Y-320 from his list), 99 (same), Appendix A at pg. 43 (cefazolin, but no mention of Y-320 or EX2016). During his deposition, Dr. Damsky testified that cefazolin is an antibiotic, that its predominant clinical use is as an antibiotic, that it inhibits both IL-15- and IL-2-induced proliferation of peripheral bone marrow cells (PBMCs), but that he was unsure whether administering cefazolin to vitiligo patients satisfies the claims. EX1046, 253:9-255:11.

70. In contrast, Y-320 is an inhibitor of IL-17 production by CD4⁺ T cells. EX1058, Title (“Y-320, Inhibits Interleukin 17 Production”), Abstract (“Y-

320 inhibited IL-17 production by CD4 T cells stimulated with IL-15 with IC₅₀ values of 20 to 60 nM.”); EX2016, 292 (“Moreover, the activities of IL-15 in RA are not limited to T cells but also extended to synoviocytes, macrophages, and osteoblasts because IL-15 can induce production of another proinflammatory cytokine, IL-17 by T cells. IL-17 works synoviocytes, macrophages, and osteoblasts to induce several inflammatory mediators including IL-6, IL-8, tumor necrosis factor- α , CC-chemokine ligand 2, matrix metalloproteinases, prostaglandin E₂, and receptor activator of NF- κ B ligand.”). IL-17 is an immunostimulatory cytokine. EX1046, 98:9-18. IL-17 is one of the signaling pathways other than JAK/STAT that IL-15 can activate. Dr. Damsky admitted that IL-15 can activate other pathways as well. EX1046, 95:10-20. The claims’ encroachment onto anything that inhibits anything that IL-15 enhances sweeps the claims even more broadly and renders them ever further untethered from the sole inhibitory working example.

C. One Anti-IL-15R α Antibody Is Not Representative of All Anti-IL-15 α Antibodies.

71. Dr. Damsky admitted during his deposition that an antibody to IL-15R α would bind more readily to IL-15R α on the outside of the cells than to IL-15R α on the inside of the cells and that the binding sites of IL-15R α for IL-15 are not accessible to an inhibitor when IL-15/IL-15R α are already associated together on the membrane. EX1046, 166:21-24 (α is typically attached to the membrane of

the bystander cell), 168:25-169:5 (In the natural state, a single cell is making the IL-15 and α , putting them together in a complex, and then presenting that complex onto the cell membrane), 207:23-208:13 (antibody to α would have an easier time getting to α when α is expressed on the outside of the cell than to α that is still within the cell), 208:15-209:22 (IL-15/IL-15R α binding sites are not accessible to an inhibitor when they are already associated together on the membrane); EX1011, 1:67-2:4 (“it is believed that IL-15 and IL-15R α associate in the endoplasmic reticulum and are transported to the cell surface as a complex for trans-presentation to other cells expressing CD122 and CD132 on the surface”). Dr. Damsky testified in his declaration that IL-15 in the body can associate with IL-15R α that is soluble that is not membrane-bound, which can trans-present the IL-15 to the $\beta\gamma$ receptors on the immune cells just like membrane-bound IL-15R α . EX2005, ¶116; *see also* EX1046, 210:4-17 (some IL-15R α is soluble, floating in solution), EX2005, ¶134 (soluble IL-15 can signal through $\beta\gamma$ without α). Antibodies to IL-15R α that target sites where it binds IL-15 may thus operate by inhibiting soluble IL-15R α not already bound to IL-15 while not inhibiting IL-15R α that is presented on the cell membrane already bound to IL-15. Such antibodies thus operate differently (with differential effects) than antibodies to IL-15R α that target different sites. EX1046, 210:24-211:6 (some IL-15R α inhibitors might impact its association with β and/or γ instead).

VII. THE '505 PATENT DOES NOT OTHERWISE PROVIDE A REPRESENTATIVE DESCRIPTION OF INHIBITORS OF IL-15 OR THE IL-15 RECEPTOR

72. Dr. Damsky argues that the '505 patent mentions "20 specific inhibitors across" nine "inhibitor classes." EX2005, ¶¶99. Dr. Damsky then manufactures his own list of 375 compounds, most of which are absent from the '505 patent, listed in Appendix A of his declaration. EX2005, ¶¶70-72. He argues that hundreds of these inhibitors "were characterized and studied for diseases involving the IL-15 signaling pathway" and were "being taught for therapeutic use." EX2005, ¶¶70, 75, 94, 118. But Dr. Damsky's Appendix A does not remedy the deficient '505 patent specification. First of all, the vast majority of the compounds Dr. Damsky points to are not discussed in the '505 patent or the documents it cites. Second, the '505 patent omits entire inhibition classes that Dr. Damsky identifies in his Appendix A. Third, Dr. Damsky does not reliably identify known inhibitors because he (a) mischaracterizes the references; and (b) admitted during cross-examination his inability to identify inhibitors. I discuss each of these issues in further detail below.

A. The '505 Specification's Disclosure Regarding Inhibitors of IL-15 or the IL-15 Receptor Is Very Limited.

73. Dr. Damsky admitted during his deposition that 26 of 32 references he cited in the Appendix A to identify inhibitors are not incorporated by reference into the '505 patent. EX1046, 261:22-262:2, 267:1-7. Moreover, by his own admission

the '505 patent mentions no more than 20 of the hundreds of compounds he chose to list. Dr. Damsky's attempts to expand the list of molecules beyond those identified in the patent merely emphasize the great magnitude of the genus of molecules potentially encompassed by the claim.

B. Entire Inhibition Classes Dr. Damsky Identifies Are Not Addressed in the '505 Patent.

74. Dr. Damsky combines disparate classes of IL-15 or IL-15 receptor inhibitors as a single class in a manner that obscures that the specification of the '505 patent fails to identify even a single example of an inhibitor within that class. For example, the only references Dr. Damsky relies on in his Appendix A as disclosing IL-15 or IL-15 receptor inhibitors within the class of "Muteins" are Exhibits 2103, 2105, 2050, and 2110. According to his appendix, these exhibits disclose 59 inhibitors. However, none of these references are cited in the '505 patent. EX1059.

75. Similarly, Dr. Damsky relies on six references in his Appendix A as disclosing IL-15 or IL-15 receptor inhibitors within the class of "fusion proteins" (Exhibits 2028, 2051, 2104, 2107, 2111, and 2114). According to his appendix, these exhibits disclose 12 inhibitors. But none of these references are cited in the '505 patent. EX1059.

76. As another example, Dr. Damsky relies on five references in his Appendix A as disclosing IL-15 or IL-15 receptor inhibitors within the class of

“nucleotides” (Exhibits 2029, 2030, 2087, 2088, and 2112). According to Dr. Damsky, these exhibits disclose 155 inhibitors, but none of these references are cited in the ’505 patent. EX1059.

77. As another example, Dr. Damsky relies on five references in his Appendix A as disclosing IL-15 or IL-15 receptor inhibitors within the class of “peptides” (Exhibits 2032, 2049, 2102, 2106, and 2108) that are not cited in the ’505 patent. According to his appendix, these exhibits disclose 20 inhibitors (1, 8, 4, 1, and 6). But Dr. Damsky’s appendix identifies only two peptides in a single reference (EX2019) that is cited in the ’505 patent. EX1059. These are not representative. Indeed, Dr. Damsky testified that they both bind to IL-15R α . EX2005, ¶71; EX2019, Abstract. As explained above, however, blocking binding of IL-15 to IL-15R α was not representative of the many other forms of IL-15 or IL-15 receptor inhibition.

78. As another example, Dr. Damsky relies on five references in his Appendix A as disclosing IL-15 or IL-15 receptor inhibitors within the class of “antibodies” (Exhibits 2027, 2031, 2085, 2105, and 2109) that are not cited in the ’505 patent. EX1059. According to his appendix, these exhibits disclose 56 inhibitors (24, 4, 24, 3, and 1). But Dr. Damsky’s appendix identifies only two antibodies in a single reference (EX1011) that he says was cited in the ’505 patent. These are not representative. Dr. Damsky testifies that these are two anti-CD122

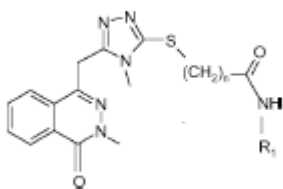
antibodies that inhibited “trans-presentation of IL-15.” EX2005, ¶67, Appendix A at 10 (HuABC2 and ABC101 CD122 antibodies). Dr. Damsky does not assert that this reference teaches that all forms of antibody inhibition of IL-15 or the IL-15 receptor operate identically. Moreover, this reference is not representative of all forms of inhibition of IL-15 and the IL-15 receptor because the HuABC2 and ABC101 antibodies are reported to inhibit both IL-15 and IL-2. EX1011, 21:54-23:15 (Examples 2-3). In contrast, Dr. Damsky insists that ChMBC7 selectively inhibits IL-15 (and not IL-2). EX2005, ¶¶155-56 (“POSA would understand that the demonstrated vitiligo treatment effect results from inhibiting IL-15 (not IL-2) signaling”).

79. The ’505 patent’s failure to even mention all the different types of IL-15 inhibition identified by Dr. Damsky, much less explain how ChMBC7 is representative of the many disparate types of IL-15 inhibition, fails to provide a representative description of the breadth of the claimed genus.

C. Dr. Damsky’s Testimony Regarding Known IL-15 Inhibitors Is Not Reliable.

80. Dr. Damsky mischaracterizes the content of the cited references and, in doing so, repeatedly confuses the intermediaries of the synthesis process for making the final chemical products as being inhibitors. For example, Dr. Damsky testifies that there were a total of 62 known small molecule inhibitors and that EX2024 discloses more than 50 of them. EX2005, ¶¶70, 81, Appendix A at pgs. 4-

10. EX2024 provides no in vivo testing, including animal testing. Instead, EX2024 performs an in vitro assay of inhibition of recombinant superagonist (RLI)-induced 32D β cell proliferation, and applies this test only to six molecules (not 50 different molecules), identified as C1, C5, G2, E1, A4, and D4. EX2024, 28:15-29:4.

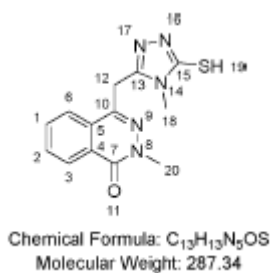
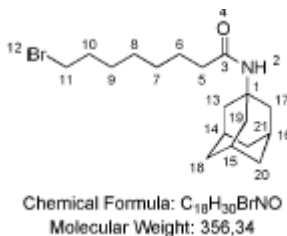
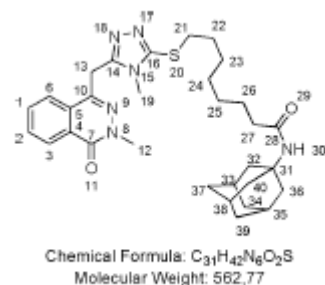


Name	R1	n	IC ₅₀ (μM) () nb of determinations
C1	dichloro-phenyl	1	10.77 + 1.97 (6)
C5	dichloro-phenyl	6	1.18 + 0.13 (4)
G2	dichloro-phenyl	7	2.45 + 0.76 (15)
E1	dichloro-phenyl	10	3.81 + 0.40 (12)
A4	adamantyle	7	1.44 + 0.20 (12)

In addition, compound D4 (wherein X =O) has the following IC₅₀ (μM): **8.73 ± 0.63**

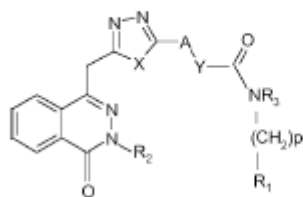
REFERENCES:

81. Dr. Damsky then proceeds to count as inhibitors the precursors used to make these compounds. Taking compound A4 as an example, EX2024 discloses using two compounds (8-bromo-N-(adamant-1-yl)octanamide and 4-((5-mercapto-4-methyl-4H-1,2,4-triazol-3-yl)methyl)-2-methylphthalazine-1 (2H)-one) as precursors, and combining them together to make the Example 6 compound. EX2024, 24:19-25:15. I have reproduced the structures of the two precursors (below left and middle) next to the structure of the Example 6 proposed inhibitor (below right).



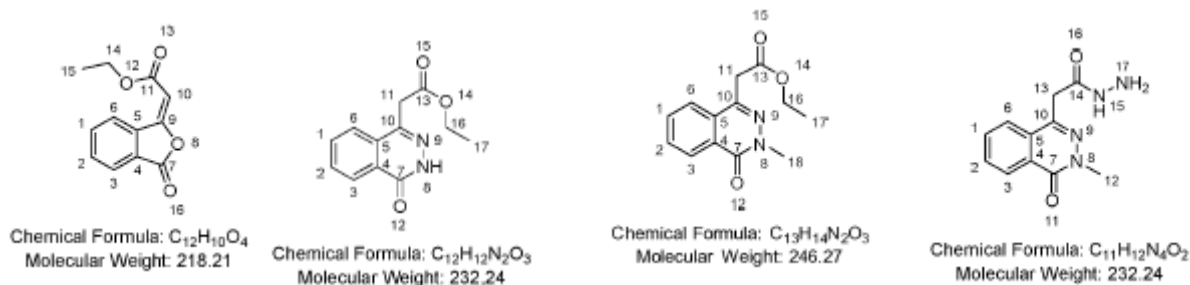
82. Dr. Damsky thus confused and counted the reagents used in Example 6 to make the molecule as two additional proposed inhibitors. EX2005, Appendix at pg. 9-10 (citing EX2024, 19:15-16, 22:8). Dr. Damsky thereby multiplies one proposed inhibitor into three. Neither of these intermediates match general formula I, the invention of EX2024.

The invention relates to compounds of general formula (1):



83. Dr. Damsky then further compounds his overcounting error by confusing and counting precursors of the precursors. For example, Dr. Damsky counts four precursors of the first precursor identified above (above left) as separate inhibitors. EX2005, Appendix at pg. 9 (citing 16:24-25, 17:14, 18:7-8, 19:1-2). But EX2024 merely discloses making these compounds (reproduced

below) as precursors, not as inhibitors. Of course, none of them match general formula I.



For a single tested compound, Dr. Damsky thus counted six compounds identified merely as precursors that do not satisfy general formula I, for an exaggeration factor of at least six-fold.

84. Additionally, Dr. Damsky's Appendix A lists the same molecules more than once, further inflating his inhibitor count. Compare EX2005, Appendix A at pg. 10 (citing EX2024, 23:4-5, 23:26-27, 24:19-20, 25:16-17, 27:22-23) with pgs. 5 (citing EX2024, 4:24-25), 5 (citing EX2024, 4:28-29), 6 (citing EX2024, 5:7-8), 9 (citing EX2024, 6:9-10), 9 (citing EX2024, 6:11-12).³ These types of errors are pervasive throughout Dr. Damsky's testimony.

³ EX2024, which is not cited in the '505 patent, accounts for 80% of the molecules Dr. Damsky identifies as small molecule inhibitors of IL-15 or the IL-15 receptor and is the only small molecule inhibitor reference Dr. Damsky points to as primarily inhibiting by targeting the β -subunit of the IL-15 receptor. None of

85. Dr. Damsky testified during his deposition that he could not tell by looking at a compound whether it is a claimed inhibitor. EX1046, 236:12-17. His inability to discern which molecules are inhibitors of IL-15 or the IL-15 receptor confirms that his testimony about a known class of inhibitors is unreliable and mistaken.

VIII. CONCLUDING STATEMENTS

86. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

87. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements

EX2013-2015 or EX2025, which Dr. Damsky identifies as primarily directed to the α -subunit of the IL-15 receptor, is representative of the proposed inhibitors in EX2024 that were never incorporated in the '505 patent

and the like so made are punishable by fine or imprisonment, or both, under
Section 1001 of Title 18 of the United States Code.

Dated: January 9, 2024

By: /R.Todd Plott/
R. Todd Plott

IX. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 11,278,505 to Richmond et al.
1005	<i>Curriculum Vitae</i> of Dr. R. Todd Plott
1006	“A Mouse Model of Vitiligo with Focused Epidermal Depigmentation Requires IFN- γ for Autoreactive CD8 ⁺ T-Cell Accumulation in the Skin” John E. Harris, et al., <i>Journal of Investigative Dermatology</i> (2012) 132, 1869-1876
1011	U.S. Patent No. 9,028,830 to Tso et al.
1012	“Phase 1 trial of IL-15 trans presentation blockade using humanized Mik-Beta-1 mAb in patients with T-cell large granular lymphocytic leukemia,” Thomas A. Waldmann et al., <i>Blood, the Journal of the American Society of Hematology</i> , 121(3), 476-484
1016	“The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design,” Thomas A Waldmann, NATURE REVIEWS IMMUNOLOGY VOLUME 6 AUGUST 2006
1018	“Resolution of psoriasis upon blockade of IL-15 biological activity in a xenograft mouse model,” Louise S. Villadsen, et al., <i>J Clin Invest.</i> 2003;112(10):1571-1580
1032	“Rapid skin repigmentation on oral Ruxolitinib in a patient with coexistent vitiligo and alopecia areata” John E. Harris et al., <i>J Am Acad Dermatol.</i> , 2016, 74(2): 370-371
1033	“Tofacitinib Citrate for the Treatment of Vitiligo: A Pathogenesis-Directed Therapy” Brittany G Craiglow and Brett A. King, <i>JAMA Dermatol.</i> (2015), 151(10):1110-2
1040	Harris Global Derm Talk Presentation
1046	Transcript of Nov. 20, 2023 Deposition of William Damsky, M.D., Ph.D

1048	<p>“Update on IL-15 vitiligo treatment,” John E. Harris, (Jan. 13, 2020), UMass Chan Medical School Vitiligo Clinic & Research Center Vitiligo Blog, available at https://www.umassmed.edu/vitiligo/blog/blog-posts/2020/01/update-on-il-15-vitiligo-treatment/ (last visited Dec. 5, 2023).</p>
1049	<p>“Tareting Interleukin-15 in Patients with Rheumatoid Arthritis,” Bo Baslund et al., <i>Arthritis & Rheumatism</i> (2005) 52(9):2686-2692</p>
1050	<p>ClinicalTrial.Gov Study Details for NCT00433875, Phase 2 AMG714 in Rheumatoid Arthritis, available at https://clinicaltrials.gov/study/NCT00433875?intr=AMG714&limit=100&rank=3 (last visited Dec. 5, 2023).</p>
1051	<p>ClinicalTrial.Gov Study Details for NCT00443326, AMG714 20060349 Multiple Dose Study in Moderate to Severe Psoriasis Subjects, available at https://clinicaltrials.gov/study/NCT00443326?intr=AMG714&limit=100&rank=1 (last visited Dec. 5, 2023).</p>
1052	<p>“Safety and efficacy of AMG714 in adults with coeliac disease exposed to gluten challenge: a phase 2a, randomized, double-blind, placebo-controlled study,” Marja-Leena Lahdeaho, et al., <i>Lancet Gastroenterol. Hepatol.</i> (2019) (12):948-959.</p>
1053	<p>“Safety and efficacy of AMG714 in adults with type 2 refractory coeliac disease: a phase 2a, randomized, double-blind, placebo-controlled, parallel-group study,” Christophe Cellier, et al., <i>Lancet Gastroenterol. Hepatol.</i> (2019) (12):960-970.</p>
1054	<p>“Identification of a potent anti-IL-15 antibody with opposing mechanisms of action <i>in vitro</i> and <i>in vivo</i>,” DK Finch, et al., <i>British Journal of Pharmacology.</i> (2011) 162:480-490.</p>
1055	<p>ClinicalTrial.Gov Search Results for Hu-Mikb1, available at https://clinicaltrials.gov/search?intr=Hu MiK-Beta-1 (last visited Dec. 5, 2023).</p>
1056	<p>“Diagnosing Vitiligo and Improving Care Provider Awareness,” Seemal Desai and William Damsky, DermView Innovations in the</p>

	Treatment of Vitiligo: Episode 4 (Nov. 30, 2021), available at https://www.dermatologytimes.com/view/diagnosing-vitiligo-and-improving-care-provider-awareness (last visited Nov. 19, 2023).
1057	“The pathogenesis of Vitiligo,” Neel Malhotra and Marlene Dytoc, J. Cutaneous Med. & Surgery. (2013) 17(3):153-172.
1058	“A New Phenylpyrazoleanilide, Y-320, Inhibits Interleukin 17 Production and Ameliorates Collagen-Induced Arthritis in Mice and Cynomolgus Monkeys,” Ushio et al., Pharmaceuticals (2014) 7:1-17.
1059	Paragraph 70 of Damsky Declaration from Deposition
2005	Declaration of Dr. Damsky
2013	WO 2014/191822
2014	WO 2014/191823
2015	US Patent Pub. No. 2016/0235762
2016	Ushio Hiroyuki et al., <i>Phenylpyrazoleanilides as Potent Inhibitor of IL-15 Dependent T Cell Proliferation. Part 2: Discovery of a New Drug Candidate, Y-320</i> , 5(4) LETTERS IN DRUG DESIGN & DISCOVERY 292-96 (2008).
2019	US Patent No. 7,736,638
2022	Wilson CG and Arkin MR, <i>Small-molecule inhibitors of IL-2/IL-2R: lessons learned and applied</i> , 348 CURR. TOP. MICROBIOL. IMMUNOL. 25-59 (2011)
2024	WO 2015/181394
2025	WO 2015/044761
2078	Budagian V et al., <i>IL-15/IL-15 receptor biology: a guided tour through an expanding universe</i> , 17(4) CYTOKINE GROWTH FACTOR REV. 259-80 (2006)

2079	Robinson TO and Schluns KS, <i>The potential and promise of IL-15 in immuno-oncogenic therapies</i> , 190 IMMUNOL. LETT. 159-68 (2017)
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