

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORTE BIOSCIENCES, INC.,
Petitioner,

v.

UNIVERSITY OF MASSACHUSETTS,
Patent Owner.

Patent No. 11,278,505

DECLARATION OF DR. ABUL ABBAS

TABLE OF CONTENTS

I.	QUALIFICATIONS	1
II.	SCOPE OF WORK.....	3
III.	LEGAL STANDARDS	4
IV.	OVERVIEW OF THE '505 PATENT	10
V.	LEVEL OF SKILL IN THE ART	16
VI.	SUMMMARY OF OPINIONS	17
VII.	TECHNICAL BACKGROUND	18
A.	Brief Immunology Tutorial	18
B.	Cytokine Signaling Pathways Are Complex and Sometimes Overlap as they Activate Leukocyte Immune Responses.....	19
C.	CD8 ⁺ T Cells Drive Development and Maintenance of Lesions in Mouse Models of Vitiligo and Alopecia and Reducing Them Was Known to Be Therapeutic	20
D.	At Least Some Inhibitors of IL-15- and/or IL-2-Induced Cellular Responses Were Known to Treat Vitiligo and Alopecia Areata	23
VIII.	ANALYSIS OF THE WRITTEN DESCRIPTION REQUIREMENT.....	26
A.	The '505 Patent's Experiment Is Not Representative of Treating Humans Having A Vitiligo Lesion	26
B.	The '505 Patent's Experiment Is Not Representative of All Inhibitors of IL-15 or IL-15R.....	28
C.	The '505 Patent's Experiment Is Not Representative of All CD122 Inhibitors.....	32
D.	The '505 Patent's Experiment Is Not Representative of Topical, Subcutaneous, or Microneedle Administration.....	39

IX.	ANALYSIS OF ENABLEMENT	39
A.	The Complex Nature of the Invention and Nascent State of the Art Favor a Finding of No Enablement.....	39
B.	Breadth of the Claims Indicate the Claims Are Not Enabled	40
C.	The Sparse Guidance (Factor 2) and Single Sole Working Example (Factor 3) in the Specification Demonstrate the Claims Are Not Enabled	41
D.	Quantity of Experimentation Necessary and Unpredictability of the Art.....	42
E.	Relative Skill of those in the Art.....	44
X.	ANALYSIS OF OBVIOUSNESS OVER XING AND HARRIS	44
i.	Claim 1	49
ii.	Claim 2	51
iii.	Claims 3-5	51
XI.	CONCLUDING STATEMENTS.....	53

I, Abul Abbas, declare as follows:

I. QUALIFICATIONS

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

2. I am Professor and Chairman Emeritus in the Department of Pathology at the University of California San Francisco School of Medicine. Prior to becoming emeritus in 2018, I was Distinguished Professor in Pathology and Chair of the Department of Pathology — positions I held for 19 years.

3. I began my academic career at Harvard Medical School in 1977. I was promoted to Professor in 1991 and I remained in that position until I left for San Francisco in 1999.

4. In addition to my academic and research responsibilities, over the years I have served on scientific advisory boards for various companies. I currently serve on scientific advisory boards for ILTOO Pharma, Neuvogen, Sarepta Therapeutics, and Cue BioPharma. In the past I have served on scientific advisory boards for Celgene, UCB Pharma, Lexicon Genetics, and Entelos Corporation, and consulted for numerous pharma and biotech companies.

5. I am an author on over 200 peer-reviewed scientific articles. I have also co-authored two immunology textbooks including “Cellular and Molecular Immunology” which is currently in its 10th edition. I have taught numerous courses and workshops on immunology and immunological diseases. I headed an NIH-funded lab for about 40 years, researching immunological questions including cytokine signaling pathways relevant to treating autoimmune disease. I also have worked in consultation with medical clinicians who treat autoimmune diseases, including vitiligo, and pharmaceutical scientists familiar with formulating drugs for administration. I have a practical knowledge of immunology and have been familiar with the art of treating autoimmune diseases.

6. I received my MBBS (which is equivalent to an M.D.) in 1969 from the All-India Institute of Medical Sciences in New Delhi, India. After receiving my degree, I became a Resident, then Chief Resident, in Pathology at Peter Bent Brigham Hospital in Boston.

7. I have studied, taught, practiced, and conducted research involving cellular interactions in immune responses, tolerance and autoimmunity, cytokines, and lymphocyte apoptosis. A major focus of my research for many years has been IL-2 signaling via the CD122/CD132 $\beta\gamma$ receptor complex and its role in regulating T cells.

8. I have served on editorial boards of several scientific journals including The Journal of Immunology, Immunity, Journal of Clinical Investigation (JCI), Cell, Immunity, Science Immunology, and Annual Review of Pathology: Mechanisms of Disease.

9. I am a Distinguished Fellow of the American Association of Immunologists. I am a member of the National Academy of Medicine (formerly known as the Institute of Medicine) and the American Associations of Arts and Sciences. I have received the Gold-Headed Cane Award from the American Society of Investigative Pathology — an award that recognizes significant long-term contributions to the field of pathology.

10. A copy of my *Curriculum Vitae*, attached as EX1003, contains further details on my education, experience, publications, and other qualifications to render an expert opinion in this matter.

II. SCOPE OF WORK

11. I understand that a petition is being filed with the United States Patent and Trademark Office for Post-Grant Review of U.S. Patent No. 11,278,505 to Richmond, et al. (“the ’505 patent,” attached as EX1001), entitled “Diagnosis and Treatment of Vitiligo.”

12. I have been retained by Forte Biosciences, Inc. (“Forte”) to offer an expert opinion on the validity of claims 1-5 of the ’505 patent assigned to

University of Massachusetts. I receive \$500 per hour for my services. No part of my compensation is dependent on my opinions or on the outcome of this proceeding.

13. I have been specifically asked to provide my opinion on the unpatentability of claims 1-5 of the '505 patent as of April 24, 2017 and April 24, 2018 (the critical date). In connection with this analysis, I have reviewed the '505 patent. I have also reviewed and considered various other documents in arriving at my opinions and may cite to them in this declaration.

III. LEGAL STANDARDS

14. I understand that the Patent Office may cancel issued claims of the '505 patent if the Petitioner (here, Forte Biosciences, Inc.) demonstrates that the claims fail to satisfy the requirements of patentability that the claims must be non-obvious and that the specification must provide adequate written description and enablement support for the full scope of the invention. I understand that the claims should be understood according to their ordinary and customary meaning as understood by a person of ordinary skill in the art ("POSA") at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. I have been provided a copy of the prosecution history of record as Exhibit 1010.

15. I understand that, in deciding whether the patent satisfies the written description requirement, one must consider the description from the viewpoint of a person skilled in the field of technology at the time of the invention. The written description requirement is satisfied if the patent specifically reasonably conveys to a person of skill in the art to which it pertains or with which it is most nearly connected that the inventor actually possessed (i.e., invented) the full scope of the claimed invention at the time of the invention.

16. I have additionally been instructed that the written description requirement may be satisfied in appropriate circumstances by a combination of the words, structures, figures, diagrams, formulas, etc., contained in the patent application. But a specification that merely renders the invention obvious does not satisfy the written description requirement if it does not reasonably convey that the applicants invented what is claimed. Indeed, if the specification merely provides a “wish” or a “plan” for obtaining the claimed invention rather than a description of the invention itself, the specification fails to provide adequate written description support. A research hypothesis does not constitute written description support for a claimed invention.

17. I understand that the full scope of a claim or any particular requirement in a claim need not be expressed in the specification in the exact same words as in the claim, nor is doing so necessarily sufficient to find written description support

for the claims. The test is whether the specification conveys to a person skilled in the field of technology of the patent at the time of filing that the applicant possessed (i.e., invented) the full scope of the claim (including each individual requirement) at the critical date.

18. I understand that where an entire genus is claimed based on invention of species within the genus, the specification must demonstrate invention of sufficient species to support a claim to a genus. The species must be sufficient to be representative of the entire claimed genus. The number of species that must be disclosed to demonstrate possession of a genus in a claim may depend 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.

19. I understand that a claim is unpatentable for lack of enablement if the specification does not contain a sufficiently full, clear, concise, and exact description of the manner and process of making and using the full scope of the claimed invention to enable a POSA to make and use the invention without undue experimentation at the critical date. However, experimentation to make and use the invention is allowable if it is not undue.

20. I understand that in deciding whether a person having skill in the art would have to engage in undue experimentation to make and use the invention, several factors may be considered:

- the nature of the invention
- the state of the art
- the breadth of the claimed invention.
- the amount of guidance presented in the patent;
- whether the patent discloses specific working examples of the claimed invention;
- the time and cost of any necessary experimentation and how routine any necessary experimentation is in the relevant field of technology;
- the predictability of the relevant field of technology; and
- the level of ordinary skill in the relevant field of technology.

21. I understand that no one factor is alone dispositive. Rather, whether the degree of experimentation required is undue may involve weighing these factors in the context of the claimed invention and the state of the art at the time of the original application, to determine whether a person skilled in the art would need to engage in undue experimentation to make and use the full scope of the claimed invention.

22. I understand that a claimed invention is unpatentable for obviousness if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious to a POSA at the time the invention was made (i.e., at the critical date).

23. It is further my understanding that a determination of obviousness requires inquiries into: (1) the scope and contents of the art when the invention was made; (2) the differences between the art and the claims at issue; (3) the level of ordinary skill in the pertinent art when the invention was made; and, to the extent they exist, (4) secondary indicia of obviousness.

24. I understand that a claim is obvious if all of the claimed elements were known in the prior art and one skilled in the art would have combined the elements as claimed with a reasonable expectation of success. I understand that obviousness may also be shown by demonstrating that it would have been obvious to modify what is taught in a single piece of prior art to create the patented invention or by combining teachings of two or more references. I understand that in order for a claimed invention to be considered obvious, there must be some rational underpinning for the proposed combination. I understand that hindsight must not be used when determining whether a POSA would make the proposed combination. Thus, a conclusion of obviousness must be firmly based on

knowledge and skill of a person of ordinary skill in the art at the time the invention was made without the use of post-filing knowledge.

25. In determining whether a particular combination of prior art teachings would have been obvious, the following are examples of approaches and rationales that may be considered:

- (a) Combining prior art elements according to known methods to yield predictable results;
- (b) Simple substitution of one known element for another to obtain predictable results;
- (c) Use of a known technique to improve similar devices (methods, or products) in the same way;
- (d) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
- (e) Applying a technique or approach that would have been “obvious to try” (choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success);
- (f) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art; or

(g) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

26. I understand that obviousness may be established by showing that all of the claimed elements were known in the prior art and one skilled in the art would have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art.

IV. OVERVIEW OF THE '505 PATENT

27. I have reviewed the '505 patent in its entirety including the specification, figures, and the claims. From this review, I have determined that the '505 patent purports to describe methods for treating “disorders associated with T cell-mediated autoimmunity.” EX1001, 6:30-33.

28. The patent indicates 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 indicates that its methods for treating disorders associated with T cell-mediated autoimmunity comprise “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, 7:19-25.

29. The '505 patent states that the “methods and compositions described herein can include the use of inhibitors of IL-15 and the IL-15 receptor.” EX1001, 7:34-35. For convenience herein, I will refer to the IL-15 receptor using the shorthand designation “IL-15R.” The '505 patent states that the therapeutic molecule to be administered may be “a small molecule inhibitor of the IL-15 receptor alpha chain,” “a small molecule inhibitor of IL-15-induced cellular responses, e.g., cefazolin...and Y-320,” “a soluble IL-15 receptor alpha chain which binds IL-15 and antagonizes the IL-15 receptor,” “an antagonistic mutant IL-15/Fc-gamma 2a fusion protein which competitively inhibits binding of IL-15 to the IL-15 receptor,” “a peptide that binds to IL-15 receptor alpha chain and inhibits IL-15 activity,” “an antibody which specifically bind the IL-2/IL-15 receptor beta subunit” (also known as CD122 and p75), “an antibody that specifically binds the IL-2/IL-15 receptor gamma subunit,” “an antibody that specifically binds the IL-15 receptor alpha subunit,” or an “antibody that specifically binds IL-15”. EX1001, 7:33-8:5.

30. The '505 patent concedes that the beta subunit (i.e., IL-15R β) “is a shared receptor for both IL-2 and IL-15.” EX1001, 6:3-4. As for the gamma chain, the '505 patent refers to it as “the IL-2/IL-15 receptor gamma subunit.” EX1001, 7:64-67 (“...an antibody that specifically binds the IL-2/IL-15 receptor gamma subunit (Hechinger et al., 2015)...”). The cited Hechinger reference, however,

correctly explains gamma (γ)-chain as shared with five cytokine receptors in addition to IL-15 receptor, for a total of six cytokine receptors for: IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. EX1030, Abstract.

31. Claim 1 of the '505 patent recites:

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.

32. The language of claim 1 thus purports to restrict the use of any inhibitor of IL-15 or of the IL-15 receptor (i.e., to any inhibitor of IL-15R α , CD122 (β), or CD132 (γ)) to treat a subject having a vitiligo lesion.

33. 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. *See also*, EX1001, 2:6-8. The language of claim 2 thus purports to restrict the use of anything, regardless of its structure, that inhibits IL-15 or any inhibitor of IL-15R α , CD122 (β), or CD132 (γ)), regardless of whether it does so directly, specifically, predominantly, or exclusively. Indeed, the inhibitory nucleic acids of claim 2 do not even physically interact with any of IL-15, IL-15R α , CD122 (β), or CD132 (γ)). The physical nature of the implicated molecules is thus completely unbounded by any limiting structural limitations. The

number and variety of the known and unknown compounds implicated by the claim are thus potentially so large as to be incalculable.

34. Claims 3-4 respectively specify that the inhibitor is administered to the lesion or to the epidermis within the lesion, which would include topical application. Claim 5 specifies that administration encompasses delivery to the epidermis within the lesion by subcutaneous injection, intradermal injection, or a microneedle array.

35. The only demonstration of the invention in the specification of the '505 patent is provided in Example 5. In this example, an antibody referred to using the code name ChMBC7 is administered to mice. EX1001, 33:1-34:45. Example 5 uses the same mouse model of vitiligo described originally by Harris (EX1006). Specifically, the '505 patent describes the model as comprising “adoptive transfer of CD8⁺ T cells that recognize the autoantigen ...(PMEL) physiologically expressed in melanocytes.” EX1001, 31:19-23; *see also id.*, 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 (Agarwal et al., 2015 [EX1034]; Harris et al., 2012 [EX1007]; Rashighi et al., 2014 [EX1020])”). In other words, CD8⁺ T cells are activated and primed to target melanocytes and, when transferred into the mouse,

induce depigmentation lesions (a similar symptom as in natural or spontaneous vitiligo) achieved through a controlled means.

36. Such contrived mice models are useful for exploring the mechanisms of injury to tissue cells (in this case, melanocytes) and possibly therapeutic potential of agents for treating these symptoms in actual disease subjects but are not representative of the complexity of the natural disease. In other words, the model provides a symptom comparable to vitiligo lesions but with a simplified cause. Because the cause of the lesions in the mouse model is known to be CD8⁺ T cells that are activated and primed to target melanocytes, reduction of CD8⁺ T cells activity will predictably address the cause of the lesions, leading to predictable reversal of the lesions. Such models are important for beginning the study of the much more complex causes of natural or spontaneous autoimmune disorders, but they are not representative of the more complex etiology of the natural or spontaneous disorders. The '505 patent does not disclose administering any inhibitor of IL-15 or IL-15R to any subject having a vitiligo lesion other than a mouse having a CD8⁺ T cell-induced depigmentation lesion. In other words, the experiment in the '505 patent is not even representative of vitiligo in mice, much less in humans or other animal species.

37. The '505 patent does not provide the sequence, structure, or epitopes bound by the ChMBC7 antibody. The '505 patent's description of the antibody is

limited to calling it “a chimeric rat/mouse antibody with diminished Fc-mediated effector functions” that it says recognizes mouse CD122 (IL-2R/IL-15R β) and blocks IL-15 signaling. EX1001, 33:20-23. The ’505 patent does not demonstrate that ChMBC7 specifically inhibits IL-15 signaling via the $\beta\gamma$ complex (as opposed to inhibiting only IL-2 signaling or both IL-15 and IL-2 signaling). The ’505 patent does not demonstrate that ChMBC7 blocks cytokine binding to the $\beta\gamma$ complex by *cis*-presentation, by *trans*-presentation, or both. The ’505 patent does not demonstrate that ChMBC7 specifically blocks high-affinity or low-affinity cytokine binding to the $\beta\gamma$ complex, or both. The ’505 patent does not demonstrate that an Fc-intact antibody would work similarly to ChMBC7, and a POSA would understand that an Fc-intact antibody likely induce additional immune responses and alter the outcome of the experiments. Example 5 does not describe topically administering ChMBC7 to the epidermis within a vitiligo lesion nor does it describe administering ChMBC7 to the epidermis within a vitiligo lesion by subcutaneous injection or a microneedle array.

38. As summarized in the table below, the ’505 patent does not provide working examples across the full scope of claims 1-5.

Claimed	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
“administered to the lesion”	No topical administration
“administered to the epidermis within the lesion by subcutaneous... administration, or a microneedle array	No subcutaneous or microneedle array

V. LEVEL OF SKILL IN THE ART

39. I have been advised that “a person of ordinary skill in the relevant field” (POSA) is a hypothetical person to whom one could assign a routine task with reasonable confidence that the task would be successfully carried out. I have been advised further that, in determining the level of ordinary skill in the art that someone would have had at the time the claimed invention was made, I should consider: (1) the levels of education and experience of persons working in the

field; (2) the types of problems encountered in the field; and (3) the sophistication of the technology.

40. Based on my specialized education, knowledge, training, and experience, I am familiar with the level of skill of a POSA as of the critical date. I understand that a person of ordinary skill in the art 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. I understand that 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. I also understand that skilled artisans also would have had practical knowledge of immunology and have been familiar with prior art pertaining to treatment of autoimmune diseases, including the patents and publications discussed herein.

VI. SUMMARY OF OPINIONS

41. As I will explain in detail below, the '505 patent was not the first disclosure of using a specific CD122 antibody for depleting CD8⁺ T cells in a mouse model, and reversing depigmentation vitiligo lesions caused by introducing

activated, melanocyte-targeted CD8⁺ T cells by depleting those T cells would have been obvious to a POSA at the critical date in view of the prior art.

42. The specification of the '505 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. Indeed, the inventors of the '505 patent were not in possession of the full scope of claimed genus of methods at the critical date. Moreover, the specification did not enable a POSA to practice the claimed genus of methods without undue experimentation.

VII. TECHNICAL BACKGROUND

A. Brief Immunology Tutorial

43. Leukocytes are also called white blood cells. They circulate through the body and the tissues of the body to respond to injury or illness. Leukocytes do so by attacking foreign substances that enter the body.

44. Lymphocytes are an important class of leukocytes found in lymph nodes and lymph fluid. Lymphocytes consist of T cells, natural killer (NK) cells, and B cells. T cells and B cells recognize specific non-self antigen markers and respond to eliminate specific pathogens. B cells respond to antigens by producing antibodies to neutralize the antigen, such as those presented by bacteria or viruses. T helper cells produce cytokines (small cell-signaling peptides) that direct the

immune response. Interleukins are a sub-type of cytokines defined by the fact that they are produced by leukocytes.

45. Cytotoxic T cells are a type of effector T cell. They produce toxic granules that induce the death and destruction of pathogen-infected cells. At the critical date, CD8 was a known marker for cytotoxic T cells. Memory-type effector T cells play a role in providing a strong immune response when reencountering a pathogen. NK cells kill other cells. NK cells can be activated by interferon cytokines, and can modulate the functions of other cells, including T cells.

B. Cytokine Signaling Pathways Are Complex and Sometimes Overlap as they Activate Leukocyte Immune Responses

46. Interleukin-2 (IL-2) is a cytokine primarily produced by activated CD4⁺ helper T cells (the other major class of effector T cells) and activated CD8⁺ cytotoxic T cells. 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). 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.

47. The CD132 (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. IL-2R also shares the CD122 (β) subunit with IL-15R.

48. 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). $\beta\gamma$ signaling, whether induced by IL-15 or IL-2, activates the JAK-STAT pathways. IL-15 or IL-2 induced activation of JAK-STAT causes various immunological effects. Among other effects, both IL-2 and IL-15 potentiate cytotoxic effector functions in tissue resident memory T (Trm) cells. EX1027, 291.

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

49. Vitiligo, alopecia areata (“AA”), and psoriasis are autoimmune diseases of the skin. EX1008, Abstract, 785. Depigmentation lesions (patches) in vitiligo are caused by the destruction of melanocytes. EX1008, 785. In AA, the patches are characterized by hair loss from destroyed follicle cells. *Id.*

50. It was known that the damage to melanocytes in vitiligo and the hair follicle in AA are caused at least in part by autoreactive CD8⁺ T cells, including tissue resident memory T cells (Trm). EX1031, Abstract; EX1019, 467. In both vitiligo and AA lesions, immune cells (often both CD8⁺ and CD4⁺ T cells) are found to have infiltrated into the lesions, though the CD8⁺ T cells may be localized to the epidermis and the follicular epidermis while the CD4⁺ T cell may remain dermal. EX1008, 785. Cytotoxic CD8⁺ T cells were thus said by some to play a key role in the destruction of melanocytes in vitiligo and hair loss in AA. EX1008,

786; 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.”)

51. Mouse models for vitiligo depigmentation had been developed long before the critical date. 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. Harris reported that the transferred melanocyte-specific CD8⁺ T cells accumulate within the skin. EX1006, 1870, 1870-1872, Figure 1b. Harris also reported that depigmentation correlates with loss of melanocytes. EX1006, 1872, Figure 3.



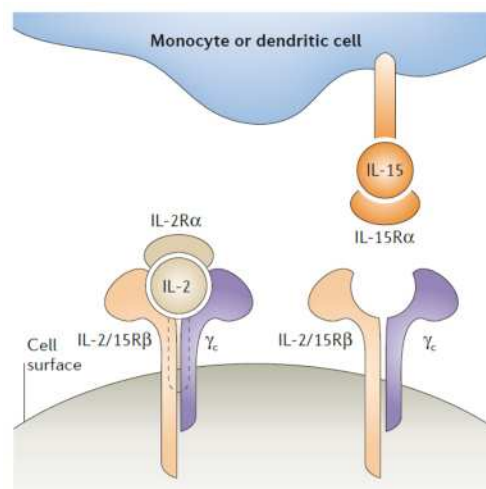
52. Because introducing the CD8⁺ T cells was known to be the cause (pathogenesis) of the specific depigmentation lesions in this mouse model of vitiligo, it was expected that reducing these same CD8⁺ T cells would reverse the lesions. Agarwal reports that treatment with an agent (i.e., simvastatin) that reduces the number of melanocyte-specific CD8⁺ T cells in the

skin also reduces depigmentation. EX1023, 1081-1082, Figures 1 & 2. With these results, Agarwal confirmed that the depigmentation lesions were caused by the transferred CD8⁺ T cells and that eliminating these CD8⁺ T cells reversed that process. EX1023, Abstract. In other words, CD8⁺ T cells were necessary and sufficient to induce the killing of melanocytes that resulted in the depigmentation lesions in this mouse model.

53. In mouse models of alopecia areata, CD8⁺ T cells were necessary and sufficient to induce development of autoimmune skin lesions. EX1008, 786; EX1034, 844. For example, Xing reports experiments in mice that spontaneously develop alopecia areata lesions in the skin. Xing reported that the affected animals accumulate autoreactive CD8⁺ T cells in the skin. EX1007, 1 (“In lesional skin biopsies from alopecic mice, CD8⁺NKG2D⁺ T cells infiltrate the epithelial layers of the hair follicle,...”). Xing declared that CD8⁺ T cells were necessary and sufficient to induce the killing of hair follicles associated with alopecia areata (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. One consistent property between these two different mouse models of autoimmune lesions of the skin is that CD8⁺ T cells were to known drive disease such that reducing the number of CD8⁺ T cells in the skin was therapeutic for treating the lesions.

D. At Least Some Inhibitors of IL-15- and/or IL-2-Induced Cellular Responses Were Known to Treat Vitiligo and Alopecia Areata

54. It was known before the critical date that both IL-2 and IL-15 are involved in the “life and death” of CD8⁺ T cells. EX1015, 771, 782 n.69; EX1016, Abstract. As discussed above, both cytokines induce $\beta\gamma$ signaling in CD8⁺ T cells, among others. For



both cytokines, their affinity for the $\beta\gamma$ receptor complex is greatly enhanced when the cytokines first associate with a unique α chain (“IL-2R α or IL-15R α ”). EX1015, Figure 1. 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, 175; EX1016, Figure 2 (shown herein).

55. Presentation of the IL-2 or IL-15 cytokine on one cell to the $\beta\gamma$ complex on another cell (common for IL-15, rare for IL-2) is called “trans-presentation,” whereas presentation of the IL-2 or IL-15 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

56. IL-2 and IL-15 were both understood under certain circumstances to be drivers of cytotoxic activity by IFN- γ producing CD8⁺ effector T cells and NK cells. EX1007, 3. They also both had been implicated in the induction and/or

maintenance of autoreactive CD8⁺ T cells. EX1007, 3-4. High levels of IL-2 were known to promote cytotoxic CD8⁺ effector cell activity, but IL-2 production also was believed to inhibit autoimmune disease by activating CD4⁺ Regulatory T cells. EX1035, Abstract.

57. One mechanism by which IL-2 was said to inhibit autoimmune disease was by promoting activation-induced cell death (AICD)—a process by which autoreactive Trm CD8⁺ T cells may be eliminated. EX1022, 175. One mechanism by which IL-15 was thought to promote autoimmune disease was by inhibiting AICD and therefore allowing autoreactive Trm CD8⁺ T cells to persist. EX1015, 774. Because at least some level of IL-2 production was necessary to maintain CD4⁺ Regulatory T cell function, complete knock-out of IL-2 production in mice was observed to cause autoimmune disorders. EX1024, Abstract, 771-72.

58. In contrast, complete knockout of IL-15 production in mice was observed to reduce the number of memory CD8⁺ T cells. EX1024, 776-777. For example, Becker et al. reported that populations of memory CD8⁺ T cells declined by attrition absent IL-15. EX1026, 1542 (“memory CD8 T cell numbers undergo a slow attrition in the absence of IL-15”). Becker et al. also reported 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, 1545. Accordingly, both IL-2 and IL-15 were

known under certain circumstances to promote autoreactive CD8⁺ T cells, but only IL-2 was also understood under certain circumstances to protect against autoimmunity.

59. Several researchers reported that certain neutralizing antibodies to IL-15 or its cytokine-specific receptor IL-15R α could deplete Trm CD8⁺ T cells. For example, Mackay et al. reported that injection of neutralizing antibodies to IL-15 and IL-15R α into the skin of mice depleted 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”). As another example, Villadsen et al. reported in a mouse model of psoriasis that antibodies against IL-15 alleviate psoriasis and deplete CD8⁺ T cells. EX1018, 1576-1578.

60. It also was reported that at least some inhibitors of IL-15- and/or IL-2-induced cellular responses could treat vitiligo or AA. For example, $\beta\gamma$ signaling induced by IL-2 or IL-15 causes Janus kinases (i.e., Jak1 and Jak3) to bind to the intracellular portions of the β and γ chains of the receptor. EX1015, 777. Certain inhibitors of Jak1 or Jak3 were reported to treat vitiligo and alopecia in humans and mice. EX1006, 1872-1874; EX1007, 5-6, FIG. 3, FIG. 4; EX1032, 370-71;

EX1033, Abstract, 1010-11. It was also reported that vitiligo or AA in mice could be treated with antibodies to IFN- γ . EX1007, 4, FIG. 2; EX1019, 467. IFN- γ production by CD8⁺ T cells is enhanced by IL-15 or IL-2 signaling.

VIII. ANALYSIS OF THE WRITTEN DESCRIPTION REQUIREMENT

A. The '505 Patent's Experiment Is Not Representative of Treating Humans Having A Vitiligo Lesion

61. I have reviewed the entirety of the '505 patent and it is my opinion that a POSA would not understand the specification of the '505 patent to convey that the applicant invented a method of treating a non-mouse model subject (e.g., human) who has a vitiligo lesion. A mouse model is useful to explore ways to create symptoms similar to those that occur in natural or spontaneous diseases as well as ways to treat or reverse those symptoms. But this does not mean that treating the mouse model of vitiligo is representative of treating an actual human patient who has developed a complicated autoimmune disease such as vitiligo.

62. As I explained above, the mouse model used in the '505 patent creates depigmentation lesions by transferring activated, melanocyte-targeting CD8⁺ effector T cells into the mice. EX1001, 29:13-40, 33:1-34:45. Because CD8⁺ effector T cells are both necessary and sufficient for these depigmentation lesions, depleting the CD8⁺ effector T cells would reasonably be expected to reverse the lesions. But the forces causing immune attack in a spontaneous autoimmune disease model (like that used in Xing) would be more complicated than the

simplistic model used in the '505 patent, and the forces causing actual vitiligo in a patient would naturally be more complicated and varied still. Based only on mouse model experiments with ChMBC7, the '505 patent recites administering the inhibitor to any "subject who has a vitiligo lesion" and does not restrict the claims to a mouse 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"). The depigmentation lesions induced in mice in the '505 patent by priming CD8⁺ effector T cells to attack melanocytes and transferring them to the mice are not representative of natural or spontaneous vitiligo in a human patient. Transferring activated and targeted CD8⁺ effector cells into the body is not how vitiligo naturally or spontaneously develops in a human patient. The '505 patent's experiments provide a POSA with little to no understanding of what might happen when using an IL-15 inhibitor or an IL-15R inhibitor in humans having vitiligo lesions. The '505 patent merely invites a POSA to undertake a research project in treating natural or spontaneous vitiligo outside the mouse model. It does not convey invention of using IL-15 or IL-15R inhibition to treat a human patient who has a vitiligo lesion.

63. Even if animal studies had shown that ChMBC7 inhibition of CD122 treated natural or spontaneous vitiligo in mice, success in mice is inadequate to demonstrate therapeutic efficacy in humans. The immune systems of these

different species are not identical. Moreover, a particular CD122 antibody might 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. Mouse studies are used for foundational research, but the only way to determine therapeutic efficacy in humans is by extensive trials.

B. The '505 Patent's Experiment Is Not Representative of All Inhibitors of IL-15 or IL-15R

64. A POSA also would not have understood from the specification of the '505 patent that the applicants had possession of (i.e., invented) treating vitiligo by administering an entire genus of inhibitors made up of inhibitors of IL-15 and IL-15R. A POSA would not understand the specification of the '505 patent to convey that the applicant were in possession of a method of treatment other than one using the specific antibody (called ChMBC7) used in the specific CD8⁺ T cell mouse model in the patent. The only way for a POSA to know if another CD122 antibody, a CD132 antibody, an IL-15 antibody, or an IL-15 α antibody would treat vitiligo would be trial and error.

65. For example, though the claims encompass all CD132 (γ chain) inhibition, this receptor subunit is shared by receptors for at least six cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21). EX1015, 771. Because CD132 signaling implicates at least six cytokine signaling pathways, inhibition of CD132 potentially implicates additional biological responses for which ChMBC7 inhibition may not

be representative. For example, some forms of CD132 depletion result in severe, combined immunodeficiency. EX1014, Abstract, 6. However, the ChMBC7 antibody was not reported to have the same effect and therefore appears not be representative of CD132 inhibition. The '505 patent provides no example of CD132 inhibition to treat a subject having a vitiligo lesion. CD132 thus provides an example of why the ChMBC7 inhibition used in the '505 patent is not representative of a genus made up of inhibiting IL-15 or the IL-15 receptor.

66. The '505 patent asserts, but does not actually demonstrate, that IL-15 inhibition is the way that ChMBC7 treated the depigmentation lesions in the mouse model. As I explained above, however, CD122 is shared by both IL-15 signaling and IL-2 signaling. An obvious approach for a POSA who wants to determine the effect of specifically inhibiting IL-15 signaling on the depigmentation lesions in the mouse model would have been to administer an IL-15-specific and/or IL-15R α -specific inhibitor to the mice and evaluate the effect, if any, on the lesions. A POSA also could have administered an IL-2-specific and/or IL-2R α -specific inhibitor to the mice and evaluate the effect, if any, on the lesions. A comparison of the results of these studies to the result of administering ChMBC7 would have provided at least some insight into the effects of IL-15-specific inhibition. Notably absent from the '505 patent is any demonstration of the effects of IL-15-specific inhibition. For example, the '505 patent does not contain even a single example

administering an IL-15 inhibitor. Nor does it contain even a single example of administering an IL-15R α inhibitor. The '505 patent assumes without data that ChMBC7 is even functioning as an IL-15 inhibitor, much less doing so exclusively. But this assumption is not supported by data and is, therefore unwarranted. The ChMBC7 inhibition demonstrated in the '505 patent has not been shown to be representative of IL-15 inhibition or inhibition of IL-15R α .

67. The '505 patent does not demonstrate a class wide effect for vitiligo treatment for IL-15/IL-15R antibodies. For example, administration of a particular IL-15 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 (DeGottardi), Abstract. 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. As some IL-15/IL-15R antibodies were known to inhibit both tissue-resident memory T cell populations and recirculating memory T cells populations and others were not able to inhibit both, a POSA would not conclude that inhibiting CD122 using ChMBC7 is representative of all IL-15/IL15R inhibition pathways.

68. Another way in which the limited disclosure of the '505 patent specification is not representative of the entirety of the claimed genus is because the ChMBC7 antibody is said to bind CD122, whereas the claims extend beyond administering molecules that act directly on IL-15 or IL-15R. As discussed above, dependent claim 2 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 therefore 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.

69. The '505 patent provides no demonstration of using upstream, indirect inhibition of IL-15/IL-15R to treat depigmentation lesions. Because the human immune system is complicated, 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 entirely). For example, a subject with a loss of function of the CD132 (γ subunit) (i.e., upstream inhibition) can experience severe immunodeficiency. EX1014, Abstract. But a more tailored result might be obtained

when administering certain CD132 antibodies. Knocking out CD122 expression entirely using inhibitory nucleic acids could block the IL-2-induced proliferation and maintenance of Treg cells that help to inhibit autoimmune diseases in a manner that administering ChMBC7 might not have done. Administering the ChMBC7 antibody is simply not representative of inhibition using nucleic acids or other means of inhibition that do not directly act on CD122 in the same manner as ChMBC7.

C. The '505 Patent's Experiment Is Not Representative of All CD122 Inhibitors

70. A POSA would not know from the specification of the '505 patent what antibody the applicant used because the '505 patent does not disclose the sequence or structure of the antibody for which it uses the code name ChMBC7. A POSA also would not know which other CD122 antibodies might work similarly to ChMBC7 because the '505 patent does not disclose how ChMBC7 works. The '505 patent merely asserts that ChMBC7 is a rat/mouse chimeric Fc-diminished mouse CD122 antibody. But that description is insufficient to know how ChMBC7 works to inhibit CD122 signaling or to know for what other antibodies ChMBC7 might be a representative species.

71. The '505 patent assumes that ChMBC7 treatment of vitiligo must result from inhibiting IL-15 signaling because IL-2/CD25 knockout mice develop autoimmunity. EX1001, 6:3-13. But some have reported that both IL-15 and IL-2

play a role in the development of forkhead box P3 (FOXP3)+ TReg cells that suppress functions on effector T cells. EX1015, 774. It was also noted that the mechanism underlying the role, if any, of IL-15 in autoimmune disease is poorly understood. EX1015, 775. Because of the complexity and unpredictability of these cytokine pathways at the critical date, a POSA would not have merely accepted the unproven assertion of the '505 patent that ChMBC7's beneficial effect on the CD8⁺ T cell-induced depigmentation lesions was the result of specifically inhibiting IL-15 signaling.

72. The '505 patent does not demonstrate that ChMBC7 is representative of all relevant CD122 inhibitory pathways, whether individually or in combination. Indeed, the '505 patent does not even disclose how ChMBC7 inhibits CD122. For example, though I do not dispute the assertion that ChMBC7 binds to mouse CD122, the '505 publication does not disclose the epitope ChMBC7 binds on mouse CD122. The '505 patent also does not demonstrate whether ChMBC7 is specifically blocking IL-15 binding to CD122 (as opposed to blocking only IL-2 binding or both IL-2 and IL-15 binding). The '505 patent does not evaluate whether ChMBC7 blocks *trans*-presentation binding of IL-15 to CD122, *cis*-presentation of IL-2 or IL-15, or both. The '505 patent does not evaluate whether ChMBC7 block only low-affinity IL-15 or IL-2 binding to CD122, high-affinity binding, or both. Different combinations of CD122 blocking would yield different

biological effects depending on the circumstances involved. ChMBC7 might preferentially inhibit certain kinds of IL-2 signaling or certain kinds of IL-15 signaling depending on how it operates. The '505 patent provides none of the information required by a POSA to reach a conclusion as to how ChMBC7 operates or to begin to extrapolate its data to any other antibodies. Without knowing what interactions ChMBC7 blocked, a POSA could not conclude that ChMBC7 inhibition of mouse CD122 was representative of all inhibition of mouse CD122.

73. 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. For example, it was known that IL-2 and IL-15 both stimulate T lymphocyte proliferation by binding to and inducing signaling by 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 an 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.

74. 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 of a 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. Because of these different ways CD122 signaling can be induced, a single species of CD122 inhibitor is not representative of all forms of CD122 inhibition.

75. Indeed, one patent that was published before the critical date states that 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. It states that some CD122 antibodies inhibit binding of IL-2 *and* IL-15 to a receptor comprising CD122 and CD132 ($\beta\gamma$). EX1011, 2:61-63. It states that other CD122 antibodies inhibit binding of IL-2 to a receptor comprising CD25/CD122/CD132. EX1011, 2:63-65. It states that 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. EX1011, 2:67-3:2, 9:27-38; *See also* EX1012, 481-82.

76. This same patent states that other CD122 antibodies inhibit binding of IL-15 to a receptor comprising CD122, CD132, and IL-15R α . EX1011, 2:67-3:2. It states that other CD122 antibodies might inhibit binding in any or all of these situations. EX1011, 3:2-5. It states that 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. It states that 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, it states that other antibodies, 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.

77. The biological effect of a given antibody will depend 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. EX1011, 10:9-14; EX1014, 6. In cells that primarily express the intermediate affinity receptor $\beta\gamma$ without a high affinity receptor α (e.g., inactive effector T cells), however, it could be harder to inhibit *trans*-presentation of IL-15 than to inhibit soluble IL-2 or IL-15. EX1011, 10:14-17. Because different cells are prone to exhibit different types of receptor presentations, 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*-). Inhibiting CD122 using the single antibody ChMBC7 is thus not representative of the biological effects of these other categories of CD122.

78. Additionally, the '505 patent also does not evaluate whether an Fc-intact version of ChMBC7 would yield the same results as ChMBC7, which is an Fc-diminished antibody. Fc-intact antibodies may further inhibit CD122 signaling by marking CD122-expressing cells for immune attack, 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.

79. Because of the unpredictability in the field and its nascency, each candidate compound would have to be individually made and tested in a particular subject to determine whether it had the desired properties.

80. The specification also does not explain what structural features of small molecules, peptides, antibodies, or nucleic acids are necessary or sufficient to perform the claimed method. The field of treating vitiligo by targeting signaling by cytokines such as IL-15 was unpredictable and at its earliest stages in 2017 and 2018. Indeed, even lab study of inhibition of IL-15 and the IL-15 receptor for treatment of vitiligo was at its early stages. The mechanism underlying IL-15 in autoimmune disease was still poorly understood. EX1015, 775. There was thus no consensus that there was a class wide property of IL-15 inhibitors and IL-15 receptor inhibitors for treating vitiligo.

81. Though POSAs knew that different means of IL-15 or IL-15R inhibition could provide disparate results depending on which ligand or subunit was targeted, where it was targeted, and how it was targeted, a POSA could not predict which structures and which modifications would have what impacts. Moreover, the unpredictability and sometimes contradictory effects of the signaling pathways sharing the IL-15 receptor subunits (e.g., CD122 and CD132) made it impossible to extrapolate the entire claimed genus based on the limited ChMBC7 antibody experiment in the '505 patent. Though Xing previously used a

different mouse CD122 antibody to deplete CD8⁺ effector T cell in the skin to treat autoimmune disease patches in mice, the '505 patent's sparse description of the ChMBC7 antibody made it impossible to reach any conclusion that there was a predictable class wide effect.

D. The '505 Patent's Experiment Is Not Representative of Topical, Subcutaneous, or Microneedle Administration

82. The '505 patent's sole working example only administered ChMBC7 by i.p. and intradermal injection. *See, e.g.*, EX1001, 29:13-40, 33:1-34:45. The patent provides no data for administering ChMBC7 to the epidermis within the lesion topically, by subcutaneous injection, or by microneedle array.

IX. ANALYSIS OF ENABLEMENT

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

83. As I explained above, the nature of the claimed invention is very complex, and the claims are functionally recited, but the state of the art was at a very early stage. Claim 1 recites no structural requirements for the inhibitor. Claim 2 recites the use of any of a small molecule, antibody, peptide, nucleic acid) but otherwise provides no structural limitations. But each of these recited categories is itself a very broad class of inhibitors.

84. Treating vitiligo in subjects ranging from mouse models to actual humans with vitiligo was very complex and unpredictable at the critical date. The idea of using cytokine signaling to treat vitiligo was just at its very earliest of

stages (e.g., mouse models in which vitiligo-like lesions were induced by priming CD8⁺ effector T cells to attack melanocytes and implanting them into the mouse). Moreover, cytokine signaling pathways were complex, biologically unpredictable, and often misunderstood.

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

85. The claims of the '505 patent are much broader than what the applicant can claim to have invented. As explained above, the claims encompass administration to any subject, including humans having natural or spontaneous vitiligo, 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. In contrast, the biological causes of natural or spontaneous vitiligo are more complicated and poorly understood. The '505 patent's cytokine blocking experiments in mice simply are not representative of the effects of cytokine blocking in humans because the immune systems of these different species are not identical. *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.

86. As I also explained above, the claims are very broad because they encompass inhibition of any of the IL-15R α , CD122, or CD132 subunits in a variety of different ways. As I explained 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, inhibiting CD122 can inhibit IL-2 signaling, IL-15 signaling, or both, in a variety of combinations each having different sets of biological consequences. As another example, the CD132 (γ) receptor subunit is shared by at least six different cytokines, and different approaches for binding this target may result in different consequences for these various pathways. As still another example, using an Fc-intact antibody is a more blunt instrument than using an Fc-diminished antibody to block certain binding interactions. These different approaches would be expected to have different results.

87. Moreover, as discussed above, the claims are broad because they do not require that the inhibitor directly, specifically, preferentially, primarily, or exclusively inhibits IL-15 or the IL-15 receptor. They do not even require physical interaction between the inhibitor and target and are even satisfied by upstream inhibition via nucleotide inhibition. Because of the breadth of what is permitted by the claims, the number of potential compounds at issue is so large that I cannot calculate it.

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

88. As I explained above, the '505 patent provides only a single example of treating depigmentation lesions induced in mice by priming CD8⁺ effector T cells to attack melanocytes and implanting them into the mouse. The '505 patent provides no evidence that this data is representative of results in natural or spontaneous vitiligo lesions or of results in animal species different than mice, such as humans).

89. Moreover, the sole inhibition example in the specification is using the ChMBC7 antibody but the specification discloses next to nothing about it other than its code name. Instead, it merely provides an invitation to engage in trial-and-error experimentation.

D. Quantity of Experimentation Necessary and Unpredictability of the Art

90. Because the specification provides no evidence as to what specifically 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. 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. Accordingly, a POSA would have to synthesize and screen each new candidate compound through an iterative, trial-and-error process to determine

whether they work or not. Even testing the candidate compounds identified in the specification would take months,

91. Because the claims encompass compounds that do not specifically or physically interact with the targets, the number of compounds implicated by the claims is even larger. As the claims contain essentially no structural requirements whatsoever, the potential number of distinct candidates is so large as to be incalculable. Though the '505 patent hypothesizes that a few identified compounds may work similarly to ChMBC7, it provides no data to support this hypothesis and does not narrow the claims to focus on tested compounds. Identifying a representative number of inhibitors in each broad category claimed would itself be a sizeable, expensive, and unpredictable research project taking weeks, months, or even years in view of the limited guidance provided by the '505 patent specification. Identifying a representative number of inhibitors across the full scope of the claims would likely occupy the efforts of multiple labs for years.

92. Once that experimentation was through, a POSA would still have to engage in another lengthy trial and error process identify working inhibitors in humans with vitiligo lesions. Natural and spontaneous vitiligo are much more complex than the patent's mouse model. The mouse model is not representative of treating natural vitiligo because the biological mechanisms naturally causing such autoimmune diseases are much more complex than the mouse model lesions. A

POSA would not view the mouse model experiments in the '505 patent as representative of treating vitiligo in a human subject.

E. Relative Skill of those in the Art

93. A POSA's education, 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 broad and functionally defined genus in the claims.

X. ANALYSIS OF OBVIOUSNESS OVER XING AND HARRIS

94. For the detailed reasons discussed in detail below, it is my opinion that each of claims 1-5 of the '505 patent is obvious as a whole. The obviousness of claims 1-5 is exemplified by disclosures in the Xing and Harris references.

95. Harris describes a "mouse model of vitiligo using adoptive transfer of autoreactive melanocyte-specific CD8⁺ T cells." EX1006, 1869. 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. Harris further explains "Points were awarded according to the following scheme: no evidence of depigmentation (0%) received a score of 0, >0–10%=1 point, >10–25%=2 points, >25–75%=3 points, >75–<100%=4 points, 100%=5 points. The

‘vitiligo score’ was the sum of the scores at all four sites, with a maximum score of 20 points.” EX1006, 1870.

96. 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).”).

97. 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).

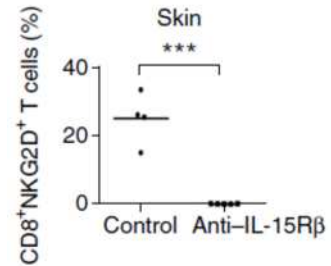
98. Xing discloses that systemic administration of a species of mouse CD122 antibody depletes autoreactive CD8⁺ T cells in the skin and prevents hair loss in a mouse model of alopecia areata.

99. In my opinion, a POSA would have been motivated to evaluate Xing's CD122 antibody (i.e., TM-β1) in the mouse model of vitiligo because Harris expressly suggests that preventing autoreactive CD8⁺ T cell accumulation in the skin has therapeutic potential for treating vitiligo.

100. It is also my opinion that 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 (“cytotoxic CD8⁺ T cells, plays a key role in the destruction of melanocytes in vitiligo (21) and hair loss in alopecia areata”).

101. 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 in part herein), i. Accordingly, it is my opinion that a POSA would

have been motivated to treat the mice lesions with TM- β 1 to reduce the autoreactive Trm cells in the skin that cause the melanocyte destruction in the mouse model.



102. Xing also teaches that subcutaneous injection administration to the epidermis at the lesion of JAK inhibitors, which act downstream of CD122/CD132 signaling, reversed the alopecia areata skin lesions and that this effect persisted for 2-3 months after cessation of treatment. EX1007, 6. Accordingly, it is my opinion that a POSA would have had reason to apply Xing's mouse CD122 antibody to the epidermis of the vitiligo skin lesions in Harris's mouse model, by subcutaneous injection, at a therapeutically effective dose.

103. It is my opinion that a POSA would have considered determining a therapeutically effective dose of Xing's mouse CD122 antibody to be a routine matter and would have involved conducting dose ranging studies known in the art. My opinion in this regard is supported by the '505 patent which states that the dosing "can be determined by standard pharmaceutical procedures" and that the "skilled artisan" will appreciate the factors that may influence the dosage. EX1001, 23:20-25, 23:29-34. The '505 patent also states 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. Accordingly, a POSA thus would have reasonably expected to be able to identify and apply a therapeutically effective amount of TM-β1 for subcutaneous administration to the epidermis within the vitiligo lesions and would have reasonably expected to thereby treat the disease.

104. 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 references such as Cheuk. Specifically, Cheuk teaches 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. Furthermore, Cheuk suggests inhibition of βγ signaling as an attractive target for treating these diseases that were putatively caused by aberrant Trm cells. EX1027, 297.

105. Accordingly, each of claims 1-5 was obvious as is exemplified by the Xing and Cheuk references.

106. Below I provide an element-by-element discussion of exemplary reasons why the combination of Harris and Xing discloses each and every element of claim 1.

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.

107. 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).

108. In my opinion, 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.

109. 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,

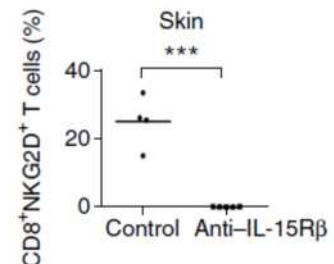


Figure 2h (reproduced in part herein), i. The amount of antibody used in Xing was comparable to that used in the '505 patent (200 μ g, 2x weekly vs. 100 μ g 3x weekly, and the reduction in the population of autoreactive CD8⁺ T cells described by Xing is comparable (if not more dramatic) than that disclosed in the '505 patent with its mouse CD122 antibody ChMBC7. EX1007, 8 (Online Methods); EX1001, 29:22-23, 33:26-35, Figure 6D. Accordingly, it is my opinion that a person of ordinary skill in the art would have expected TM- β 1 administration as described by Xing to achieve similar reductions in depigmentation in the mouse model as provided in the '505 patent with ChMBC7.

110. As I discussed above, a skilled artisan would have considered determining a therapeutically effective dose of Xing's mouse CD122 antibody to be a routine matter. This is confirmed by the '505 patent which discloses 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.

111. My opinion that claim 1 is obvious is based 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.

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.

112. As I 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.

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.

113. 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.

114. Administration of an inhibitor to vitiligo lesions in a manner satisfying claims 3-5 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 method with JAK inhibitors, a POSA would be motivated to use this method or a similar method to locally deliver the active compound to subcutaneous area below the affected skin to so increase the efficiency of the administration. Thus, it would have been obvious to use it to deliver TM- β 1 antibody to vitiligo lesions.

115. Furthermore, persons of ordinary skill in the art knew 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...”).

116. Accordingly, it is also my opinion that it would have been obvious to deliver the TM- β 1 antibody by injection to vitiligo lesions.

117. Accordingly, it is my opinion that each of claims 3-5 as a whole was obvious.

XI. CONCLUDING STATEMENTS

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

119. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: December 22, 2022

By: /Abul Abbas/
Abul Abbas