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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

**PETITION FOR POST-GRANT REVIEW OF
U.S. PATENT NO. 11,278,505**

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LISTING OF CHALLENGED CLAIMS

1. A method of treating a subject who has a vitiligo lesion, the method comprising:
 - identifying a subject in need of treatment; and
 - administering a therapeutically effective amount of an inhibitor of IL-15 or the IL-15 receptor to the subject.
2. The method of claim 1, wherein the inhibitor is a small molecule inhibitor, an antibody, a peptide inhibitor, or an inhibitory nucleic acid targeting IL-15 or the IL-15 receptor.
3. The method of claim 1, wherein the inhibitor is administered to the lesion.
4. The method of claim 3, wherein the inhibitor is administered to the epidermis within the lesion.
5. The method of claim 3, wherein the inhibitor is administered to the epidermis within the lesion by subcutaneous or intradermal administration, or a microneedle array.

Pursuant to the provisions of 35 U.S.C. § 321 et seq., and 37 C.F.R. Part 42, Forte Biosciences, Inc., (“Petitioner”) hereby requests post-grant review of United States Patent No. 11,278,505 to Jillian M. Richmond et al. (hereinafter “the ’505 patent,” EX1001) that issued on March 22, 2022, and is currently assigned to the University of Massachusetts (“Patent Owner” or “PO”). This petition demonstrates it is more likely than not that at least one of claims 1-5 of the ’505 patent is unpatentable for failure to satisfy 35 U.S.C. §§112 and/or 103 and that claims 1-5 of the ’505 patent should be found unpatentable and canceled.

I. INTRODUCTION

Vitiligo is a localized autoimmune disorder in which the body’s immune cells kill the body’s own melanocytes in a patch of the body’s skin, resulting in depigmentation patches called lesions. In December 2008, a WIPO publication resulting from an application by the United States of America (WO 2009/002562) taught that inhibiting the binding of interleukin-15 (IL-15) or the IL-15/IL-15R α complex to the dimeric complex formed by CD122 and CD132 ($\beta\gamma$ complex) with an interfering antibody could be used to reduce T cell activity (including memory T cells) for the treatment of autoimmune diseases, including vitiligo. EX1009, [0004]-[0006], [0009]-[0011], [0020], [00220]-[00221], [00226]. Despite the earlier disclosures in the ’562 publication, the ’505 patent (claiming priority to 2017) broadly claims and preempts the ability of the public to administer to *any*

subject who has a vitiligo lesion a therapeutically effective amount of **any** inhibitor of IL-15 **or any** inhibitor of the IL-15 receptor (IL-15R). EX1001, claims.

The '505 patent claims should be cancelled under 35 U.S.C. §112(a) because their scope is far broader than any invention that is disclosed and enabled by the specification. The claims are overbroad at least with respect to (1) the multiple and disparate types of inhibition encompassed; (2) the incalculable number of disparate and undefined chemical structures with potential to inhibit those pathways; and (3) the unrestricted identity of the subject (e.g., mouse model vs. actual human patient) receiving treatment. For example, the claims encompass using any inhibitor of IL-15 or IL-15R (including any of the IL15R α , CD122/ β , or CD132/ γ subunits) and do not even require that the inhibitor physically interact with any of these targets of inhibition. CD122/ β is shared by at least two signaling pathways (IL-2 and IL-15), and CD132/ γ is shared by at least six signaling pathways. The claims thus encompass multiple, disparate types of inhibition.

Moreover, the claims are limited by no (claims 1-, 3-5) or almost no (2) structural requirements, and are instead defined purely functionally. The number and nature of the compounds implicated is thus so large as to be incalculable. And the claims are not restricted to treating lesions in a simplified mouse model where lesions are induced by CD8⁺ T cell transference—the only working example given in the patent—but encompass the much more complicated task of treating human

patients with natural or spontaneous vitiligo lesions. Indeed, the '505 patent's mouse model is not representative of treating natural vitiligo, as the biological mechanisms naturally causing such autoimmune diseases are much more complex than the mouse model lesions.

The immense claim scope is not commensurate with the sparse disclosure of the '505 patent specification. The '505 patent's data is limited to a mouse model that induces vitiligo lesions by transferring activated and melanocyte-targeted CD8⁺ effector T cells to the mouse so that they will kill the mouse's melanocytes. To that mouse model, the '505 patent administered a particular Fc-diminished CD122/ β antibody called ChMBC7 that depleted CD8⁺ effector T cells and thereby reversed the vitiligo lesions these cells created. The '505 patent never disclosed the sequence or structure that corresponds to this antibody code name, never disclosed where this antibody binds, and never demonstrated that it specifically inhibits IL-15 signaling as opposed to IL-2 signaling. The '505 patent never demonstrated that ChMBC7 inhibition is representative of all CD122 inhibition.

But the broad claims of the '505 patent even extend far beyond Fc-diminished CD122 inhibition to include different physical targets (IL-15, IL-15R α , and CD132/ γ , and to include molecules that do not even physically interact with either IL-15 or IL-15R (e.g., nucleic acid inhibitors). The specification provides no demonstration that ChMBC7 mouse CD122 antibody inhibition is representative of

all these different inhibition pathways. Moreover, the specification never demonstrated that ChMBC7 inhibition works to treat vitiligo lesions other than lesions induced in a CD8⁺ effector T cell-dependent mouse model. In view of the nascency and unpredictability of inhibiting $\beta\gamma$ signaling to treat vitiligo, especially across a range of subjects including human patients with natural or spontaneous vitiligo lesions, the very minimal guidance provided by the patent is insufficient to demonstrate the inventors were in possession of or enabled the full genus claimed. Accordingly, all claims of the '505 patent are invalid under 35 U.S.C. §112(a).

All claims also are unpatentable for obviousness under 35 U.S.C. §103. PO obtained allowance of the claims over the '562 publication by arguing PO was the first to provide data showing that inhibiting IL-15 signaling actually treated vitiligo. As discussed above, the '505 patent's data is limited to treating lesions caused by introducing activated and melanocyte-targeted CD8⁺ effector T cells, so that depletion of those cells was an obvious means for eliminating the lesions. But reversing lesions by depleting the CD8⁺ effector T cells that were used to cause them was not unexpected. As demonstrated by the prior art Xing reference, which was not before the Examiner during prosecution, administering an antibody to inhibit CD122 reduced CD8⁺ effector T cells and prevented development of alopecia areata lesions in a relevant mouse model. Xing also taught that local (e.g., subcutaneous) administration of downstream inhibitors reduced CD8⁺ effector T

cell-driven skin lesions, and the '505 patent admits that determining the appropriate dosage was a matter of routine experimentation for a person of ordinary skill in the art (POSA). Accordingly, the '505 patent claims are obvious based on evidence the Examiner previously had no occasion to consider.

Accordingly, Post-Grant Review should be instituted and the challenged claims canceled.

A. Technological Background

This petition is supported by the Declaration of Dr. Abul Abbas who is Professor Emeritus of Pathology and Laboratory Medicine at University of California, San Francisco. EX1002; EX1003 (cv). Dr. Abbas is an expert in cytokine signaling, and particularly regarding the $\beta\gamma$ signaling complex (which is activated by each of the IL-2 and IL-15 cytokines). EX1002, ¶¶1-10. The petition also is supported by the Declaration of Dr. R. Todd Plott, who is a board-certified dermatologist with 30 years of experience diagnosing and treating autoimmune diseases of the skin including vitiligo. EX1004; EX1005 (cv); *see* EX1004, ¶¶1-8.

As Drs. Abbas and Plott explain, the '505 patent was not the first to use a specific CD122 antibody for depleting CD8⁺ T cells in a mouse model, and reversing depigmentation vitiligo lesions by depleting the activated, melanocyte-targeted CD8⁺ T cells that caused them would have been obvious to a POSA at the relevant time in view of the prior art. However, the specification of the challenged

patent does not demonstrate that its CD122 antibody was representative of all ways of inhibiting IL-15 receptor signaling to treat vitiligo or was representative of treating natural or spontaneous vitiligo in a human patient. EX1002, ¶¶41-42; EX1004, ¶¶33-36. Accordingly, the inventors of the '505 patent were not in possession of the claimed genus of methods at the priority date, nor did the specification enable a POSA to practice the claimed genus of methods without undue experimentation.

i. Complex and Sometimes Overlapping Cytokine Signaling Pathways Activate Leukocyte Immune Responses

Leukocytes, also called white blood cells, circulate through the body and tissues to respond to injury or illness by attacking foreign substances that enter the body. EX1002, ¶43. Lymphocytes are an important class of leukocytes found in lymph, and consist of T cells, natural killer (NK) cells, and B cells. EX1002, ¶44. T cells and B cells recognize specific non-self antigen markers and respond to eliminate specific pathogens. EX1002, ¶44. B cells respond by producing antibodies to neutralize bacteria and viruses. EX1002, ¶44. T helper cells produce cytokines (small cell-signaling peptides) that direct the immune response. EX1002, ¶44. Interleukins are cytokines produced by leukocytes.

Cytotoxic effector T cells produce toxic granules that induce the death of pathogen-infected cells. EX1002, ¶45. CD8 was a known marker for cytotoxic T cells that destroy the target. EX1002, ¶45. Memory-type effector T cells play a role

in providing a strong immune response when reencountering a pathogen. EX1002, ¶45. NK cells kill other cells, can be activated by interferon cytokines, and can modulate the functions of other cells, including T cells. EX1002, ¶45.

Interleukin-2 (IL-2) is a cytokine primarily produced by activated CD4⁺ helper T cells and activated CD8⁺ cytotoxic T cells. EX1002, ¶46. IL-2 signaling occurs when IL-2 binds to the IL-2 receptor (IL-2R), a complex that consists of up to three subunits: IL-2R alpha (α , CD25), beta (β , CD122) and gamma (γ , CD132). EX1002, ¶46. IL-2 binding to either the $\beta\gamma$ complex (with low affinity, expressed by memory CD8⁺ T cells and NK cells) or to the CD25- $\beta\gamma$ complex (with high affinity, highly expressed on regulatory T cells and activated T cells) results in $\beta\gamma$ signaling. EX1002, ¶46. The γ subunit is shared by all members of the four-alpha-helix-bundle family, which includes IL-4R, IL-7R, IL-9R, IL-15R, and IL-21R. EX1002, ¶47. IL-2R also shares the β subunit with IL-15R. EX1002, ¶47. IL-15 also induces $\beta\gamma$ signaling by binding either to the $\beta\gamma$ complex (with low affinity) or by binding first to its alpha-receptor subunit IL-15R α (with higher affinity). EX1002, ¶48. $\beta\gamma$ signaling, whether induced by IL-15 or IL-2, activates the JAK-STAT pathways and various immunological effects. EX1002, ¶48. Among other effects, both IL-2 and IL-15 potentiate cytotoxic effector functions in tissue resident memory T (Trm) cells. *Id.*; EX1027, 297.

ii. CD8⁺ T cells Drive Development and Maintenance of Lesions in Mouse Models of Vitiligo and Alopecia and Reducing Them Was Known to Be Therapeutic

Vitiligo, alopecia areata (AA), and psoriasis are common autoimmune diseases of the skin. EX1008, Abstract, 785; EX1004, ¶37. Vitiligo is caused by the destruction of melanocytes and results in the appearance of white patches on the body, while AA is characterized by patchy hair loss primarily on the scalp. EX1008, 785; EX1004, ¶¶37-38; EX1002, ¶49. Vitiligo has long been treated by administering immunosuppressant agents to the lesions, such as glucocorticoid steroids and calcineurin inhibitors. EX1004, ¶37; EX1008, 785. Vitiligo also has been treated using narrow-band UVB light therapy. EX1004, ¶37; EX1008, 785.

AA was primarily treated with intralesional steroid injections or by inducing contact dermatitis. EX1008, 785. Differences in the treatment approach may be due to the location within the skin rather than the pathogenesis of each disease. EX1008, 785; EX1004, ¶38. For example, Melanocyte destruction in vitiligo is primarily limited to the epidermis, whereas inflammation in AA is localized around the hair bulb deep in the dermis, so that steroids are most effective when injected intradermally. EX1008, 785; EX1004, ¶38.

It was known that the damage to melanocytes in vitiligo and the hair follicle in AA is caused by autoreactive CD8⁺ T cells, including tissue resident memory T cells (Trm). EX1031, Abstract, 729, 732; EX1019, 467. Vitiligo and AA lesions

are characterized by immune cell infiltration, which consists primarily of T cells, including both CD8⁺ and CD4⁺ subtypes. EX1008, 786; EX1002, ¶50. The CD8⁺ cells are commonly found infiltrating the epidermis in vitiligo and the follicular epidermis in AA, while the CD4⁺ cells remain dermal. EX1008, 786; EX1002, ¶50. Cytotoxic CD8⁺ T cells were said to play a key role in the destruction of melanocytes in vitiligo and hair loss in AA. EX1008, 787; EX1020, Abstract (“Vitiligo patients have increased numbers of autoreactive, melanocyte-specific CD8⁺ T cells in the skin and blood, which are directly responsible for melanocyte destruction.”); EX1021, 737 (“The pathogenesis of [alopecia areata] involves hair follicle attack by autoreactive CD8⁺ T cells.”); EX1002, ¶50; EX1004, ¶39.

Prior to the '505 patent, mouse models of vitiligo had been developed. For

example, Harris described a mouse model of vitiligo in which $CD8^{+}$ T cells recognizing the melanocyte-specific antigen “PMEL” are transferred into host mice. EX1006, Abstract, 1870. The pathogenesis in this mouse model thus can be ascribed to the presence of autoreactive $CD8^{+}$ T cells. EX1002, 50. Harris observes that the transferred melanocyte-specific $CD8^{+}$ T cells accumulate within the skin. EX1006, 1870; *see also id.*, 1870-1872, Figure 1b (reproduced herein). Harris also observes that depigmentation correlates with loss of melanocytes. EX1006, 1872, Figure 3; EX1002, ¶51. In this same vitiligo model, it also was shown that treatment with an agent (i.e., simvastatin) that reduces the number of melanocyte-specific $CD8^{+}$ T cells in the skin also reduces depigmentation. EX1023, 1081-1082, Figures 1 & 2; EX1002, ¶52; EX1004, ¶40.

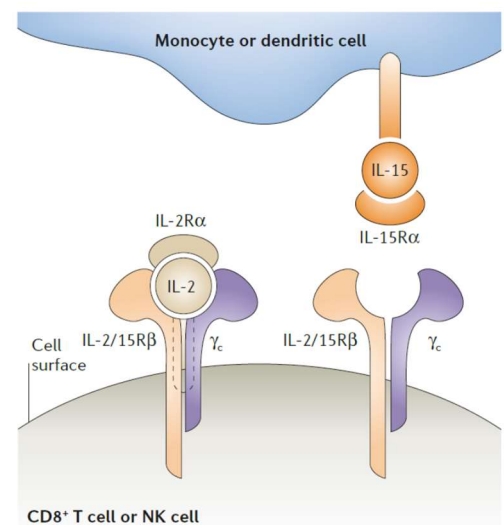


In a mouse model of alopecia areata (AA), autoreactive $CD8^{+}$ T cells accumulate in the skin of affected animals. EX1007, 1 (“In lesional skin biopsies from alopecic mice, $CD8^{+}NKG2D^{+}$ T cells infiltrate the epithelial layers of the hair follicle,...”). These $CD8^{+}$ T cells were known to be necessary and sufficient to

induce the killing of hair follicles associated with AA. EX1007, Abstract (“[W]e show that cytotoxic $CD8^+NKG2D^+$ T cells are both necessary and sufficient for the induction of AA in mouse models of disease.”), 2, Figure 1; EX1009, 786; EX1034, 844. Accordingly, in mouse models of vitiligo and alopecia areata, it was known that $CD8^+$ T cells drive disease and that reducing the number of $CD8^+$ T cells in the skin is therapeutic for treating vitiligo and alopecia areata. EX1002, ¶53; EX1004, ¶¶41-42.

iii. Vitiligo and Alopecia Areata Could Be Treated By At Least Some Inhibitors of IL-15- and/or IL-2-Induced Cellular responses.

Prior to the earliest claimed filing date of the '505 patent, POSAs appreciated that IL-2 and IL-15 are involved in the “life and death” of $CD8^+$ T cells. EX1015, 782 n.69, 771; EX1016, Abstract; EX1002, ¶54. Both IL-2 and IL-15 induce $\beta\gamma$ signaling in $CD8^+$ T cells, among others, with greater affinity if they first associate with a unique α chain (“IL-2 $R\alpha$ or IL-15 $R\alpha$ ”). EX1015, Figure 1; EX1002, ¶54. The γ chain is a shared subunit activated by each of IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. EX1015, 771; EX1022, 174; EX1016, Figure 2 (shown herein); EX1002, ¶54. Presentation of a cytokine on one cell to the $\beta\gamma$ complex on another cell (more common for IL-15 than IL-2) is called



“*trans*- presentation.” EX1015, 771; EX1002, ¶55. Presentation of a cytokine to the $\beta\gamma$ complex on the same cell (more common for IL-2 than for IL-15) is called “*cis*- presentation.” EX1015, 771; EX1002, ¶55.

IL-2 and IL-15 were both well-known drivers of cytotoxic activity by IFN- γ -producing CD8⁺ effector T cells and NK cells and had been implicated in the induction and/or maintenance of autoreactive CD8⁺ T cells. EX1007, 3; EX1007, 3-4; EX1002, ¶56. A baseline level of IL-2 inhibited autoimmune disease by activating CD4⁺ Regulatory T cells, but high levels of IL-2 promote cytotoxic CD8⁺ effector cell activity. EX1035, Abstract; EX1002, ¶57 (discussing EX1022, 175). Accordingly, complete knock-out of IL-2 production in mice was known to cause autoimmune disorders. EX1024, Abstract, 771-72; EX1002, ¶57.

Without IL-15, populations of memory CD8⁺ T cells decline by attrition. EX1026, 1542 (“memory CD8 T cell numbers undergo a slow attrition in the absence of IL-15”). It was known that “IL-15 is not essential for the generation of memory CD8 T cells, but is required for homeostatic proliferation to maintain populations of memory cells over long periods of time.” EX1026, Abstract, *see id.*, 1545; EX1002, ¶58. Accordingly, complete knockout of IL-15 production in mice was known to reduce the number of memory CD8⁺ T cells. EX1024, Abstract, 771-72.

Skilled artisans also knew that Trm CD8⁺ T cells could be depleted with neutralizing antibodies to IL-15 or its cytokine-specific receptor. EX1002, ¶59. For example, injecting neutralizing antibodies to IL-15 and IL-15R α into the skin of mice depletes tissue-resident memory (“Trm”) CD8⁺ T cells. EX1017, 1107 (“This antibody was injected into the skin flank at the site of Trm cell establishment.... We found that the number of skin Trm cells was diminished by more than half following antibody administration....”), 1109 (“For IL-15 blocking assays, mice were treated with anti-IL-15+IL-15R α chain antibody ...by either intradermal injection”). Villadsen demonstrated in a mouse model of psoriasis that IL-15 antibodies deplete CD8⁺ T cells and alleviate psoriasis. EX1018, 1576-1578.

Skilled artisans also understood that both vitiligo and AA could be treated by at least some inhibitors of IL-15- and/or IL-2-induced cellular responses. EX1004, ¶46. For example, it was known that $\beta\gamma$ signaling is mediated by Janus kinases (i.e., Jak1 and Jak3) which bind to the intracellular portions of the β and γ chains of the receptor. EX1015, 777. Inhibition of Jak1 or Jak3 treated both vitiligo and AA in humans and mice. EX1007, 5-6, Fig. 3, Fig. 4; EX1032, 370-71; EX1033, Abstract, 1010-11. It was also known that mice with vitiligo or AA could be treated with antibodies to IFN- γ which is produced by CD8⁺ T cells in response to IL-15. EX1027, 297; EX1019, 467; EX1002, ¶60.

Additional prior art reference of particular relevance to the prior art

unpatentability of claims 1-5 of the '505 patent are discussed below.

B. The '505 Patent

The '505 patent is entitled “Diagnosis and treatment of vitiligo” and purports to describe methods for treating “disorders associated with T cell-mediated autoimmunity.” EX1001, 6:30-33. The '505 patent further explains that certain embodiments are directed to vitiligo while others are directed to disorders such as alopecia areata. EX1001, 6:33, 7:14-18. The '505 patent does not restrict its treatment methods to administration of a single active agent, but instead purports to extend to “systemic or (more preferably) local delivery of a therapeutically effective amount of an inhibitor of IL-15, the IL-15 receptor, a Sp[h]ingosine-1-receptor inhibitor, and/or the downstream signaling molecules JAK1 and 3” to a subject in need of treatment. EX1001, 7:16-25; EX1002, ¶¶27-28; *see also id.*, ¶¶29-30; EX1004, ¶¶24-25.

The '505 patent broadly claims a method of treating vitiligo in a subject comprising administering a therapeutically effective amount of an inhibitor of IL-15 or its receptor (i.e., IL-15R α ; CD122/IL-2R β /IL-15R β ; or CD132, common γ chain). EX1002, ¶¶31-32; EX1004, ¶¶26-27.

1. A method of treating a subject who has a vitiligo lesion, the method comprising:

identifying a subject in need of treatment; and

administering a therapeutically effective amount of an inhibitor of IL-15 or the IL-15 receptor to the subject.

The claims do not recite that the treatment reverses or reduces a vitiligo lesion, that such effects must be durable for any amount of time (e.g., after cessation of treatment), or even that a particular blood concentration of inhibitor must be achieved.

Dependent claim 2 is directed to various classes of “inhibitor” including small molecules, antibodies, peptides, and inhibitory nucleic acids targeting IL-15 or the IL-15 receptor. EX1002, ¶33. Claim 3-5 specify that administration encompasses delivery to the “epidermis” of a vitiligo lesion, including by subcutaneous injection. EX1002, ¶34; EX1004, ¶¶28-29. As summarized in the table below, the ’505 patent does not provide working examples across the full scope of claims 1-5. EX1002, ¶38; *see also* EX1004, ¶30.

Claimed	Method Exemplified
“a subject who has a vitiligo lesion”	CD8 ⁺ T cell Mouse Model No natural or spontaneous vitiligo No human patient
Small molecule inhibitor of “IL-15 or the IL-15 receptor”	None
Antibody inhibitor of “IL-15”	None
Antibody inhibitor of “the IL-15 receptor”	One Chimeric Rat/Mouse Antibody targeting Mouse CD122. None targeting IL-15 α or CD132
Peptide inhibitor of “IL-15 or the IL-15 receptor”	None

Nucleic acid inhibitor of “IL-15 or the IL-15 receptor”	None
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Indeed, the sole working example in the patent is treating a CD8⁺ T cell-induced mouse model vitiligo with an Fc-diminished chimeric rat/mouse CD122 antibody referred to as ChMBC7. EX1001, 33:1-34:45. The '505 patent presents no evidence that administering a Fc-intact CD122 antibody would work similarly. EX1002, ¶¶35-37.

C. Prosecution History

The '505 patent was filed as U.S. Application No. 16/608,116 (“the '116 application”) on October 24, 2019. It represents the national stage of International Application No. PCT /US2018/029185, filed November 1, 2018, which claims priority to U.S. Provisional Patent Application No. 62/489,191 filed on April 24, 2017.

Prosecution of the '505 patent involved (1) cancellation of claims directed to administering an effective amount of an S1P1 inhibitor to treat vitiligo; and (2) one non-final obviousness rejection.

The Examiner rejected claims 1-5 of the '116 application in view of WO 2009/002562 to Pavlakis (EX1009). EX1010, 55-57. The Examiner asserted that the '562 publication discloses “a method for treating an autoimmune disorder ...in a human subject, comprising administering to a human subject in need thereof an effective amount of an antibody that specifically binds to IL-15/IL-15Ra

complexes and reduces the binding of the IL-15/IL-15Ra complexes to the beta-gamma receptor complex” and further discloses vitiligo as an exemplary autoimmune disorder. *Id.*

Patent Owner responded “Pavlakakis relates to agents that modulate IL-15-mediated function for the prevention, treatment and/or management of diseases involving IL-15- mediated signaling” but does not “teach[] nor suggest[] a method of treating a subject who has a vitiligo lesion.” EX1010, 36-37. Patent Owner further argued “the inventors of the present application surprisingly discovered that treatment with an IL-15R β blocking antibody effectively depleted autoreactive Trm, inhibited their function, and resulted in durable reversal of disease in mice.” EX1010, 38.

A notice of allowance followed. EX1010, 13-15. In the reasons for allowance, the Examiner accepted Patent Owner’s arguments regarding surprising results. However, the Xing reference describing depletion of autoreactive Trm CD8⁺ T cells with CD122 antibody and reversing AA lesions through topical application of downstream JAK inhibitors was not before the Examiner. As discussed below in Sections VIII and IX, Xing demonstrates that reversing CD8⁺ T cell-induced skin lesions in the mice model by using a CD122 antibody to deplete CD8⁺ T cells was obvious. Moreover, support for the claims under Section 112 was never addressed during prosecution.

D. Level of Skill in the Art

A person of ordinary skill in the art (POSA) of the '505 patent in April 2017 or April 2018 would have had an advanced degree (e.g., Ph.D., M.D., M.S., or equivalent), in a field related to medicine, immunology, molecular biology, cell biology, microbiology, pathology, biochemistry, peptide chemistry, or a related field, and at least 3-5 years of experience in treating autoimmune diseases or researching cytokine signaling pathways relevant to treating autoimmune diseases. This individual would have worked in consultation with a team including, e.g., a medical doctor who diagnoses and treated vitiligo, and a pharmaceutical scientist familiar with formulating drugs for administration. Moreover, skilled artisans also would have practical knowledge of immunology and have been familiar with prior art pertaining to treatment of autoimmune diseases, including the patents and publications discussed herein. EX1002, ¶¶39-40; EX1004, ¶¶31-32. Furthermore, the prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

This petition is supported by the declaration testimony (EX1002) of Dr. Abul K. Abbas. Dr. Abbas is an emeritus professor in the UCSF Pathology department. He received his MBBS degree (MD equivalent) in India in 1969, and received residency and research fellow training in the Department of Pathology of Peter Bent Brigham Hospital and Harvard University. He spent more than four

decades researching immunology as a professor at Harvard medical school (1977-1999) and UCSF medical school (1999-2018) until he retired in 2018. During his career, he published more than 200 papers in the immunology field including papers regarding IL-2 regulation in autoimmune and inflammatory disease, and tissue resident T cells in autoimmune response. He is also the author of 5 immunology textbooks, and has been an editor of several scientific journals – Immunity, The Journal of Immunology, Journal of Clinical Immunology. Dr. Abbas is well-qualified to provide expert opinions on IL-15/IL-15R inhibition (which shares subunits with IL-2/IL-2R) and implications in T cell regulation and autoimmune diseases (including skin autoimmune diseases such as vitiligo). His curricular vitae are attached as EX1003. His education, experience, and training qualify him to opine regarding the perspective of a POSA at the relevant time. *See* EX1002, ¶¶1-10, 40.

This petition is also supported by the declaration testimony (EX1004) of Dr. Plott. Dr. Plott received his M.D. in 1989 and has spent the past 30 years in clinical practice treating dermatological conditions, including the dermatological autoimmune conditions vitiligo, alopecia areata, and psoriasis. Dr. Plott is well qualified to provide expert opinions on the treatment of these autoimmune diseases and the perspective of the POSA at the relevant time related thereto. *See* EX1004, ¶¶1-8, 32. His curricular vitae are attached as EX1004.

E. Summary of the Asserted References

i. Xing

“Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition” by Xing, et al, (“Xing,” EX1007) was published in *Nature Medicine* on August 17, 2014. Xing is prior art under 35 U.S.C. §102(a)(1).

Xing describes experiments performed in a mouse strain that spontaneously develops alopecia areata (“AA”). EX1007, 1. Alopecic lesions in the skin of mice are characterized by the accumulation of autoreactive CD8⁺ T cells. EX1007, 1 (“In lesional skin biopsies from alopecic mice, CD8⁺NKG2D⁺ T cells infiltrate the epithelial layers of the hair follicle,...”). Xing explains that these CD8⁺ T cells are necessary and sufficient to induce disease. EX1007, Abstract (“[W]e show that cytotoxic CD8⁺NKG2D⁺ T cells are both necessary and sufficient for the induction of AA in mouse models of disease.”), 2, Figure 1. Xing discloses that a specific CD122 antibody (named TM-β1) “blocked the accumulation of CD8⁺NKG2D⁺ T cells in the skin” and prevented AA lesions. EX1007, 3-4, Figure 2.

Xing was not before the Examiner of the '505 patent.

ii. Harris

“A Mouse Model of Vitiligo with Focused Epidermal Depigmentation Requires IFN-γ for Autoreactive CD8⁺ T-Cell Accumulation in the Skin” by John

E. Harris, et al (“Harris,” EX1006) was published in the *Journal of Investigative Dermatology* on February 2, 2012. Harris is prior art under 35 U.S.C. §102(a)(1).

Harris describes “an adoptive transfer mouse model of vitiligo using melanocyte-specific CD8⁺ T cells, which recapitulates the human condition by inducing epidermal depigmentation while sparing the hair.” EX1006, Abstract. The mice in the model had autoreactive CD8⁺ T cells in regions with depigmented skin. EX1006, 1872. Harris describes these mice as providing a “platform to fully investigate disease mechanisms and treatment” of vitiligo. EX1006, Abstract.

II. GROUNDS FOR STANDING AND AVAILABILITY OF POST-GRANT REVIEW

Petitioner certifies that, under 37 C.F.R. § 42.204(a), the ’505 patent is available for post-grant review. The earliest claimed priority date of the ’505 patent is April 24, 2017. This petition is filed within nine months of issuance of the ’505 patent. Petitioner has not filed a civil action challenging the validity of any claim of the ’505 patent. Petitioner is not barred or estopped from requesting post-grant review of the ’505 patent on the grounds identified.

III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)): Forte Biosciences, Inc. is the real party-in-interest.

Related Matters (37 C.F.R. § 42.8(b)(2)): None

Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)):

Lead Counsel: Michael T. Rosato (Reg. No. 52,182)

Back-Up Counsel: Jad A. Mills (Reg. No. 63,344); Michael J. Hostetler
(Reg. No. 47,664); Sonja R. Gerrard (Reg. No. 72,802)

Service Information – 37 C.F.R. § 42.8(b)(4). Petitioner hereby consents to
electronic service.

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**IV. STATEMENT OF THE PRECISE RELIEF REQUESTED FOR EACH CLAIM
CHALLENGED 37 C.F.R. §42.204(B)**

Petitioner requests review of claims 1-5 of the '505 patent under 35 U.S.C.
§321. The grounds for relief are as follows:

Ground	Claims	Description
1	1-5	Lack of written description under 35 U.S.C. §112
2	1-5	Lack of enablement under 35 U.S.C. §112
3	1-5	Obvious under 35 U.S.C. §103 in view of Xing and Harris

V. CLAIM CONSTRUCTION

Claims should be understood according to their ordinary and customary meaning as understood by POSA at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. 37 C.F.R. §42.200; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-14 (Fed. Cir. 2005) (en banc). The Board need construe claims only to the extent necessary to resolve a controversy. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). Petitioner submits that the claims should be understood according to their plain meaning and that no construction should be necessary to institute this petition.

VI. [GROUND 1] CLAIMS 1-5 LACK WRITTEN DESCRIPTION

The claims of the '505 patent lack written description support and must be canceled because the specification fails to reasonably convey to a POSA that the applicant invented the broad invention that is claimed. 35 U.S.C. §§112(a) (written description support required), 321(b) (PGR grounds for cancellation), 282(b)(3)(A) (invalidity for §112). To provide the required written description, the specification must clearly allow a POSA to recognize that the inventor invented what is claimed. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The written description requirement functions to “ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the

inventor's contribution to the field of art as described in the patent specification.”

Id. at 1353-54. The specification therefore must demonstrate conception and at least constructive reduction to practice of “the complete and final invention with all its limitations.” *Id.* at 1353. A specification that merely renders the invention obvious does not satisfy the written description requirement. *Id.*

The '505 patent claims lack written description support because they are overly broad and functionally defined and because the specification fails to disclose a representative number of species commensurate with the scope of the claim. Where a method claim defines its boundaries in terms of using a vast genus of chemical compounds, especially where the boundaries of this genus are defined at least in part using functional language, the specification “must demonstrate invention of sufficient species to support a claim to a genus.” *Id.* at 1349; *see also id.* at 1340-41 (“The [method] claims are thus genus claims, encompassing ***the use of*** all substances that achieve the desired result of reducing the binding of NF-KB to NF-KB recognition sites.”),¹ 1350 (specification must “support the scope of the genus”). Claim 1 provides no structural requirement for either of the two recited genera ((i) inhibitors of IL-15 and (i) inhibitors of the IL-15 receptor). Instead, it claims the method functionally (any form of inhibition of IL-15 or the IL-15

¹ All emphases added unless otherwise indicated.

receptor). EX1002, ¶¶31-33. Accordingly, the “specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.” *Ariad*, 598 F.3d at 1349.

The challenged claims lack written description support because the claimed invention is an extremely broad genus comprising several, very broad sub-genera, and the specification is not commensurate with, and does not reasonably convey invention of, the entire scope of the claimed invention. Claim 1 is so broad that it encompasses **any method** of treating **any subject** who has a vitiligo lesion, if that method comprises (a) identifying a subject in need of treatment; and (b) administering to the subject a therapeutically effective amount of **any inhibitor** of IL-15 **or** the IL-15 receptor (i.e., all inhibition of IL-15 α , CD122, or CD132). The patent also claims the use of any small molecule, antibody, peptide, or nucleic acid targeting IL-15 or the IL-15 receptor, among other inhibitors, for treating vitiligo. EX1001, claim 2; *see also id.*, 2:6-8. In other words, the claims encompass a vast genus of different types of inhibition in a vast genus of subjects. EX1002, ¶¶31-33; EX1004, ¶¶26-27, 30.

The claims are not restricted to using compounds that specifically or preferentially inhibit IL-15 signaling, or even to an IL-15 signaling-specific binding partners (e.g., IL-15/IL-15R α). EX1002, ¶¶29-33, 63, 68, 86-87; EX1004,

¶¶24, 43. Indeed, the only working example in the specification is limited to using a specific, Fc-diminished rat/mouse chimeric antibody called ChMBC7 to target mouse CD122 (IL-2R β /IL-15R β), one half of the mouse $\beta\gamma$ receptor complex that conveys both IL-2 and IL-15 signaling. The specification does not establish that ChMBC7 preferentially blocks IL-15 signaling (to the exclusion of, e.g., IL-2 signaling), and merely hypothesizes without any supporting evidence that blocking CD132 (the γ subunit common to IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 signaling), IL-15, or IL-15R α might work comparably to ChMBC7. EX1002, ¶¶37, 66, 69, 71-72, 76, 86. The claims are not restricted to inhibiting *trans*-presentation or *cis*-presentation of IL-15, or both, and the specification fails to explain whether inhibiting one or both of these pathways is necessary or sufficient to achieve the intended result. EX1002, ¶¶37, 72-77. Based only on its experiments using ChMBC7 to deplete the CD8⁺ T cells in a CD8⁺ T cell-induced lesion mice model, the '505 patent would preempt the use of a very broad genus of inhibition pathways to treat vitiligo in any subject, including humans. EX1002, ¶¶85; EX1004, ¶¶24-27, 42-45. The claims are thus overly broad at least with respect to (1) the inhibitory pathways; (2) the chemical structures used to inhibit those pathways; and (3) the subject receiving treatment. *See also* Sections I.A.i, iii above.

A. Inadequate Representation for the Broad Genus of Inhibition Pathways Claimed

As discussed above, the only inhibition pathway employed in the '505 patent specification to treat vitiligo is administering the Fc-diminished rat/mouse chimeric monoclonal antibody ChMBC7. Based on this single species of a particular kind of CD122 inhibition with a specific type of Fc-diminished antibody, the patent seeks to preempt all forms of inhibiting IL-15 signaling, including all CD122 inhibition pathways, all CD132 inhibition pathways, all IL-15R α inhibition pathways, and all pathways for inhibiting the IL-15 cytokine itself. But the '505 patent fails to demonstrate that the ChMBC7 CD122 inhibition pathway is representative of all other CD122 inhibition pathways (whether inhibiting *trans*-presentation, *cis*-presentation, or both, at low affinity and/or high affinity), much less that it is representative of all CD132 inhibition pathways, all IL-15R α inhibition pathways, and all IL-15 inhibition pathways. EX1002, ¶¶64-69; EX1014, Abstract, 6; EX1013, Abstract; EX1004, ¶¶43-45; EX1008, 786; *see also* Sections I.A.i, iii above.

The patent does not describe the sequence or structure that corresponds to this antibody code name, does not describe the epitope where this antibody binds CD122 or explain how it inhibits $\beta\gamma$ signaling (e.g., *cis*- and/or *trans*-presentation), and provides no evidence that this antibody specifically inhibits IL-15 signaling (e.g., as opposed to inhibiting IL-2 signaling) or that an Fc-intact

antibody would work similarly. EX1002, ¶¶37, 70. By claiming the enormously broad genus of treating vitiligo using any means of IL-15 or IL-15R inhibition, the '505 patent merely draws “a fence around the outer limits of a purported genus” of treating vitiligo by administering any inhibitor of either IL-15 or the IL-15 receptor. *See Ariad*, 598 F.3d at 1350. But this is not an adequate substitute for “showing that one has invented a genus and not just a species.” *Id.* at 1350. Accordingly, the broadly claimed methods of using various genera of inhibition pathways to treat vitiligo lack written description support.

i. Inadequate Representation for Inhibitors that Do Not Physically Interact with IL-15 or IL-15R

The claimed genus of inhibition is so broad that it is not even limited to administering molecules that act directly on IL-15 or IL-15R. EX1002, ¶¶68-69. This is demonstrated at least by dependent claim 2, which further recites that the inhibitor is “an inhibitory nucleic acid targeting IL-15 or the IL-15 receptor.” EX1001, claim 2; *see also id.*, 2:6-8. The '505 patent explains that “Inhibitory Nucleic Acids Targeting IL-15 or IL-15R” specifically bind, or are complementary to “mRNAs” that encode the “target,” rather than physically interacting with the IL-15 or IL-15R target itself. *See, e.g.*, EX1001, 8:23-29. Claim 1 thus encompasses the use of **anything** that inhibits IL-15 **or** IL-15R, whether or not the inhibitor physically interacts with IL-15/IL-15R or not.

The fact that the claims encompass indirect inhibition of IL-15/IL-15R confirms that the specification lacks written description support for the full scope of the claimed invention. As Dr. Abbas explains, the human immune system is very complicated, and inhibiting a pathway at a particular point in the pathway (e.g., rat/mouse chimeric ChMBC7 antibody inhibition of mouse CD122) cannot be assumed to be representative of what would happen when inhibiting the same pathway at a different point (e.g., using inhibitory nucleic acid to knock out CD122 expression). EX1002, ¶¶61-69. For example, a subject with a loss of function of the CD132 (γ subunit) (i.e., upstream inhibition) can experience severe immunodeficiency, but a more tailored result might be obtained when administering certain CD132 antibodies. EX1002, ¶69. Similarly, inhibition of CD122 expression using inhibitory nucleic acids could block expression of Treg cells that help to inhibit the autoimmune response that causes vitiligo and AA in a manner that administering ChMBC7 might not. EX1002, ¶69. As Dr. Abbas testifies, the sole inhibitory pathway explored in the specification (ChMBC7 antibody in mice) is not representative of inhibition using nucleic acids or any other means of inhibition that do not directly act on CD122 in the same manner as ChMBC7. EX1002, ¶¶66-68. For this additional reason, the broadly claimed methods of using various genera of inhibition pathways to treat vitiligo lack written description support.

ii. Inadequate Representation for CD122 Inhibition

Even if the claims were limited to using CD122 inhibition (though they are much broader than that), their breadth would still be far greater than any invention in the specification. EX1002, ¶¶70-81. As Dr. Abbas explains, there were multiple CD122 inhibitory pathways that potentially impact the expression, function, or interaction of CD122 such that using the single CD122 antibody was not representative of the broad genus of CD122 inhibition. To begin, the sole working example in the '505 patent used an Fc-diminished CD122 antibody that was not representative of any and all CD122 antibodies that are Fc-intact antibodies. EX1002, ¶¶70-72. Fc-intact antibodies may also inhibit CD122 signaling by marking CD122-expressing cells for immune response, potentially resulted in less targeted or even uncontrolled effects. The '505 patent provides no reason to conclude the ChMBC7 antibody was representative of the inhibitory effects of Fc-intact antibodies to CD122. EX1002, ¶78.

ChMBC7 also was not representative of blocking CD122 inhibition at least because CD122 plays a role in multiple cytokine-mediated signaling pathways. Not only is CD122 (and the CD122/CD132 complex) shared by IL-2 and IL-15, but it was known that CD122 inhibition implicates disparate biological effects *in vivo* depending on which combination of signaling pathways is blocked by the specific antibody and how they are blocked. EX1002, ¶73. For example, it was known that

IL-2 and IL-15 both stimulate T lymphocyte proliferation by binding to and inducing the signaling of the same CD122/CD132 ($\beta\gamma$ receptor) with intermediate affinity, with a cytokine-specific α receptor subunit increasing the affinity of each cytokine for the dimeric receptor. EX1012, 479 (“both IL-2 and IL-15 can induce proliferation of cells that express only an intermediate-affinity [$\beta\gamma$] receptor”); *see also* EX1015, 771, 774 (IL-15 and IL-2 both signal through $\beta\gamma$); EX1011, 1:19-2:12, 8:36-43 ($\beta\gamma$ receptor is intermediate affinity receptor for IL-2 and IL-15). Inhibiting CD122 (and thereby IL-15 signaling via CD122) thus could result in different biological effects depending on whether the pathway inhibited low-affinity binding or high-affinity binding or both and whether it did so only in relation to IL-15 or also in relation to IL-2. EX1002, ¶73.

For example, administration of a particular CD122 antibody to rhesus macaques was reported in 2016 to significantly reduce tissue effector memory T cell populations but not recirculating memory T cell populations. EX1013, Abstract. But the ’505 patent asserts that the persistence of depigmentation of vitiligo requires circulating memory T cells and that ChMBC7 inhibition depleted human melanocyte antigen pre-melanosome protein (PMEL) T cells (not just memory-phenotype). EX1001, 32:36-67, 33:24-30, 33:48-53, Figs. 6A-6D. Accordingly, inhibiting CD122 using ChMBC7 cannot be said to be representative of all CD122 inhibition pathways. EX1002, ¶67.

The '505 patent does not demonstrate that ChMBC7 is representative of all these CD122 inhibitory pathways, whether individually or in combination. EX1002, ¶72. Indeed, the '505 patent does not even disclose in which of these disparate inhibitory pathways ChMBC7 functions. Though the '505 patent assumes that the beneficial effect of ChMBC7 inhibition on vitiligo must result from inhibiting IL-15 signaling because IL-2/CD25 knockout mice develop autoimmunity (EX1001, 6:3-13), others in the field observed that both IL-2 and IL-15 can prevent FOXP3⁺ Treg cells from exerting their suppressive functions on effector T cells and that the mechanism underlying IL-15 in autoimmune disease was still poorly understood. EX1015, 774-76. In other words, ChMBC7's CD122 inhibition conceivably treats vitiligo through IL-2 inhibition rather than through IL-15 inhibition. EX1002, ¶72. Accordingly, inhibiting CD122 using ChMBC7 cannot be said to be representative of all IL-15 inhibition pathways. EX1002, ¶¶72-74.

In addition to failing to provide representation for all CD122 inhibitory pathways with respect to (1) intermediate and high affinity binding; and (2) selective or combination inhibition of IL-15 and IL-2 signaling, ChMBC7 inhibition is not representative with respect to (3) how the cytokine is presented to the $\beta\gamma$ receptor complex. For example, both IL-15 and IL-2 bind the $\beta\gamma$ receptor to cause signaling using both *trans*- (different cell) and *cis*- (same cell) presentation,

with the most common type of presentation differing between the two cytokines. See, e.g., EX1015, 771, 774; EX1012, Abstract. Waldman provides an example CD122 antibody (Hu-Mik β 1) that is said to efficiently block both IL-2 and IL-15 mediated proliferation relying on *trans* presentation to $\beta\gamma$ -expressing cells, but not to block cytokine-mediated proliferation of cells that express high affinity IL-2- or IL-15 specific heterotrimeric receptors for that cytokine in *cis* presentation. EX1012, 479, 481-82. Thus, the '505 patent provides no basis to conclude that ChMBC7 inhibition was representative of all forms of CD122 inhibition. EX1002, ¶74.

Other sources confirm that a single CD122 antibody is not representative of the broad genus of CD122 inhibition. For example, some CD122 antibodies inhibit IL-2-dependent proliferation on cells bearing the $\beta\gamma$ receptor but do not inhibit IL-2-dependent proliferation on cells bearing CD25 (IL-2R α) complexed with $\beta\gamma$ and do not inhibit *trans*-presentation of IL-15. EX1011, 2:35-48. Some CD122 antibodies inhibit binding IL-2 **and** IL-15 to a receptor comprising CD122 and CD132 ($\beta\gamma$). EX1011, 2:61-63. Other CD122 antibodies inhibit binding of IL-2 to a receptor comprising CD25/CD122/CD132. EX1011, 2:63-65. Other CD122 antibodies inhibit binding of IL-15 presented in *trans*-, bound to an IL-15R α , to the CD122/CD132 $\beta\gamma$ receptor (EX1011, 2:65-67), but might not effectively block IL-15 action on cells that express heterotrimeric IL-15 receptors in *cis*-presentation.

EX1012, 481-82. Other CD122 antibodies inhibit binding of IL-15 to a receptor comprising CD122, CD132, and IL-15R α . EX1011, 2:67-3:2. Still other CD122 antibodies might inhibit binding in any or all of these situations. EX1011, 3:2-5. Some CD122 antibodies might have the capacity to substantially inhibit receptors incorporating CD122 from binding to and signaling for cell proliferation in response to both IL-2 and IL-15. EX1011, 9:22-26. Some CD122 antibodies might inhibit binding of both the low and high affinity receptors incorporating CD122 to both IL-2 and IL-15 and might inhibit IL-15 binding both in *cis*- and in *trans*-presentations. EX1011, 9:27-29. In contrast, others, such as Mik- β 1 and Hu-Mik- β 1, which only weakly inhibit soluble IL-15-mediated proliferation of CD122 cells, demonstrated no detectable ability to inhibit IL-2-mediated proliferation of cells bearing the high affinity IL-2 receptor including CD122, and lacked substantial ability to inhibit IL-15 presented in *trans*. EX1011, 9:30-38. In view of the diversity of different forms of CD122 inhibition and the sparse direction and evidence provided in the '505 patent regarding ChMBC7 inhibition, a POSA would not conclude that ChMBC7 inhibition was representative of all CD122 inhibition, much less that it was representative of all IL-15 or IL-15R inhibition, absent evidence establishing as much. EX1002, ¶¶75-76; EX1004, ¶53.

Another reason that a POSA would not conclude that ChMBC7 inhibition is representative of all forms of CD122 inhibition is because the biological effect of a

given antibody further depends on the receptors expressed by the cells encountering the antibody. For example, a CD122 antibody might effectively inhibit IL-15 *trans*-presentation to cells expressing the $\beta\gamma$ complex but without substantially inhibiting cells (e.g., activated mature T lymphocytes and Treg cells) that highly express the high affinity IL-2 receptor CD25/CD122/CD132. *See* EX1011, 10:9-14; EX1014, 6. In contrast, in cells that primarily express the intermediate affinity receptor $\beta\gamma$ without a high affinity receptor α (e.g., inactivated effector T cells), it may be harder to inhibit *trans*-presentation of IL-15 than to inhibit soluble IL-2 or IL-15. EX1011, 10:14-17; EX1002, ¶¶76-77. As Dr. Abbas explains, the biological effects of the claimed inhibition will be different depending on which binding interactions are inhibited in which combinations (e.g., IL-2 *cis*-, IL-15 *cis*-, IL-15 *trans*-). EX1002, ¶77. Accordingly, inhibiting CD122 using the single antibody ChMBC7 is not representative of the biological effects of these other categories of CD122 inhibition because the effect of any particular CD122 inhibition depends on the particular combination of signaling pathways inhibited. EX1002, ¶¶70-81; *see also* Sections I.A.i, iii above.

iii. Inadequate Representation of CD132 Inhibition

The failure of the '505 patent to demonstrate that ChMBC7 inhibition is representative of the genus of CD122 inhibition is just the tip of the iceberg. The claims also encompass CD132 (γ chain) inhibition. This receptor subunit is shared

by at least six cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21). EX1015, 771; EX1030, Abstract. As Dr. Abbas explains, CD132 inhibition pathways thus implicated countless biological responses for which ChMBC7 inhibition was not representative. EX1002, ¶¶64-69. Indeed, some forms of CD132 depletion resulted in severe, combined immunodeficiency. EX1014, Abstract, 6; EX1002, ¶69. Accordingly, CD132 provides another example of why the ChMBC7 inhibition used in the '505 patent is not representative of the broad genus of inhibiting IL-15 or the IL-15 receptor. EX1002, ¶¶64-69; *see also* Sections I.A.i, iii above.

B. Inadequate Representation for the Use of the Broad Genus of Chemicals Claimed

In addition to failing to provide a representative disclosure for the various broad means of inhibition claimed for treating vitiligo, the specification also fails to provide a representative disclosure for the various broad genera of molecules to be used to achieve that inhibition. A sufficient description for a genus requires disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Ariad*, 598 F.3d at 1350. Though written description does not necessarily require a structure-by-structure recitation of every species within the entire genus, a specification that amounts to “no more than a ‘wish’ or ‘plan’ for obtaining the claimed [invention] rather than a description of the [invention] itself” fails to provide adequate written

description support. *Id.* at 1350; *see also id.* at 1353 (“patent is not a hunting license,” “research hypotheses do not qualify for patent protection”).

The specification describes using only a specific, Fc-diminished rat/mouse chimeric monoclonal mouse CD122 antibody called ChMBC7. The patent does not describe the structure of this antibody, does not describe where this antibody binds CD122, and does not explain what epitopes should be targeted by the antibody to achieve the desired treatment. As Dr. Abbas explains, ChMBC7 is not representative of all CD122 antibodies, much less all inhibitors of CD132, IL-15, or IL-15R α . EX1002, ¶¶61-81.

Claim 2 depends from claim 1 and further confirms the enormous and unsupported breadth of the claims with respect to multiple genera of molecules to be used. Claim 2 further recites that “the inhibitor is a small molecule inhibitor, an antibody, a peptide inhibitor, or an inhibitory nucleic acid targeting IL-15 or the IL-15 receptor.” EX1001, claim 2; *see also id.*, 2:6-8. As Dr. Abbas explains, because the claims contain no (claims 1, 3-5) or next to no structural requirements (claim 2), the number of candidate molecules at issue is simply incalculable. EX1002, ¶¶83-87. Because of the unpredictability in the field and its nascency, each candidate compounds would have to be individually made and tested in a particular subject to determine whether it had the desired properties. EX1002, ¶¶79-81, 83-87.

In view of the unbounded limits of compounds at issue, the '505 patent's sparse disclosure cannot be said to be representative of the entire genus. For example, the '505 patent does not identify the structure of even a single inhibitory nucleic acid targeting IL-15 or the IL-15 receptor. The sparse examples given for each category (none of which are used even prophetically in the '505 patent to perform the claimed method) are too few, and the guidance in the patent too sparse, to be representative of any of these broad genera. EX1002, ¶¶80-81. Moreover, none of the dependent claims meaningfully narrows the enormous scope of the inhibitors recited in claim 1 to even one of these overbroad genera.²

² Although claim 2 recites various sub-genera of inhibitors, the claim is satisfied by an inhibitor falling within any of these sub-genera (e.g., an inhibitory nucleic acid targeting IL-15 or the IL-15 receptor) and also does not require that the inhibitor physically interact with IL-15 or IL-15R themselves. Whatever structural requirements claim 2 recites (e.g., small molecule, nucleic acid) for the inhibitor are still incredibly broad and generic and provide no meaningful limitation to the scope of the genus. Claims 3-5 do not purport to add further limitations to the identity of the inhibitor, but merely recite known means of administering dermatological therapeutics. EX1004, ¶¶28-29.

Aside from the specific antibody (rat/mouse chimeric Fc-diminished ChMBC7) actually used in the '505 patent, the '505 patent provides nothing more than a wish for a particular result (e.g., IL-15 inhibition that treats vitiligo) and a research hypothesis that different compounds than the one used in the '505 patent might achieve that result. The '505 patent hypothesizes that inhibitors of IL-15 or the IL-15 receptor might be used to achieve that result. EX1001, 7:34-8:5. But the '505 patent again fails to explain why the Fc-diminished ChMBC7 antibody would be representative of these different molecules, and never explains whether and why the invoked molecules would be representative of all other compounds that can inhibit IL-15 or the IL-15 receptor. EX1002, ¶¶78. The specification certainly does not explain what structural features of small molecules, peptides, antibodies, or nucleic acids are necessary or sufficient to perform the claimed method. EX1002, ¶¶79-80. By claiming the enormously broad genus of treating vitiligo using an incalculable number of disparate compounds without disclosure of representative species for the full scope of the genus, the '505 patent merely draws “a fence around the outer limits of a purported genus” without showing that the applicant “invented the genus and not just a species.” *See Ariad*, 598 F.3d at 1350.

C. Inadequate Representation for the Broad Genus of Subjects Claimed

Based only on its mice experiments with ChMBC7 in treating lesions induced by transferring activated, melanocyte-targeting CD8⁺ effector T cells into

mice, the '505 patent would preempt the use of a very broad genus of inhibition to treat any type of vitiligo in any subject, including humans. The claims broadly recite administering the inhibitor to the “subject who has a vitiligo lesion” and do not restrict the claims to a mice model. EX1001, claim 1; *see also id.*, 4:44-52 & Figs. 9A-9E (discussing clinical setup for a human “subject”), 29:48-64 (discussing skin biopsies obtained from human patient study “subjects”); EX1004, ¶¶26-27, 35; EX1002, ¶¶31-33, 62. But the specification only discloses administering the ChMBC7 mouse CD122 antibody to mice having lesions induced solely by transference of activated, melanocyte-targeting CD8⁺ effector T cells. *See, e.g.*, EX1001, 29:13-40, 33:1-34:45; EX1004, ¶¶24; EX1002, ¶¶35, 62. As Drs. Abbas and Plott explain, lesions induced in mice by transference of activated, melanocyte-targeting CD8⁺ effector T cells are not representative of natural or spontaneous vitiligo, the biological causes of which are more complicated than orchestrated transference of a monolithic, cell population primed to attack melanocytes. EX1002, ¶¶36, 61-63; EX1004, ¶¶39-43.

As Drs. Abbas and Plott also explain, cytokine blocking experiments in mice are not representative of the effects of cytokine blocking in humans because the immune systems of these different species are not identical. EX1002, ¶¶63, 83-85 ; EX1004, ¶¶36, 47-49, 52. Indeed, CD122 antibodies may specifically bind CD122 of one animal species (e.g., cynomolgus CD122) and lack significant binding for

other species (e.g., mouse and dog CD122). *See, e.g.*, EX1011, 9:14-20. The only way to determine whether a hypothesis based on mouse studies is valid in humans is by trial and error. EX1002, ¶¶64, 85, 89-92; EX1004, ¶¶43-45, 49-51.

Accordingly, the breadth of the claimed subject provides another reason that the claims lack written description support.

D. Additional Factors Confirm No Written Description Support

In addition to the incredibly great discrepancy between the scope of what is claimed and the scope of what was actually provided in the specification, additional factors support concluding the claims lack written description. In evaluating written description support, the number of species that must be disclosed to demonstrate possession of a genus in a claim depends on (1) the maturity of the science or technology; (2) the existing knowledge in the particular field; (3) the predictability of the aspect at issue; and (4) the extent and content of the prior art. *See Ariad*, 598 F.3d at 1351.

Regarding the first factor, the science or technology at issue, inhibiting IL-15 signaling to treat autoimmune diseases such as vitiligo, was nascent, not mature. As Dr. Plott explains, the mouse models being used for modeling treatment of vitiligo by inhibiting signaling of CD122 was a long way from actually treating vitiligo and this entire field was still at its beginning in 2017. EX1004, ¶¶36, 47-48. As Dr. Abbas explains, even lab study of inhibition of IL-15 and the IL-15

receptor for treatment of vitiligo was at its early stages. EX1002, ¶¶80-81. As Jabri reflects, the mechanism underlying IL-15 in autoimmune disease was still poorly understood. EX1015, 775; *see also* Sections I.A.i, iii above. Because the field of treating vitiligo with an inhibitor of IL-15 or the IL-15 receptor was at its very beginning, there certainly was no consensus that there was a class wide property of IL-15 and IL-15 receptor inhibitors for treating vitiligo. EX1002, ¶¶80-81; EX1004, ¶¶48-49. Accordingly, this factor supports the conclusion that specification fails to provide written description support for the invention recited by the claims.

The second and third factors similarly supports the conclusion that the specification fails to provide written description support for the invention recited by the claims. As Dr. Abbas explains, and as explained in Section VI.A above, the knowledge of the field was such that POSAs knew that disparate means of IL-15 or IL-15R could provide very disparate results depending on which ligand or subunit was targeted, where it was targeted, and how it was targeted. EX1002, ¶81; *see also* Sections I.A.i, iii above. Despite knowing that the differences in the means of inhibition and the structure used to inhibit IL-15 or the IL-15 receptor mattered a lot, a POSA could not predict which structures and which modifications would have what impacts. EX1002, ¶81. Indeed, the mechanism underlying IL-15 in autoimmune disease was still poorly understood. EX1015, 775. The

unpredictability of the varied, sometimes overlapping, and sometimes contradictory effects of the signaling pathways sharing the IL-15 receptor subunits made it impossible to extrapolate the entire claimed genus based on the limited ChMBC7 antibody experiment in the '505 patent. EX1002, ¶81. As explained in Section I.C above, the applicant obtained allowance of the '505 patent claims despite a teaching in the '562 publication that an antibody blocking binding of the IL-15/IL-15R α to the $\beta\gamma$ complex would deplete effector and memory T cells and thereby treat autoimmune diseases, including vitiligo, by blocking IL-15 signaling. As PO only obtained allowance of the claims over the prior art by arguing that the '562 publication failed to provide data to support its teachings, PO cannot now argue that the state of the art was sufficiently predictable to extrapolate the entire genus of IL-15 and IL-15 receptor inhibition from ChMBC7 inhibition.

Accordingly, both the existing knowledge in the particular field and the lack of predictability of the aspects at issue supports the conclusion that the specification failed to provide written description support for the invention recited by the claims.

Finally, the extent and content of the prior art reveals that the inventors were not the first to use a mouse CD122 antibody to deplete CD8⁺ effector T cell in the skin to treat autoimmune disease patches in mice. As explained in Section VIII below, before the critical date, Xing used a different mouse CD122 antibody (TM- β 1) for this purpose in the related autoimmune disease AA. EX1002, ¶¶99-101;

EX1004, ¶¶50, 60. The applicant's inventive contribution thus cannot be use of a genus of IL-15 or IL-15R inhibitors, but, at most, the use of the specific rat/mouse chimeric Fc-diminished ChMBC7 monoclonal antibody employed in the '505 patent for lesions in the CD8⁺ T cell driven mouse model. To the extent the disclosures of the '562 publication in view of the knowledge of a POSA at the critical data, alone or combination with Harris and Xing, are insufficient to render the claims obvious, the disclosures of the '505 patent specification are certainly inadequate to demonstrate invention of the entire genus of using any IL-15 inhibitor or any IL-15R inhibitor in any subject. *See Research Corp. Techs. v. Microsoft Corp.*, 627 F.3d 859, 870 (Fed. Cir. 2010) (written description is a more exacting standard compared to obviousness).

The failure of the specification to provide adequate written description support for the claims is not a close question. In *Ariad*, the Court reversed a jury verdict of adequate written description where the specification failed to “adequately describe the claimed methods for reducing NF-κB activity, including adequate description of the molecules that Ariad admits are necessary to perform the methods.” 598 F.3d at 1355. Though the specification identified “three classes of molecules [specific inhibitors, dominantly interfering molecules, and decoy molecules] potentially capable of reducing NF-κB activity,” “hypothesized” that they were potentially capable of reducing NF-κB activity, and even provided

“example structures” for one of these classes (decoys), this did not demonstrate that the specification described using those molecules to reduce NF-κB activity. *Id.* at 1355-57. The patent’s bare assertion that NF-κB “‘would bind the decoy’ and thereby ‘negative regulation can be affected’” failed to provide a “descriptive link” between the table of specific decoy molecules and reducing NF-κB activity, as a matter of law. *Id.* at 1357. The court concluded that “the vast scope of these generic claims” could not be supported by disclosure of a single embodiment. *Id.* at 1358 (citing *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) (holding that “[a]fter reading the patent, a person of skill in the art would not understand” the patentee to have invented a generic method where the patent only disclosed one embodiment of it); *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345-46 (Fed. Cir. 2000) (noting that the “scope of the right to exclude” must not “overreach the scope of the inventor's contribution to the field of art as described in the patent specification”); *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993) (“Claiming all DNA[s] that achieve a result without defining what means will do so is not in compliance with the description requirement; it is an attempt to preempt the future before it has arrived.”)).

Here, the only subject matter actually described in the specification as treating depigmentation lesions is the rat/mouse chimeric Fc-diminished ChMBC7 species of mouse CD122 antibody in the CD8⁺ T cell-induced mouse model. The

specification's hypotheses that different CD122 antibodies, IL-15R α antibodies, IL-15R γ antibodies, some small molecule inhibitors, some peptide inhibitor, some unidentified inhibitory nucleic acids, or some unidentified IL-15 inhibitors "could be used" to treat vitiligo in this and other subjects fail to demonstrate the inventors actually invented the claimed methods using any of these things. At most, the specification provides a "wish" for a desired result and a "research plan" that some future inventor could pursue. This is not enough to satisfy the written description requirement of §112.

Although the '505 patent repeats prior art teachings about how IL-15/IL-15R inhibition could treat vitiligo by depleting CD8⁺ cytotoxic circulating and tissue-resident T cells, it never explains how the sole antibody used in its only working example interacted with CD122 to treat vitiligo in a manner that would permit a POSA to know which inhibitors would or would not treat vitiligo. For example, the '505 patent does not disclose the antibody's structure, the epitope it binds, how that binding modulates CD122, and how that inhibitor modulates additional immune system signaling pathways (e.g., IL-2). Like prior cases where courts have found a specification inadequate to support a broad, functional claim, the '505 patent's scant details are simply insufficient to justify the great breadth of the many, disparate methods encompassed by the claims. *See, e.g., Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330 (Fed. Cir. 2021) (reversing jury verdict finding

written description where claim was so broad as to encompass any scFv for binding any target, provided scant details about which scFv can bind to which target antigens, provided only two example, one for each of two targets, provided no detail about them beyond their designation code, and provided insufficient detail to permit a POSA to determine how or whether they are representative of the entire genus), *cert. denied*, 143 S. Ct. 402 (2022); *Idenix Pharms. LLC v. Gilead Sciences Inc.*, 941 F.3d 1149 (Fed. Cir. 2019) (claims invalid for lack of written description as a matter of law because the specification failed to provide sufficient blaze marks to direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV and provided no indication that any nucleosides outside those disclosed in its 18 formulas would be effective to treat HCV, much less an indication as to which of those undisclosed nucleosides would be effective); *Abbvie Deutschland GMBH v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014) (patent specification disclosing amino acid sequences of 300 antibodies having a range of IL-12 binding affinities was still insufficient to claim entire genus of fully human antibodies that bind and neutralize human IL-12). Accordingly, each of claims 1-5 should be found to lack written description support in the specification and cancelled.

E. Inadequate Representation for the Dependent Claims

The remaining dependent claims (3-5) lack written description support for the same reasons discussed above for claims 1-2.

Claim 3 recites the inhibitor is administered to the lesion. Claim 5 depends from claim 3 and further recites the inhibitor is administered to the epidermis within the lesion by subcutaneous or intradermal administration, or a microneedle array. But the '505 patent's sole working example using the Fc-diminished mice/rat chimeric mouse CD122 antibody ChMBC7 only administered it by i.p. and intradermal injection. *See, e.g.*, EX1001, 29:13-40, 33:1-34:45. The patent thus provides no data for administering the antibody to the epidermis within the lesion topically, by subcutaneous injection, or by microneedle array. EX1002, ¶82; EX1004, ¶54. Accordingly, dependent claim 5 lacks written description for this additional reason.

VII. [GROUND 2] CLAIMS 1-5 LACK ENABLEMENT

Claims 1-5 of the '505 patent must be cancelled because the specification does not “contain a written description of...the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.” 35 U.S.C. §112(a); *see also* 35 U.S.C. §§321(b) (PGR grounds for cancellation), 282(b)(3)(A) (invalidity for §112).

The specification must enable the full scope of the invention without undue experimentation. *Wyeth and Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). This is true even for method claims that are directed to a new use of an existing class of compounds. *Id.* at 1385. A claim is not enabled where the specification discloses only a starting point for further iterative research in an unpredictable and poorly understood field. *Id.* at 1386; *Enzo Life Sciences v. Roche Molecular Sys.*, 928 F.3d 1340, 1345-46 (Fed. Cir. 2019) (where claims require both a particular structure and functionality, no enablement where specification fails to teach POSA which of the many embodiments of the broad claims would exhibit that required functionality of being both hybridizable and detectable upon hybridization); *see also Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1086-87 (Fed. Cir. 2021) (even where claims include structural requirements, enablement of claims with functional requirements can be particularly focused on the breadth of those functional requirements, especially where predictability and guidance fall short), *cert. granted limited to Question 2 of the petition*, 148 S. Ct. 399 (Nov. 4, 2022). As discussed above, the '505 patent merely discloses ChMBC7 antibody inhibition of CD122 to treat a CD8⁺ T cell induced vitiligo lesions in a mouse model, but does not disclose how to make and use the full scope of IL-15/ IL-15 receptor (IL-15R α , CD122, or CD132) inhibition to treat vitiligo,

especially not across the genus of subjects claimed. Accordingly, the claims are not enabled.

In *Wyeth*, the method claims to treating restenosis (narrowing of an artery) by administering an effective amount of rapamycin (a class of compounds having a shared structure) lacked enablement support in the specification as a matter of law where the specification disclosed using only a single rapamycin species, called sirolimus. 720 F.3d at 1382, 1384. The unpredictability of the chemical arts, the complexity of the invention, and the limited knowledge of treatment of restenosis using rapamycin at the time of the invention support a finding of no enablement. *Id.* The claimed scope was broad because it encompassed using not only the known compounds but any other compounds that met the claims' structural requirements and satisfied the functional requirements of having immune-suppressive and antirestenotic effects. *Id.* at 1385. The specification was not enabling because it was silent about how to structurally modify sirolimus, let alone in a way that would preserve the recited utility. *Id.*

Though the specification described assays that could be used to ascertain whether a rapamycin compound exhibited the recited functional effects, and though subsequent testing performed during litigation showed that four compounds known at the priority date to have the same macrocyclic ring as sirolimus also had immunosuppressive and antirestenotic effects, the limited guidance in the

specification was still too narrow to enable the broad claims as a matter of law. *Id.* at 1385. The amount of experimentation required to practice the full scope of the claims was significant, as it would require synthesizing and screening each of at least tens of thousands of compounds satisfying the structural requirements of the claims to see if they had immunosuppressive and antirestenotic effects because, “until you test [the compounds], you really can’t tell whether they work or not.” *Id.* The iterative, trial-and-error process provided by the specification thus merely provided a starting point for further research but did not enable the full scope of the genus without undue experimentation. *Id.* at 1386.

The same analysis applies here. The chemical arts are unpredictable, treating autoimmune diseases such as vitiligo (especially in any subject, whether mouse or human) using cytokine signaling inhibitors is a very complex invention, and the limited knowledge at the time of the invention about using cytokine signaling inhibition to treatment vitiligo in the genus of subjects claimed supports a finding of no enablement. *Wyeth*, 720 F.3d at 1384; EX1002, ¶¶79-84, 90; *see also id.*, ¶¶46-48, 54-57, 61-63, 64-65, 67, 72-74, 75-81; EX1004, ¶¶36, 55-61; *see also id.*, ¶¶48-50.

Indeed, the claimed scope is even broader than in *Wyeth* because here there are no structural requirements in most claims (only minimal structural requirements in claim 2), and the claims encompass treating vitiligo across the

broad genus of claimed subjects using any known and an incalculable number of unknown compounds that satisfy the functional requirements of inhibiting IL-15 or IL-15R. *See Wyeth*, 720 F.3d at 1385. The specification is not enabling because it fails to demonstrate which targets are necessary or sufficient to achieve the desired effect, let alone essential structural requirements for achieving that effect. *See id.* The amount of experimentation required to practice the full scope of the claims is significant, as it would require synthesizing and screening an incalculable number of compounds (because the claims have no structural requirements) to see if they had the IL-15/IL-15R inhibitory and desired therapeutic vitiligo effects and, “until you test [the compounds], you really can’t tell whether they work or not.” *Id.*; EX1002, ¶¶33, 63-64, 85, 89-92; EX1004, ¶¶36, 59; *see also id.*, ¶¶43-45, 48-49. The iterative, trial-and-error process provided by the specification thus merely provides a starting point for further research but does not enable the full scope of the genus without undue experimentation. *Wyeth*, 720 F.3d at 1386. Accordingly, the claims should be cancelled.

The discussion that follows analyzes enablement by reviewing individual factors the Federal Circuit has said may be relevant to determining enablement of a claim. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999) (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)); *id.* at 1367-68, 1374-75 (no enablement where patent broadly claimed “fundamental aspects of genetic

antisense technology,” but the specification only provides working examples of the application of the technology to three genes of the prokaryote *E. coli* and none in eukaryotes).

A. The Complex Nature of the Invention and Nascent State of the Art Favor a Finding of No Enablement

The claims recite a method of treating a subject who has a vitiligo lesion, the method comprising identifying a subject in need of treatment and administering to the subject a therapeutically effective amount of any inhibitor of IL-15 or IL-15 receptor. The nature of the claims and the nascent state of the art (*Wands* factors 4 and 5) weigh against finding enablement. *Wands*, 858 F.2d at 737. The claims involve a complex invention of treating the autoimmune disease vitiligo across a broad genus of subjects (ranging from, e.g., mouse models to actual disease in humans) using inhibitors of complex and biologically unpredictable cytokine signaling pathways. EX1002, ¶84; EX1004, ¶59; *see also* Sections I.A.i, iii above. There was limited knowledge about using cytokine signaling inhibition to treat vitiligo outside the context of mouse models in which vitiligo-like lesions were induced by priming CD8⁺ effector T cells to attack melanocytes and implanting them into the mouse. EX1002, ¶¶83-85; EX1004, ¶¶36, 47-49, 55-57. Though inhibiting IL-15-induced signaling by blocking binding of IL-15 to the βγ receptor had been proposed as a treatment for autoimmune diseases including vitiligo almost a decade before the critical date, PO obtained allowance of the claims by

arguing that the nascent state of the art at critical date made the claimed invention non-obvious absent prior art evidence of efficacy. EX1010, 38 (discussing EX1009). Though the prior art provided reason and reasonable expectation of success for an embodiment within the scope of the claims (*see* Section VIII below), the state of the art was so nascent that the Examiner did not evaluate the prior art Xing reference disclosing this evidence.

Further compounding the complex nature of the claimed invention, the claims recite a broad genus of treatment methods that are defined only functionally. EX1002, ¶¶33, 85-87, 93; EX1004, ¶¶36, 57. Claim 1 recites no structural requirements for the inhibitor whatsoever. Claim 2 recites the use of any of several broad classes of inhibitors (small molecule, antibody, peptide, nucleic acid) but provides no structural limitations beyond these broad classes as a whole.

For the forgoing reasons, the complex nature of the invention and the nascent state of the art strongly favor a finding of no enablement.

B. Breadth of the Claims Indicate the Claims Are Not Enabled

The extremely large breadth (*Wands* factor 8) of the purely functional claims also strongly favors a finding of no enablement. weigh against finding enablement. *Wands*, 858 F.2d at 737. The claims are extremely broad at least with respect to the (1) multiple genera of inhibitory pathways; (2) multiple genera of structures used for each those inhibitory pathways; and (3) the broad and disparate genus of

subjects implicated. EX1002, ¶¶33, 85-87, 93; *see also id.*, ¶¶61-63, 64-69, 70-81; EX1004, ¶¶35-36, 57; *see also id.*, ¶¶42-44.

In addition to claiming the use of any inhibitor of IL-15, the claims also encompass inhibition of the IL-15 receptor, including inhibition of any of the IL-15R α , CD122, or CD132 subunits. As discussed at length above, each of these four sub-genera of inhibition is itself very broad, and inhibiting one subunit in a particular manner is not representative of the effects of inhibiting the other subunits or of inhibiting the same subunit in a different manner. For example, the CD122 (β) receptor subunit is shared by both receptors of the IL-15 and the IL-2 cytokines. Depending on how one inhibits CD122, they might preclude all CD122 signaling, preclude CD122 signaling by preventing it from associating with CD132, only preclude signaling induced by IL-2, only preclude signaling induced by IL-15, preclude all signaling induced by both IL-2 or IL-15, or preclude only some signaling from one or both of IL-2 and IL-15. EX1002, ¶86. These different types of inhibition will have their own set of biological consequences. EX1002, ¶86. The diverse categories of inhibition encompassed by the claims are only increased by their inclusion of inhibitors of the CD132 (γ) receptor subunit, which is shared by at least six different cytokines. As still another example, the claims encompass using Fc-intact antibodies to target IL-15 or the IL-15 receptor for destruction as well as using Fc-diminished antibodies to block certain binding

interactions. Because they encompass many disparate and broad genera of inhibition without any operative structural limitations, the claims essentially recite a desired result (treating a subject who has vitiligo by administering an inhibitor of IL-15 or the IL-15 receptor) without specifying how to do it. EX1002, ¶¶33, 85-87, 93; *see also id.*, ¶¶61-63, 64-69, 70-81; Sections I.A.i, iii above.

Moreover, the claims also do not require that the inhibitor specifically, preferentially, primarily, or exclusively inhibit IL-15 or the IL-15 receptor. Accordingly, the claims encompass the use of a vast number of diverse inhibitory pathways to treat a subject who has vitiligo when IL-15/IL-15R inhibition may play only a very minor role (or even no role) in achieving the therapeutic effect. *See, e.g.*, EX1002, ¶¶37, 70-77, in particular at 72. Indeed, dependent claim 2 confirms that claim 1 does not even require that the inhibitor physically interact with IL-15 or any subunit of the IL-15 receptor. Instead, the claims are satisfied by upstream inhibition, such as nucleotide inhibitors that result in downregulating IL-15, IL-15R α , CD122, or CD132 by interacting with upstream genetic code. EX1002, ¶87. Accordingly, the scope of the claims is not even limited by the structures of the four targets of inhibition.

The claimed scope also is very broad because it encompasses using not only the few known compounds that are invoked (but never administered) in the specification, but also any other compounds that meet the claims' functional

requirements. As discussed above the claims are essentially devoid of any structural requirements. *See, e.g.*, EX1002, ¶¶31-33. Though claim 2 recites broad genera with limited functional requirements (small molecule, antibody, peptide, nucleic acid), claim 2 is not limited to any one of these genera and each genus is itself incredibly broad. The breadth of each subgenus is exacerbated by the fact that the claims do not require the inhibitor to directly, physically, or specifically inhibit IL-15 or the IL-15 receptor. The scope of compounds at issue is thus unbounded by the structures of these targets. Indeed, the number of potential compounds is so large that it is truly incalculable. EX1002, ¶87.

The claimed scope also is very broad because it encompasses administration to any subject, ranging from an orchestrated mouse model as used in the patent to natural or spontaneous vitiligo having a much more complicated etiology. EX1004, ¶¶35-36, 57; *see also id.*, ¶¶42-44. The claims broadly recite administering the inhibitor to the “subject who has a vitiligo lesion” and do not restrict the claims to a mice model. EX1001, claim 1; *see also id.*, 4:44-52 & Figs. 9A-9E (discussing clinical setup for a human “subject”), 29:48-64 (discussing skin biopsies obtained from human patient study “subjects”). But the specification only discloses administering the mouse CD122 antibody called ChMBC7 to mice having lesions induced solely by transference of activated, melanocyte-targeting CD8⁺ effector T cells. *See, e.g.*, EX1001, 29:13-40, 33:1-34:45. As Drs. Abbas and Plott explain,

lesions induced in mice by transference of activated, melanocyte-targeting CD8⁺ effector T cells are not representative of natural or spontaneous vitiligo, the biological causes of which are more complicated than orchestrated transference of a monolithic, cell population primed to attack melanocytes. EX1002, ¶¶85-87; EX1004, ¶¶58-59.

As Drs. Abbas and Plott also explain, cytokine blocking experiments in mice are not representative of the effects of cytokine blocking in humans because the immune systems of these different species are not identical. EX1002, ¶¶63, 83-85 ; EX1004, ¶¶36, 47-49. Indeed, CD122 antibodies may specifically bind CD122 of one animal species (e.g., cynomolgus CD122) and lack significant binding for CD122 of other species (e.g., mouse and dog CD122). *See, e.g.*, EX1011, 9:14-20. The only way to determine whether a hypothesis based on mouse studies is valid in humans is by trial and error. EX1002, ¶¶64, 85, 89-92; EX1004, ¶¶43-45, 49-51, 59. Accordingly, the breadth of the claimed subject provides another reason that the claims lack enablement support.

For the forgoing reasons, the extremely great breadth of these functionally-defined genus claims strongly indicate the claims are not enabled.

C. The Sparse Guidance (Factor 2) and Single Sole Working Example (Factor 3) in the Specification Demonstrate the Claims Are Not Enabled

The sparse guidance and isolated working example (*Wands* factors 2 and 3) in the specification weigh against finding enablement. *Wands*, 858 F.2d at 737.

The '505 patent provides only a single example of treating vitiligo-like lesions induced in mice by priming CD8⁺ effector T cells to attack melanocytes and implanting them into the mouse. EX1002, ¶¶35, 62; EX1004, ¶¶24-25, 33-34.

There is no evidence that this data is representative of results in natural or spontaneous vitiligo lesions or of results in animal species different than mice (e.g., humans). EX1002, ¶¶36, 88; *see also id.*, ¶¶61-63; EX1004, ¶¶36, 39, 42-44, 57, 60.

Moreover, the sole inhibition example in the specification is using ChMBC7 antibody inhibition of CD122. But the specification does not disclose the sequence or structure the corresponds to the code name ChMBC7, or even the species of CD122 inhibition performed by ChMBC7. It is merely identified by a code name. EX1002, ¶89. As discussed above in Sections I.A.i, iii and VII.B, CD122 inhibition can inhibit various types of IL-2 signaling, of IL-15 signaling, or both, with varying biological consequences. But the specification does not disclose what species or combination of species of CD122 inhibition were employed to achieve the reported effects. The '505 patent assumes that ChMBC7 inhibits IL-15 binding

but provides no evidence to support this assumption. The specification certainly does not demonstrate that ChMBC7 is not also inhibiting IL-2 binding. EX1002, ¶¶37, 72. The specification fails to explain why ChMBC7 binding of CD122 would be representative of CD122 antibodies that may interact with CD122 differently (e.g., blocking IL-15 only, blocking IL-2 only, blocking both IL-15 and IL-2 in varying degrees, inducing immune responses with intact-Fc). EX1002, ¶¶64-81, in particular at ¶72.

The specification hypothesizes that any inhibitor of IL-15, IL-15R α , CD122, or CD132 may be used to treat a subject who has vitiligo but never accounts for the differences in specificity and functionality of the disparate signaling pathways discussed above. It fails to explain why ChMBC7 binding of CD122 would be representative of CD132 antibodies, IL-15 antibodies, IL-15R α antibodies, or non-antibody physical inhibitors of all of the above. The specification also fails to explain why ChMBC7 binding of CD122 would be representative of inhibitors that do not physically interact with any of IL-15 or its receptor subunits. EX1002, ¶¶64-81, 91. The specification merely raises the research question of whether any claimed form of inhibition other than ChMBC7 could treat vitiligo. The sparse guidance and sole working example are simply too narrow in comparison to the broad scope of the claimed invention to enable the claim without undue experimentation. *See, e.g., ALZA Corp. v. AndrX Pharms., LLC*, 603 F.3d 935, 941

(Fed. Cir. 2010) (claims not enabled where 10 lines of specification mentioning non-osmotics and referring to textbook discussing how to make and use various types of non-osmotic sustained release dosage forms provided only a starting point further research through an iterative trial and error process).

D. Quantity of Experimentation Necessary and Unpredictability of the Art

The quantity of experimentation required and the unpredictability of the art (*Wands* factors 1 and 7) weigh strongly against enablement. *Wands*, 858 F.2d at 737. Because the specification provides no evidence as to what combination of characteristics of ChMBC7 inhibition made it useful for treating CD8⁺ T cell-induced depigmentation lesions in mice, the only way to determine whether other forms of inhibition claimed by the '505 patent would achieve the desired result even in the mouse would be to individually test them. As Dr. Abbas explains, even very small changes to the structure of a compound (e.g., small molecule or antibody) can have very large and disparate effects on biological function. EX1002, ¶¶79-81, 90. Each new candidate compound thus would have to be synthesized and screened through an iterative, trial-and-error process to determine whether they work or not. EX1002, ¶¶90-92. Even testing the candidate compounds identified in the specification would take months, which is itself enough to demonstrate undue experimentation. EX1002, ¶91. *Idenix Pharms. LLC v. Gilead Sciences Inc.*, 941 F.3d 1149 (Fed. Cir. 2019).

Because the claims provide no (claims 1 and 3-5) or next to no (claim 2) structural limitations, and even encompass compounds that do not specifically or physically interact with the targets, the number of compounds implicated by the claims is so large that it is truly incalculable. EX1002, ¶¶83-87. The '505 patent's hypothesis that a few identified compounds may work similarly to ChMBC7 does not meaningfully narrow the scope of compounds at issue. EX1002, ¶91.

Identifying a representative number of inhibitors even in each broad category claimed would itself be a sizeable, expensive, and unpredictable research project taking weeks, to months, or even years in view of the limited guidance provided by the '505 patent specification. EX1002, ¶91. Identifying a representative number of inhibitors across the full scope of the claims would likely occupy the efforts of multiple labs for years. *Id.*

Even if the specification had identified the forms of inhibition that achieve the claimed effects and the representative compounds for accomplishing those forms of inhibition (it did not), it would still require undue experimentation to practice the claims across the full scope of subjects. As discussed above, the claims are not limited to a mouse subject having lesions induced by activated CD8⁺ T cell transference, but also include natural and spontaneous vitiligo in mouse species as well as in different species, including humans. As Drs. Abbas and Plott testify, the mouse model for vitiligo is not representative of treating natural vitiligo, as the

biological mechanisms naturally causing such autoimmune diseases are much more complex than the mouse model lesions. EX1002, ¶¶92; EX1004, ¶¶42-43, 60. As Drs. Abbas and Plott further confirm, a POSA would not view the mouse model experiments in the '505 patent as representative of treating vitiligo in a human subject. EX1002, ¶¶85, 91-92; EX1004, ¶¶36, 60-61.

In view of the forgoing, the unpredictability in the field and extent of experimentation necessary to enable the full scope of the claimed invention strongly indicate the claims are not enabled.

E. Relative Skill of those in the Art

The relative skill of those in the art (*Wands* factor 6) is neutral in this case. *Wands*, 858 F.2d at 737. Though a POSA would have had a high level of education and experience (See Section I.D above), this knowledge, training, and experience would not provide the guidance necessary to overcome the lack of guidance in the specification, the complexity of the invention, the nascency of the field, and the unpredictability of the art and enable them to make a use the extremely broad and functionally defined genus claims. EX1002, ¶¶93; EX1004, ¶¶60-61. Accordingly, this factor is neutral.

As the factor-by-factor analysis confirms, claims 1-5 should be cancelled for lack of enablement.

VIII. [GROUND 3] CLAIMS 1-5 ARE OBVIOUS OVER XING AND HARRIS

A. Brief Summary

The present ground demonstrates that an embodiment squarely encompassed by the claims of the '505 patent would have been obvious to a POSA before the critical date. Obviousness of even a single embodiment encompassed by a claim renders the entire claim invalid. *See, e.g., Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1300 (Fed. Cir. 2007). As discussed in detail above, the only working example in the '505 patent is administering a mouse CD122 antibody that reduced CD8⁺ T cells to a mouse model in which depigmentation lesions had been induced by transferring activated, melanocyte-antigen-recognizing CD8⁺ T cells into the mice. In view of the plain language of the claims and of the specification, this embodiment falls within the broad scope of the claims. But treating depigmentation lesions whose existence in the mouse model depended on CD8⁺ T cells, by reducing those CD8⁺ T cells, is found in the prior art at the time and would have been readily apparent to a POSA and obvious. As such, the challenged claims are rendered obvious by an obvious embodiment encompassed by the claims and equivalent to the only working example in the patent.

As explained in detail below, each of claims 1-5 of the '505 patent is obvious as a whole in view of Xing and Harris. EX1002, ¶94. Xing showed that

systemic administration to mice of a species of mouse CD122 antibody depleted their CD8⁺ cytotoxic T cells and prevented the development of autoimmune skin lesions (specifically alopecia areata) that otherwise arose spontaneously in these mice. Xing also showed that topical administration of a downstream inhibitor of CD122/CD132 signaling (JAK inhibitors) reversed existing skin lesions and that this effect persisted for 2-3 months after cessation of treatment (i.e., at least as long as the 8 weeks monitored in the challenged patent). EX1002, ¶¶98, 101-02. Harris describes a simplified mouse model for vitiligo lesions, in which the depigmentation lesions are induced by introducing CD8⁺ cytotoxic T cells and are straightforwardly reversed by depleting those same CD8⁺ cytotoxic T cells. EX1002, ¶¶95-97. Because of the nature of the lesions involved in the mouse model (for which CD8⁺ cytotoxic T cells were both necessary and sufficient for lesion existence), a POSA had good reason and a reasonable expectation of success for administering a therapeutically effective amount of Xing's mouse CD122 antibody (e.g., topically) to the epidermis of the lesions of the mice in Harris to deplete the CD8⁺ cytotoxic T cells that were causing the vitiligo lesions, and thereby treat the lesions. EX1002, ¶¶99, 103-06; EX1004, ¶¶33-36.

B. Detailed Analysis of the Obviousness of the Claims

Harris describes a “mouse model of vitiligo using adoptive transfer of autoreactive melanocyte-specific CD8⁺ T cells.” EX1006, 1869. This is the same

mouse model used in the only working example in the '505 patent. *See, e.g.*, Section I.B above. In Harris's mouse model, vitiligo lesions appear 4-5 weeks after the cells are transferred. EX1006, 1870. As Harris explains, "the extent of depigmentation at four easily visible locations, including the ears, nose, rear footpads, and tail" is easily determined and scored. EX1006, 1870. The '505 patent describes using the same mouse model of vitiligo as Harris, including the same depigmentation scoring. EX1001, 28:55-57 ("Vitiligo was induced as previously described (Harris et al., 2012)."), 28:66-29:3 ("Vitiligo score was objectively quantified ..., using a point scale based on the extent of depigmentation at four easily visible locations, including the ears, nose, rear footpads, and tails as described previously (Harris et al., 2012)."); EX1002, ¶¶95, 107.

Harris discloses that autoreactive CD8⁺ T cells accumulate in the lesions. EX1006, 1872-1873; *see also* EX1001, 31:23-27 ("Previous studies using this model revealed that adoptively transferred, autoreactive T cells accumulate within the epidermis of the skin during the progression of vitiligo ...") (citing EX1006; EX1020; EX1027). Harris discloses that administration of neutralizing antibody to IFN- γ results in depletion of autoreactive Trm CD8⁺ T cells in the skin and prevents depigmentation. EX1006, 1872-1874, Figure 5. Based on these data, Harris suggests "prevent[ing] CD8⁺ T cell accumulation in the skin" has "therapeutic potential" for treating vitiligo. EX1006, 1870; *see also* EX1023,

Figures 2 & 3 (showing that treatment with simvastatin reduces autoreactive Trm CD8⁺ T cells in the skin and prevents depigmentation); EX1002, ¶97.

Xing discloses that systemic administration of a species of mouse CD122 antibody depletes autoreactive CD8⁺ T cells in the skin and prevents hair loss in a mouse model of alopecia areata. EX1002, ¶98. A POSA would have had good reason to administer Xing's CD122 antibody (i.e., TM-β1) in Harris's mouse model of vitiligo because Harris expressly suggests that preventing autoreactive CD8⁺ T cell accumulation in the skin has therapeutic potential for treating vitiligo. EX1002, ¶99. Furthermore, a POSA would have wanted to reduce the number of autoreactive CD8⁺ T cells because these cells were known to cause destruction of melanocytes in the mouse model. *E.g.*, EX1006, 1869 (explaining that autoreactive CD8⁺ T cells have a "direct role...in melanocyte destruction"), 1870 (explaining that "prevent[ing] CD8⁺ T cell accumulation in the skin" has "therapeutic potential" for vitiligo); *see also* EX1008, 786 ("CD8⁺ T cells are both necessary and sufficient for melanocyte destruction in vitiligo...."), 787 ("[C]ytotoxic CD8⁺ T cells[] play[] a key role in the destruction of melanocytes in vitiligo (21) and hair loss in alopecia areata."); EX1002, ¶100.

Xing teaches that administration of the TM-β1 antibody to mice reduces the number of CD8⁺ T cells in the skin. EX1007, Abstract, 4, 8, Figure 2h (reproduced

Figure 3 is a dot plot showing the percentage of CD8⁺NKG2D⁺ T cells in the skin for two groups: Control and Anti-IL-15R β . The y-axis is labeled 'CD8⁺NKG2D⁺ T cells (%)' and ranges from 0 to 40. The Control group has a mean of approximately 25%, while the Anti-IL-15R β group has a mean of approximately 0%. A horizontal bar with three asterisks (***) indicates a significant difference between the groups.

Group	CD8 ⁺ NKG2D ⁺ T cells (%)
Control	~25
Anti-IL-15R β	~0

Figure 3 is a dot plot showing the percentage of CD8⁺NKG2D⁺ T cells in the skin for two groups: Control and Anti-IL-15R β . The y-axis is labeled 'CD8⁺NKG2D⁺ T cells (%)' and ranges from 0 to 40. The Control group has a mean of approximately 25%, while the Anti-IL-15R β group has a mean of approximately 0%. A horizontal bar with three asterisks (***) indicates a significant difference between the groups.

Group	CD8 ⁺ NKG2D ⁺ T cells (%)
Control	~25
Anti-IL-15R β	~0

Figure 3 is a dot plot showing the percentage of CD8⁺NKG2D⁺ T cells in the skin for two groups: Control and Anti-IL-15R β . The y-axis is labeled 'CD8⁺NKG2D⁺ T cells (%)' and ranges from 0 to 40. The Control group has a mean of approximately 25%, while the Anti-IL-15R β group has a mean of approximately 0%. A horizontal bar with three asterisks (***) indicates a significant difference between the groups.

Group	CD8 ⁺ NKG2D ⁺ T cells (%)
Control	~25
Anti-IL-15R β	~0

31:19-23. Accordingly, a POSA thus would have reasonably expected to be able to identify and apply a therapeutically effective amount of TM- β 1 for subcutaneous administration to the epidermis within the vitiligo lesions and would have reasonably expected to thereby treat the disease. EX1002, ¶¶103, 109-111.

The rational underpinnings and reasonable expectation of success of a POSA for applying Xing's antibody to Harris's mouse model is further supported by prior art (e.g., Cheuk) teaching that tissue-resident memory T cells (Trm cells) are activated by IL-15 in vitiligo, that JAK/STAT inhibition downstream of CD122 reversed vitiligo lesions, and that Xing's mouse CD122 antibody prevented hair loss in a mouse model of spontaneous alopecia areata. EX1027, 297. Indeed, Cheuk suggests inhibition of $\beta\gamma$ signaling as an attractive target for treating these diseases that were putatively caused by aberrant Trm cells. EX1027, 297; *see also* Sections I.A.ii-iii above. Accordingly, each of claims 1-5 was obvious at the critical date based on evidence (e.g., Xing and Cheuk) that were never considered by the Examiner. EX1002, ¶104.

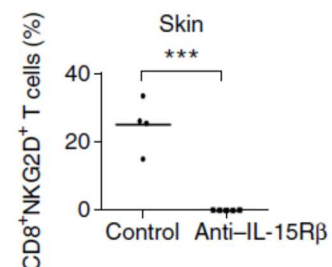
As discussed on an element-by-element basis below, the combination of Harris and Xing discloses each and every element of claim 1. EX1002, ¶¶105-06.

i. Claim 1

1. A method of treating a subject who has a vitiligo lesion, the method comprising: identifying a subject in need of treatment; and administering a therapeutically effective amount of an inhibitor of IL-15 or the IL-15 receptor to the subject.

Harris describes a “mouse model of vitiligo using adoptive transfer of melanocyte specific CD8⁺ T cells.” EX1006, 1869. Within weeks of treatment, mice develop patchy depigmentation (i.e., vitiligo) lesions within areas “including the ears, nose, feet, tail, and occasionally on the trunk under the hair.” EX1006, 1871. Harris describes objectively quantifying vitiligo in mice using a point scale for scoring the “extent of depigmentation at four easily visible locations, including the ears, nose, rear footpads, and tail.” EX1006, 1870; *see also id.* (describing assignment of vitiligo score for experimental mice), Figure 1C (illustrating a typical vitiligo score in mice). A person of ordinary skill in the art would have considered the mice described by Harris—the same mouse model used in the ’505 patent—to be subjects who have a vitiligo lesion in need of treatment as required by claim 1. EX1002, ¶¶107-08.

Xing describes administering a therapeutically effective amount of a CD122 (IL-15R β) inhibitor to mice developing autoimmune AA skin lesions. Specifically, Xing discloses that administration of 200 μ g of TM- β 1 intraperitoneally twice a week for 12 weeks reduces the number of autoreactive CD8⁺ T cells in the skin to nearly undetectable levels. EX1007, Abstract, 4, 8, Figure 2h (reproduced in part herein), i. The amount of antibody used in Xing was comparable to that used in the ’505 patent (200 μ g, 2x weekly vs. 100 μ g 3x



weekly), and the reduction in the population of autoreactive CD8⁺ T cells described by Xing is comparable (if not more dramatic) than that disclosed in the '505 patent with its mouse CD122 antibody ChMBC7. EX1007, 8 (Online Methods); EX1001, 29:22-23, 33:26-35, Figure 6D. Accordingly, a POSA would have expected TM-β1 administration as described by Xing to achieve similar reductions in depigmentation as provided in the '505 patent with ChMBC7. EX1002, ¶109; *see also* Sections I.A.ii-iii above.

To the extent Patent Owner argues that experimental verification is required for determining the therapeutically effective amount of TM-β1, the '505 patent admits that the dosage of the therapeutic compounds will vary from compound to compound. The '505 patent explains that dosing “can be determined by standard pharmaceutical procedures” and that the “skilled artisan” will appreciate factors that may influence the dosage and the time required to effectively treat a subject. EX1001, 23:20-25, 23:29-34. The '505 patent also admits that the dosage may vary “depending on the dosage form employed and the route of administration utilized” (EX1001, 23:27-49), and leaves to the skilled artisan the task of identifying the therapeutically effective dose of any antibody in any subject other than the mouse model of vitiligo (adoptive transfer of CD8⁺ T cells that recognize PMEL autoantigen) used in its study. EX1001, 31:19-23; EX1002, ¶110.

Here, obviousness is predicated on the same mouse model of vitiligo used in the '505 patent. An antibody which, like ChMBC7, reduces the number of autoreactive CD8⁺ T cells in the skin would be expected to yield the same result in the vitiligo mouse model—that is, reduced depigmentation. EX1002, ¶¶103, 109-111. The law does not require more from the prior art to demonstrate obviousness than the patent discloses. *See In re Paulsen*, 30 F.3d 1475, 1481 n.9 (Fed. Cir. 1994) (noting the specification would not be enabling if held to the same standard urged for the reference); *In re Epstein*, 32 F.3d 1559, 1568 (Fed. Cir. 1994) (noting appellant's specification lacks the same detail urged as making the reference inadequate); *SRI Int'l, Inc. v. Internet Sec. Sys.*, 511 F.3d 1186, 1192-94 (Fed. Cir. 2008) (finding unpersuasive arguments that the prior art was not enabling where the disclosure between the prior art and challenged patent were highly similar); *Analog Devices, Inc., v. Xilinx, Inc.*, IPR2020-01625, Paper 43, 25-27 (Apr. 14, 2022) (finding unpersuasive arguments regarding deficiencies in the prior art where “the asserted prior art's level of disclosure is commensurate with the disclosure of the [challenged] patent.”).

ii. Claim 2

2. The method of claim 1, wherein the inhibitor is a small molecule inhibitor, an antibody, a peptide inhibitor, or an inhibitory nucleic acid targeting IL-15 or the IL-15 receptor.

As discussed above, Xing uses the CD122 (IL-15R β) antibody TM- β 1. Accordingly, claim 2 is obvious in view of Xing and Harris for the same reasons discussed above for claim 1. EX1002, ¶112.

iii. Claims 3-5

3. The method of claim 1, wherein the inhibitor is administered to the lesion.
4. The method of claim 3, wherein the inhibitor is administered to the epidermis within the lesion.
5. The method of claim 3, wherein the inhibitor is administered to the epidermis within the lesion by subcutaneous or intradermal administration, or a microneedle array.

Claims 3-5 all require administration of inhibitor “to the lesion.” While claims 4 and 5 further require administration to the epidermis, claim 5 confirms that administration to the epidermis may be accomplished “by subcutaneous or intradermal administration.” The ’505 patent presents no working examples of administering an inhibitor to the epidermis within the lesion topically, by subcutaneous injection, or by microneedle array. EX1002, ¶113.

As discussed above in Section VIII.B.i, claim 1 was obvious in view of the prior art. *See also* Sections I.A.ii-iii above. Administration of an inhibitor to vitiligo lesions in a manner satisfying claims 3-5 also would have been obvious in view of the prior art. Xing discloses administration of a downstream inhibitor of $\beta\gamma$ signaling using a subcutaneously implanted osmotic mini-pump. EX1007, 8 (Online Methods). While Xing exemplified this administration methods with JAK

inhibitors, it would have been obvious to use the same method to deliver TM- β 1 antibody to vitiligo lesions. EX1002, ¶114.

Furthermore, it was known in the art that antibodies could be delivered to the skin of mice by injection. For example, Mackay describes injection of neutralizing antibodies to IL-15 and IL-15R α into the skin of mice. EX1017, 1109 (“For IL-15 blocking assays, mice were treated with anti-IL-15+IL-15R α chain antibody ...by either intradermal injection”). Mackay further discloses that such injections deplete tissue-resident memory (“Trm”) CD8⁺ T cells in the skin. EX1017, 1107 (“We found that the number of skin Trm cells was diminished by more than half following antibody administration...”). Accordingly, it would have also been obvious to deliver the TM- β 1 antibody by injection to vitiligo lesions. EX1002, ¶114-15.

Accordingly, each of claims 3-5 as a whole was obvious. EX1002, ¶¶113-17; EX1004, ¶¶28-29.

IX. MATERIAL DIFFERENCES FROM PROSECUTION WARRANT INSTITUTION

The sole rejection during prosecution asserted WO 2009/002562 as rendering the claims obvious by teaching a method of treating an immune disorder, the method comprising administering an effective amount of an antibody that specifically binds to IL-15/IL-15Ra complexes and reduces the binding of the IL-15/IL-15Ra complexes to the $\beta\gamma$ signaling complex. EX1010, 56 (citing EX1009,

Abstract, Claim 8). The Examiner asserted that the '562 publication identified vitiligo as an example autoimmune disorder that can be prevented, treated, and/or managed using the method and disclosed that the agents may be formulated for transdermal and intradermal administration. EX1010, 57 (citing EX1009, [00226], [00162]).

PO obtained allowance of the claims over the '562 publication by arguing that the '562 publication provided no suggestion “to pick vitiligo specifically from the numerous disorders listed,” that “there is zero evidence” in the '562 publication “that an inhibitor of IL-15 or the IL-15 receptor could actually be used to treat a subject who has a vitiligo lesion, and that the inventors of the '505 patent “surprisingly discovered that treatment with an IL-15R β blocking antibody effectively depleted autoreactive Trm [tissue-resident memory T cells], inhibited their function, and resulted in durable reversal of disease in mice.” EX1010, 14-15. The Examiner stated that “[t]hese arguments have been found to be fully persuasive and the rejection has been withdrawn.” *Id.*, 15. In the “Reasons for Allowance,” the Examiner stated that the prior art does not disclose “the limitation that a therapeutically effective amount of an inhibitor of IL-15 or the IL-15 receptor is administered to the subject,” or “an obvious variant” thereof. *Id.*

The Examiner never issued any rejection under 35 U.S.C. §112, and never provided any analysis of whether the specification provides written description and

enablement support for the claims. The Examiner never evaluated whether ChMBC7 inhibition was representative of all the disparate forms of IL-15 or IL-15R inhibition or even discussed the fact that there are disparate forms of IL-15 and IL-15R inhibition (IL-15R α , CD122, CD132). *See also* Sections I.A.i, iii and VI-VII above. The Examiner never evaluated whether ChMBC7 inhibition was representative of upstream nucleic acid inhibition of any of claimed sub-genera means of inhibition. Nor did the Examiner discuss or demonstrate awareness of the differences between CD122 inhibition and CD132 inhibition, or between various forms of CD122 inhibition. Accordingly, the §112 arguments presented in the instant petition have not been previously presented to the Office and it was material error for the claims to issue in light of what was known in the art regarding the existence of disparate forms of IL-15 and IL-15R inhibition.

The Examiner also never considered, much less asserted, Xing or any reference cumulative thereto. Indeed, as discussed in detail below, Xing discloses the very things the Examiner believed were missing from the prior art. For example, Xing demonstrates that systemic administration of TM- β 1 depleted CD8⁺ effector T cells and prevented hair loss in a mouse model of spontaneous alopecia areata. *See* Sections I.A.ii and VIII above. As Harris 2014 explains, alopecia areata is an autoimmune disease of the skin in which the cytotoxic T cells target and kill the hair follicles (as opposed to melanocytes in vitiligo). Xing demonstrated that

systemic administration of the mouse CD122 antibody called TM-β1 prevented progression of alopecia areata by preventing accumulation of cytotoxic CD8⁺ T cells in the skin and by abrogating MHC upregulation. *See* Sections I.E.i and VIII above. Xing thus demonstrates that the Examiner erred by accepting PO's argument that the prior art does not disclose "the limitation that a therapeutically effective amount of an inhibitor of IL-15 or the IL-15 receptor is administered to the subject," or an obvious variant of the claimed method (i.e., for alopecia).

Xing thus provides new and non-cumulative evidence that a POSA had good reason and a reasonable expectation of success for treating CD8⁺ T cell-induced vitiligo lesions by using a mouse CD122 antibody to deplete the CD8⁺ T cells causing the depigmentation. Xing demonstrated that TM-β1-mediated blockade of CD122 prevented disease development and progression and that inhibiting IFN-γ production downstream of IL-15 through topical administration of JAK inhibitors effectively eliminated existing lesions. This therapeutic effect persisted for several months after cessation of treatment (the '505 patent only evaluated treatment outcomes for 8 weeks after cessation of treatment). Accordingly, a POSA had good reason and a reasonable expectation of success following the teachings of Harris and Xing to use TM-β1-mediated blockade of mouse CD122 in mice having a CD8⁺ T cell-induced vitiligo lesion to suppress the T cells causing lesions. *See*

Sections I.E and VIII above. The '505 patent's results thus were not unexpected in view of the prior art.

The rational underpinnings and reasonable expectation of success of a POSA for applying Xing's antibody to Harris's mouse model is further supported by additional prior art not considered during prosecution (e.g., Cheuk) teaching that tissue-resident memory T cells (Trm cells) are activated by IL-15 in vitiligo, that JAK/STAT inhibition downstream of CD122 reversed vitiligo lesions, and that Xing's mouse CD122 antibody prevented hair loss in a mouse model of spontaneous alopecia areata. EX1027, 297. Indeed, Cheuk suggests inhibition of $\beta\gamma$ signaling as an attractive target for treating these diseases that were putatively caused by aberrant Trm cells. EX1027, 297; *see also* Sections I.A.ii-iii above. Accordingly, the new evidence and argument presented in the petition warrants review of the claims of the '505 patent.

Regardless of whether these issues might have been considered during prosecution, there is material error. First, the record is not well-developed on the art and issue presented here, which constitutes material error. *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential) (recognized material error for failing to develop the record fully regarding salient prior art). Second the petition addresses these issues in detail and demonstrates the current claims never should

have issued. For example, the petition presents new evidence in the form of highly-qualified expert testimony as well as new references demonstrating the specification is not commensurate with the scope of the claims and that the same result achieved in the patent was obvious in view of the prior art.

Because there are material differences between the art and arguments presented here and what was considered during prosecution, and because the challenged claims issued based on the material error of failing to consider the §112 evidence and the §103 evidence discussed herein, including the Xing and Cheuk references, institution should be granted.

X. CONCLUSION

For the reasons set forth above, claims 1-5 of the '505 patent are unpatentable. Petitioners therefore request that a post-grant review of these claims be instituted and that the claims be canceled.

Respectfully submitted,

Dated: December 22, 2022

/Michael T. Rosato/
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

XI. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 17,757 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: December 22, 2022

/Michael T. Rosato/

Michael T. Rosato, Lead Counsel

Reg. No. 52,182

XII. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(B) AND 42.203

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XIII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 11,278,505 to Richmond et al.
1002	Declaration of Dr. Abul Abbas
1003	<i>Curriculum Vitae</i> of Dr. Abul Abbas
1004	Declaration of Dr. R. Todd Plott
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
1007	“Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition” Luzhou Xing, et al., <i>Nature Medicine</i> ,
1008	“Vitiligo and alopecia areata: apples and oranges?,” John E. Harris, <i>Experimental Dermatology</i> , 2013, 22, 785-789
1009	International Publication No. WO 2009/002562 to Pavlakis et al.
1010	File History for Application No. 16/608,116
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

1013	DeGottardi et al., "Effect of anti-IL-15 administration on T cell and NK cell homeostasis in rhesus macaques," <i>The Journal of Immunology</i> . Aug. 15, 2016, 197(4) H83-98.
1014	"Human IL-2 Receptor α Chain Deficiency," Chaim M. Roifman, <i>Pediatric Research</i> 48, 6-11.
1015	"IL-15 functions as a danger signal to regulate tissue-resident T cells and tissue destruction," Bana Jabri and Valérie Abadie, <i>NATURE REVIEWS IMMUNOLOGY VOLUME 15 AUGUST 2015</i>
1016	"The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design," Thomas A Waldmann, <i>NATURE REVIEWS IMMUNOLOGY VOLUME 6 AUGUST 2006</i>
1017	"T-box Transcription Factors Combine with the Cytokines TGF- β and IL-15 to Control Tissue-Resident Memory T Cell Fate," Laura K. Mackay, et al., <i>Immunity</i> 43, 1101-1111
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
1019	"Understanding autoimmunity of vitiligo and alopecia areata," Jillian F. Rork, et al., <i>Curr Opin Pediatr</i> 2016, 28:463-469
1020	CXCL10 Is Critical for the Progression and Maintenance of Depigmentation in a Mouse Model of Vitiligo," Mehdi Rashighi, et al., <i>ScienceTranslationalMedicine.org</i> 12 February 2014 Vol 6 Issue 223 223ra23
1021	"JAK inhibitors in dermatology:The promise of a new drug class," William Damsky and Brett A. King, <i>J AM ACAD DERMATOL</i> APRIL 2017
1022	"Targeting the interleukin-15/interleukin-15 receptor system in inflammatory autoimmune diseases," Thomas A Waldmann, <i>Arthritis Res Ther</i> 2004, 6:174-177

1023	“Simvastatin prevents and reverses depigmentation in a mouse model of vitiligo,” Priti Agarwal et al., Journal of Investigative Dermatology, Volume 135, Issue 4, April 2015, 1080-1088
1024	“Reversible Defects in Natural Killer and Memory CD8 T Cell Lineages in Interleukin 15-deficient Mice,” Mary K. Kennedy, et al., J. Exp. Med., Volume 191, Number 5, March 6, 2000 771-780
1025	Intentionally Left Blank
1026	“Interleukin 15 is required for proliferative renewal of virus-specific memory CD8 T cells” Todd C Becker et al., Journal of Experimental Medicine (2002) 195(12): 1541-8
1027	“CD49a Expression Defines Tissue-Resident CD8 ⁺ T Cells Poised for Cytotoxic Function in Human Skin,” Stanley Cheuk, et al., Immunity 46, 287-300
1028	Intentionally Left Blank
1029	Intentionally Left Blank
1030	“Therapeutic activity of multiple common γ -chain cytokine inhibition in acute and chronic GVHD,” Anne-Kathrin Hechinger, et al., BLOOD, 15 JANUARY 2015 x VOLUME 125, NUMBER 3
1031	“Alopecia areata: Animal models illuminate autoimmune pathogenesis and novel immunotherapeutic strategies,” Amos Gilhar et al, <i>Autoimmunity Reviews</i> 15 (2016) 726-735
1032	“Rapid skin repigmentation on oral Ruxolitinib in a patient with coexistent vitiligo and alopecia areata” John E. Harris et al., J Am Acad Dermatol., 2016, 74(2): 370-371
1033	“Tofacitinib Citrate for the Treatment of Vitiligo: A Pathogenesis-Directed Therapy” Brittany G Craiglow and Brett A. King, JAMA Dermatol. (2015), 151(10):1110-2

1034	“Autoimmune disease induction in a healthy human organ: a humanized mouse model of alopecia areata”, Amos Gilhar et al., J. Invest. Dermatol., 2013; 133(3); 844-847
1035	“Low-dose IL-2 for In vivo expansion of CD4 ⁺ and CD8 ⁺ regulatory T cells in nonhuman primates,” A. Aoyama et al., Am J. Transplant, 2012; 112(9):2532-7

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.205(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Post Grant Review (and accompanying Exhibits 1001-1024, 1026, 1027, 1030-1035) by overnight courier (Federal Express or UPS) and via USPS on this 22nd day of December, 2022, on the Patent Owner at the correspondence address of the Patent Owner's Counsel as follows:

U.S.P.S.MailingAddress:	FISH & RICHARDSON P.C. P.O. Box 1022, Minneapolis, MN 55440-1022
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Courier Address:	60 South Sixth Street, Suite 3200, Minneapolis, MN 55402
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Respectfully submitted,

Dated: December 22, 2022

/Michael T. Rosato/
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