

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. R. TODD PLOTT

FORTE - EXHIBIT 1004

Forte Biosciences, Inc. v. University of Massachusetts

PGR2023-00014

TABLE OF CONTENTS

I.	QUALIFICATIONS	1
II.	SCOPE OF WORK.....	2
III.	LEGAL STANDARDS	3
IV.	OVERVIEW OF THE '505 PATENT	9
V.	LEVEL OF SKILL IN THE ART	12
VI.	SUMMARY OF OPINIONS.....	13
VII.	AUTOIMMUNE DISEASES OF THE SKIN	15
VIII.	EVALUATION OF WRITTEN DESCRIPTION	22
	A. The '505 Patent's Specification Does Not Convey Invention of Treating Humans Having A Vitiligo Lesion	24
	B. The '505 Patent's Specification Does Not Convey Invention of Treating a Subject Having A Vitiligo Lesion Using Any Inhibitor of IL-15 or IL-15 Receptor	25
	C. The '505 Patent's Specification Does Not Convey Invention of Topical, Subcutaneous, or Microneedle Administration of the Claimed Inhibitor	25
IX.	EVALUATION OF ENABLEMENT	26
X.	CONCLUDING STATEMENTS.....	28

I, R. Todd Plott, 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 a Board-certified Dermatologist serving as the Chief Medical Officer for Epiphany Dermatology.

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

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

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

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

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

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

II. SCOPE OF WORK

9. I am informed 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,” EX1001), entitled “Diagnosis and Treatment of Vitiligo.”

10. I have been retained by Forte Biosciences, Inc. (“Forte”) to offer an expert opinion regarding the validity of claims 1-5 of the ’505 patent assigned to University Of Massachusetts. I have been asked to provide my opinions based on a critical date of April 24, 2017 and April 24, 2018. In connection with this analysis, I have relied on my specialized education, knowledge, training and experience. I also reviewed and considered the ’505 patent and various other documents cited in this declaration. Forte pays \$1,075 per hour for my services. No part of my compensation is dependent on my opinions or on the outcome of this proceeding.

III. LEGAL STANDARDS

11. 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.

12. 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 specification 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.

13. 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 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.

14. 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 patent applicant possessed (i.e., invented) the full scope of the claim (including each individual requirement) at the critical date.

15. 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.

16. 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.

17. 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.

18. 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.

19. 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 which is April 2017 or April 2018 for the '505 patent).

20. 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.

21. 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.

22. I understand that 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.

23. 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

24. I have reviewed the '505 patent in its entirety including the specification and figures. I have observed that the '505 patent uses CD8⁺ T-cell transference to induce depigmentation lesions in mice and then uses agents to deplete CD8⁺ T-cells to reverse the depigmentation. I found data in the patent for only administering a single antibody, called ChMBC7, to this mouse model. *See* EX1001, 33:1-34:45 (Example 5). The antibody is described only with this code name and the explanation that the antibody has “diminished Fc-mediated effector functions” and binds somewhere to the CD122 (β) signaling subunit shared by the IL-2 and IL-15 cytokines. EX1001, 6:3-21, 33:1-34:45. The '505 patent explains that this target is only one of the possible ways to inhibit IL-15 signaling and that inhibiting this target does not specifically inhibit IL-15 signaling because CD122 is a shared receptor with IL-2. EX1001, 7:33-67, 6:3-4. Example 5 does not describe administering ChMBC7 to a vitiligo lesion topically, or using subcutaneous injection or a microneedle array.

25. I reviewed the '505 patent in its entirety and I did not find any other data in the '505 patent purporting to relate to IL-15 inhibition. I did not find any data demonstrating treatment of natural or spontaneous vitiligo in any subject. I did

not find data demonstrating treatment of any species of vitiligo in any species of subject other than the mouse model. For example, I did not find any data in the patent about using IL-15 inhibition in a human having a vitiligo lesion.

26. I understand that the scope of an invention in a patent is defined by the claims of the patent. Claim 1 of the '505 patent, for example, states.

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.

27. From my perspective as a clinician with years of experience of treating vitiligo and identifying subjects in need of treatment, I read the claim as applying not only to the mouse model for which the patent contains an experiment, but also other subjects. These include mice that spontaneously or naturally develop vitiligo, as well as humans and other animals species. The patent specification contains no inhibition data in humans. Instead, it contains generic discussions about studies that might be performed to evaluate efficacy in humans. *E.g.*, EX1001, 23:43-59. Accordingly, I read the claims as extending to any subject who has a vitiligo lesion, regardless of the species of the subject or the type of vitiligo at issue.

28. I understand that claims 2-5 depend from claim 1 and therefore contain all of the requirements of claim 1 in addition to what is recited in the

dependent claims. 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. Claim 3-5 relate to administration by delivery to the “epidermis” of a vitiligo lesion, including by using subcutaneous injection or a “microneedle array.”

29. From the perspective of a clinician, claims 3-4 encompass topical administration to the epidermis within the lesions as well as subcutaneous, intradermal or microneedle array injection administered to the epidermis within the lesion. Claim 5 requires subcutaneous, intradermal or microneedle array injection administered to the epidermis within the lesion. Each of these modes of administration were routine and common in the field of vitiligo treatment at the time. Indeed, before the critical date, where an active agent ameliorated any symptom of vitiligo through systemic injection, local application (through topical application to the epidermis in the lesion or via subcutaneous, intradermal, or microneedle array injection) would have been anticipated by a clinician to increase the therapeutic efficacy profile of the agent by reducing unnecessary systemic side effects and by targeting the therapeutic activity to the tissue of need (at potentially higher doses).

30. Based on the language of the claims, I also understand that the method does not rule out administration of additional active ingredients, such as a JAK

inhibitor. For example, the patent states the method may include “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.

V. LEVEL OF SKILL IN THE ART

31. I have been advised that “a person of ordinary skill in the relevant field” 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.

32. From my perspective as a medical practitioner who treats vitiligo, a person of ordinary skill in the art (POSA) of the '505 patent in April 2017 or April 2018 likely would have had a relevant advanced degree and would have worked together in a team with other qualified individuals with expertise in medicine, immunology, molecular biology, cell biology, microbiology, pathology, biochemistry, peptide chemistry, or related fields. A POSA likely would have had

several years of experience in treating autoimmune diseases or researching cytokine signaling pathways relevant to treating autoimmune diseases. A POSA also could have worked in consultation with a pharmaceutical scientist familiar with formulating drugs for administration.

VI. SUMMARY OF OPINIONS

33. The '505 patent describes using a single mouse CD122 antibody, called ChMBC7, in a CD8⁺-dependent mouse model of autoimmune skin depigmentation lesions to treat the lesions by depleting CD8⁺ T cells. EX1001, 33:1-67.

34. The use of specific CD122 antibodies in a CD8⁺-dependent mouse model of autoimmune skin lesions to treat autoimmune skin lesions by depleting CD8⁺ T cells was known in the art (e.g., EX1007) and also was obvious to a person of ordinary skill in the art (POSA) at the relevant time. Because the transference of melanocyte-targeting CD8⁺ T cells into mice was known to induce depigmentation lesions as a model for vitiligo, and because depleting those CD8⁺ T cells was known to treat depigmentation lesions, (e.g., EX1006) it would have been obvious to use mouse CD122 antibodies that were known to deplete CD8⁺ T cells to deplete the CD8⁺ T cells in the mouse model and thereby treat the depigmentation lesions.

35. From the perspective of a medical practitioner who diagnosed and treated vitiligo at the critical date, the '505 patent specification did not convey to a

POSA that the inventors were in possession of (or invented) at the critical date any method of treating vitiligo other than doing so using the ChMBC7 antibody in the CD8⁺ T cell-dependent mouse model. For example, the specification did not convey possession or invention of treating natural or spontaneous vitiligo in any species of subject, and does not convey possession or invention of any type of vitiligo in a human. From the perspective of a medical practitioner, the specification did not convey possession or invention of treating vitiligo in the entire genus of subjects encompassed by the claims or in a representative set of species across that broad genus. From the perspective of a medical practitioner, the specification also did not convey possession or invention of using any other IL-15 or IL-15 receptor inhibitor other than the ChMBC7 antibody to treat any species of vitiligo.

36. From the perspective of a medical practitioner who diagnosed and treated vitiligo at the critical date, the '505 patent specification would not have enabled a POSA to make and use any method of treating vitiligo other than doing so using the ChMBC7 antibody in the CD8⁺ T cell-dependent mouse model. Treating vitiligo is not a simple or predictable art. Instead, it is complex and unpredictable. Treating it using cytokine inhibition was only at its nascent stages in 2017 or 2018. The claims as issued are very broad, encompassing treating many different kinds of vitiligo in any species of subject. This claim scope encompasses

a diverse collection of diseases sharing a commonality of depigmentation lesions but arising from a variety of known and unknown causes. From the perspective of a medical practitioner, the '505 patent's data from the mouse model would not enable treatment of natural or spontaneous vitiligo, especially not in humans. The only way for a POSA to know which compounds were IL-15 or IL-15 receptor inhibitors and useful for treating vitiligo in a given subject would be to test the specific compounds through a repetitive, trial and error process. Though a POSA would likely have an advanced degree and much expertise, the disclosures of the '505 patent simply would be inadequate to enable a POSA to make and use the full scope of the genus of methods claimed by the '505 patent.

VII. AUTOIMMUNE DISEASES OF THE SKIN

37. Vitiligo, alopecia areata (AA), and psoriasis are all common autoimmune diseases of the skin. EX1008, Abstract, 785. Vitiligo is caused by the immune system destroying pigment-producing cells in the skin called melanocytes. EX1008, 2. When the melanocytes are killed, this causes white depigmentation patches in the skin. EX1008, 785. Treating vitiligo includes ameliorating its symptoms to relieve the suffering of the patient, in whole or in part. Vitiligo has long been treated by administering glucocorticoid steroids and calcineurin inhibitors or other immunosuppressant agents to the lesions to locally suppress the lymphocytes in the epidermis and dermis of the affected area. EX1008, 785.

Vitiligo also was treated using narrow-band UVB light therapy. EX1008, 785. In some cases, vitiligo can be a progressive autoimmune disease where lesions expand or new lesions develop over time. Where vitiligo is actively progressing, one desired therapeutic effect of treatment includes stopping the progression of the disease by stopping new lesions from developing. Optimally, treatment would eliminate existing lesions.

38. In AA, rather than destroying melanocytes, the body's immune system destroys hair follicle cells located deep within the skin. AA is thus characterized by patchy hair loss, primarily on the scalp. EX1008, 785. AA was conventionally treated with intralesional steroid injections or by inducing contact dermatitis. EX1008, 785. Though the origin of both diseases is an autoimmune response, the treatments are different at least because of the location of inflammation within the skin. EX1008, 785. For example, an active ingredient that is effectively administered to treat vitiligo may not penetrate deep enough in some circumstances to effectively treat AA. This is true because melanocyte destruction in vitiligo is primarily located in the epidermis, but inflammation in AA is localized around the hair bulb deep in the dermis. EX1008, 785. Accordingly, steroids are most effective in AA when injected intradermally.

39. Among other things, cytotoxic CD8⁺ T cells were said to play a 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.”). Accordingly, some labs developed mice models for vitiligo in which CD8⁺ T cells were used to induce depigmentation lesions as an imperfect proxy for natural or spontaneous vitiligo. Such experiments were useful for early research but were not predictive of actual therapeutic efficacy in treating natural or spontaneous vitiligo. They certainly were not representative or predictive of the ability to treat vitiligo in humans.

40. As an example of such a mouse model, Harris et al. described a mouse model of vitiligo in which they transferred CD8⁺ T cells that were primed to attack melanocyte cells (which express a melanocyte-specific antigen into host mice to induce depigment lesions. EX1006, Abstract, 1870. Because it was known how these lesions were caused in these mice, it was also predictable how to treat these lesions (i.e., by depleting the attacking CD8⁺ T cells). Harris confirmed that these CD8⁺ T cells accumulated within the skin and correlated with melanocyte destruction. EX1006, 1870-72, Figures.



1b, 3. Agarwal showed that simvastatin administration reduced the CD8⁺ T cells in the skin and reduces depigmentation. EX1023, 1081-1082, Figures 1 & 2. By demonstrating treatment of these lesions in this mouse model, a lab could take the very earliest steps of determining whether a candidate drug had some potential for further investigation for treating natural or spontaneous disease.

41. Mouse models were not exclusively made for vitiligo. For example, a lab that used a mouse model for spontaneous AA observed that affected animals also accumulated 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,...”). They concluded that CD8⁺ T cells were necessary and sufficient to induce the killing of hair follicles associated with alopecia areata in that model (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. Just as with the vitiligo mouse model, in the mouse model of AA, it was said that CD8⁺ T cells drive the disease and that reducing the number of CD8⁺ T cells in the skin is therapeutic for treating the diseases.

42. Vitiligo that occurs in actual patients is not as simple as the mouse model in Harris. In cases where vitiligo develops naturally or spontaneously, such as in humans, depigmentation can derive from different causes. For example, in some families where multi-generational vitiligo is observed, certain genes are believed to correlate with vitiligo diagnosis. In some cases, trauma induces vitiligo via koebnerization, whereas the same trauma would not induce vitiligo in another patient or in the same patient at another location. As another example, segmental vitiligo induced along a dermatome. A POSA would not assume that vitiligo is a monolithic disease with a single, simple cause as straightforward as transferring activated CD8⁺ T cells into the body. Indeed, in my experience, CD8⁺ T cell counts are higher on average in vitiligo lesions but not in every case. Accordingly, from the perspective of a clinician diagnosing and treating vitiligo at the critical

date, the mouse model used in the '505 patent, which is the same model used years earlier in Harris, is not representative or predictive of treatment of natural or spontaneous vitiligo in any subject, much less in a human.

43. Indeed, a POSA would have understood that the immune systems of different animal species are not identical. For example, a CD122 antibody may specifically bind one animal species (e.g., cynomolgus) CD122 but lack significant binding for other species (mouse and dog) CD122. *See, e.g.*, EX1011, 9:14-20. For a POSA reading the specification of the '505 patent, determining whether a hypothesis for treating vitiligo in humans is valid would require trial and error experimentation. Attempting to treat vitiligo with an inhibitor of IL-15 or IL-15 receptor was at its very earliest stages of animal experimentation in 2017 and 2018. There was no expectation or consensus among clinicians that there was a class wide property of IL-15 and IL-15 receptor inhibitors for treating vitiligo.

44. Indeed, because so little was known about the full spectrum of causes of various forms of vitiligo in humans, the treatment of vitiligo at the time could be an unpredictable, trial-and-error exercise even using the proven therapeutics (e.g., hydrocorticoids). Where the first line treatments did not work, it was even more unpredictable whether experimental treatments would be beneficial. From the perspective of a clinician diagnosing and treating vitiligo at the critical date, the '505 patent's mouse data did not convey that the inventors were in possession of or

had invented treating human vitiligo using the ChMBC7 antibody or the broader genera of CD122 inhibition of IL-15 or IL-15 receptor inhibition. To the contrary, these mouse model experiments at most suggested that further research was warranted.

45. In contrast to the ease with which agents known to deplete CD8⁺ T cells could be used to reverse depigmentation lesions induced by CD8⁺ T cell transference in mouse models, developing a new treatment for vitiligo in humans is no easy task. Indeed, several promising treatments for vitiligo were investigated through trial and error process but ultimately failed in humans. For example, TNF- α was believed to be involved in the pathogenesis of vitiligo and AA, however, treating patients with inhibitors of TNF- α did not treat either disease and, in some cases, made symptoms worse. EX1008, 786. These and other failures would make a clinician especially reticent to attribute early mouse model results as representative of treating human subjects. In my opinion, a clinician certainly would not believe on the basis of early mouse model studies using a particular antibody (e.g., ChMBC7) that an entire genus of CD122 inhibition or IL-15 and IL-15R inhibition for treating vitiligo had been invented.

46. Before 2017, there were promising early results for using Janus Kinase (JAK) inhibitors to treat vitiligo and AA lesions in mice and humans. EX1033, Abstract, 1110 (“We report a case of generalized vitiligo for which

treatment with tofacitinib citrate, an oral Janus kinase 1/3 inhibitor, resulted in significant repigmentation.”); EX1007, 1 (“Systemically administered pharmacological inhibitors of Janus kinase (JAK) family protein tyrosine kinases..., eliminated the IFN signature and prevented the development of AA, while topical administration promoted hair regrowth and reversed established disease.”); EX1032, 370 (“[W]e report a case of rapid, but not durable, repigmentation and hair regrowth in a 35-year-old man with concurrent vitiligo and AA during treatment with oral ruxolitinib.”). JAK inhibitors were anti-inflammatory agents. The activity of IL-15 and IL-2 was said to be upstream of the JAK pathways. EX1015, 777. Accordingly, it had been suggested in the literature that at least some inhibitors of IL-15 or IL-2 signaling may be useful for treating these diseases.

VIII. EVALUATION OF WRITTEN DESCRIPTION

47. I have been asked to explain from the perspective of a clinician diagnosing and treating vitiligo at the critical date: (1) the maturity of the field of treating vitiligo by inhibiting cytokine signaling; (2) the existing knowledge in this field; (3) the predictability of using IL-15 or IL-15 receptor inhibition to treat vitiligo; and (4) whether prior art teachings extended the teachings of the ’505 patent from the mouse model described therein to treatment of natural or spontaneous vitiligo in human patients.

48. From the perspective of a clinician, inhibiting cytokine signaling to treat autoimmune diseases such as vitiligo, was nascent, at its very beginnings of experimentation in 2017 and 2018. It was not a mature or well-developed field of treatment. Additionally, as I explained above, the mouse model used for modeling treatment of vitiligo by inhibiting signaling of CD122 was not representative of actually treating vitiligo. There was no consensus among practitioners that there was a class wide property of IL-15 and IL-15 receptor inhibitors for treating vitiligo.

49. From the perspective of the clinician, the state of knowledge about inhibiting cytokine signaling to treat autoimmune diseases such as vitiligo was low and the field itself was highly unpredictable. Medical practitioners would not have extrapolated to using an entire genus of IL-15 and IL-15 receptor inhibitors based on the limited ChMBC7 mouse CD122 antibody experiment in the '505 patent. The only way to know whether there was a class wide effect would be to engage in the cumbersome and iterative, trial-and-error process of testing individual inhibitors.

50. Regarding the extent and content of the prior art, they demonstrate that it was obvious to use a mouse CD122 antibody (e.g., TM- β 1) that was known to deplete CD8⁺ T cells to deplete CD8⁺ T cells in the mouse model to reverse the depigmentation lesions caused by the CD8⁺ T cells. But a POSA would not have

extrapolated this expectation from the mouse model described to treatment of natural or spontaneous vitiligo in human patients.

51. I have also been asked to opine from the perspective of a medical practitioner diagnosing and treating vitiligo at the critical date whether the specification reasonably conveys possession of invention of the genus of methods encompassed by the claims. It does not. Below I discuss several examples of why that is the case. Based on my analysis, it is my opinion from the perspective of a medical practitioner POSA that each of claims 1-5 of the '505 patent lacks written description support in the specification.

A. The '505 Patent's Specification Does Not Convey Invention of Treating Humans Having A Vitiligo Lesion

52. As I explained above, the mouse model used in the '505 patent is a highly simplified model of skin depigmentation lesions having a single, identified cause (CD8⁺ T cells transference) that was both necessary and sufficient for the lesions. When a specific antibody was known to deplete those CD8⁺ T cells, it was predictable that this antibody would reverse the lesions caused by those cells in the mouse model. But this simple mouse model was not representative of the complex causes of natural and spontaneous vitiligo. From the perspective of a clinician who diagnosed and treated vitiligo patients at the critical date, the '505 patent's ChMBC7 mouse experiments would not have conveyed that the inventors were in possession of or had invented any method of treating vitiligo in human patients.

B. The '505 Patent's Specification Does Not Convey Invention of Treating a Subject Having A Vitiligo Lesion Using Any Inhibitor of IL-15 or IL-15 Receptor

53. As I explained above, a POSA also would not have understood from the specification of the '505 patent that the applicant had possession of treating vitiligo by administering any inhibitor of IL-15 or IL-15 receptor. From the perspective of a clinician who has diagnosed and treated vitiligo patients at the critical date, the '505 patent's ChMBC7 mouse experiments would not have conveyed that different CD122 antibodies would necessarily work the same as ChMBC7 in the mouse model (or in any other subject). A POSA certainly would not extrapolate based on the limited data and guidance in the '505 patent that there was a class wide effect for all inhibitors of IL-15 or IL-15 receptor, including small molecules, antibodies, peptides, or inhibiting nucleic acids.

C. The '505 Patent's Specification Does Not Convey Invention of Topical, Subcutaneous, or Microneedle Administration of the Claimed Inhibitor

54. The '505 patent's only inhibitor example attributed to IL-15 or IL-15 receptor inhibition was i.p. (intraperitoneally) or intradermal injection of ChMBC7 mouse CD122 antibody. *See, e.g.*, EX1001, 29:13-40, 33:1-34:45. This example does not include topical administering of ChMBC7 to the epidermis within the lesion. Nor does it use subcutaneous injection or microneedle array.

IX. EVALUATION OF ENABLEMENT

55. I have been asked to explain from the perspective of a medical clinician diagnosing and treating vitiligo at the critical date whether: (1) the claimed invention is complex or simple; (2) whether the field of maturity of treating vitiligo by inhibiting cytokine signaling was nascent or well-established; (3) whether the claims are broad or not; whether the specification provides (4) guidance and (5) working examples for the full scope of the claimed invention; (6) whether using IL-15 or IL-15 receptor inhibition to treat vitiligo was predictable or not; (7) how much experimentation would be required to enable a POSA to make and use the full scope of the invention; and (8) whether the level of skill of the POSA would enable them to overcome any deficiencies in the foregoing.

56. From the perspective of a clinician, inhibiting cytokine signaling to treat autoimmune diseases such as vitiligo was complex and nascent, at its very beginnings of experimentation in 2017 and 2018. It was not a mature or well-developed field of treatment.

57. The claims are very broad at least because they encompass treating natural or spontaneous vitiligo, which are complex diseases, in addition to simply treating the depigmentation lesions in the mouse model described in the '505 patent. They also were broad because they claim all inhibitors of IL-15 or IL-15 receptor, when a POSA would not extrapolate from their mouse study to the entire

class of IL-15/IL-15 receptor inhibition. There was no consensus among practitioners that there was a class wide property of IL-15 and IL-15 receptor inhibitors for treating vitiligo.

58. In contrast to the great breadth of the claims, the specification provides very little guidance to a POSA to make and use the full scope of the invention. Other than inviting the POSA to extrapolate and experiment, the specification provides essentially no guidance to understand what drugs would have the intended effect and which would not. The '505 patent merely identifies the result that is desired (treating vitiligo with IL-15 or IL-15 receptor inhibitors) but does not guide the POSA as to how to practice this invention. Its only working example (a particular mouse CD122 antibody in a contrived mouse model) is simply too narrow for a POSA to extrapolate to the claimed genus.

59. As I explained above, the state of knowledge about inhibiting cytokine signaling to treat autoimmune diseases such as vitiligo was low and the field itself was highly unpredictable. Accordingly, based on the limited information in the '505 patent, the only way to know how to perform the full scope of the claim would require a cumbersome and iterative, trial-and-error process of testing individual inhibitors.

60. Regarding whether the level of skill of the POSA would enable them to overcome any deficiencies in the foregoing, they would not. The research

project the claim is asking people to perform is not something routine from the perspective of a POSA. It certainly would have been obvious before the critical date to use a mouse CD122 antibody (e.g., TM- β 1) that was known to deplete CD8⁺ T cells to deplete CD8⁺ T cells in the mouse model to reverse the depigmentation lesions caused by the CD8⁺ T cells. But a POSA would not have known how to extrapolate this expectation from the mouse model described to the treatment of natural or spontaneous vitiligo in human patients.

61. From the perspective of a clinician diagnosing and treating vitiligo patients at the critical date, the '505 patent's specification would not have enabled a POSA to make and use the claimed invention without requiring significant, expensive, complex, and time-consuming experimentation. Because of the scope of what is claimed and the very limited knowledge contributed by the specification, from the perspective of a clinician, the amount of experimentation required would be extremely burdensome and success would be speculative.

X. CONCLUDING STATEMENTS

62. 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.

63. 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 21, 2022

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