

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. DAMSKY

I declare that all statements made herein of my knowledge are true, that all statements made herein 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.

By: /



Date: October 3, 2023

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GLOSSARY

Abbreviation	Description
'505 patent	U.S. Patent No. 11,278,505
AA	Alopecia areata
AIA	America Invents Act
Board or PTAB	Patent Trial and Appeal Board
CD	Celiac disease
FDA	U.S. Food and Drug Administration
Forte or Petitioner	Forte Biosciences, Inc.
GvHD	Graft versus host disease
JAK-STAT	Janus kinase-signal transducer and activation of transcription
ID	Institution Decision (dated July 3, 2023)
IFN- γ	Interferon- γ
IL-15	Interleukin-15
<i>Italicized and Bold</i>	Emphasis added unless indicated otherwise
NKG2D	Natural Killer Group 2 Member D
PBMC	Peripheral blood mononuclear cell
PMEL	Premelanosome protein
PoC	Proof-of-concept
POSA	person of ordinary skill in the art
Trm	Tissue resident memory T cells

UMass or Patent Owner	University of Massachusetts
USPTO or Office	U.S. Patent and Trademark Office

I, William Damsky, M.D., Ph.D., hereby declare as follows:

I. Introduction

1. I have been retained by Finnegan, Henderson, Farabow, Garrett & Dunner, LLP on behalf of Patent Owner University of Massachusetts as an independent expert in the subject matter of U.S. Patent No. 11,278,505, including the field of vitiligo. I am being compensated for the time I spend on this matter, but no part of my compensation depends on the outcome of this proceeding.

II. Professional Background and Qualifications

2. I am a board-certified dermatologist that evaluates and treats patients with inflammatory skin diseases including vitiligo. Patients suffering from vitiligo are often referred to me by other dermatologists who have been unsuccessful in treating their patients' disease. In fact, it is not uncommon for patients to travel from throughout the continental United States for my evaluation and treatment.

3. I am also a board-certified dermatopathologist that diagnoses vitiligo under the microscope when a skin biopsy is required. As a dermatopathologist, I have developed new methods to look at immune cell polarization in skin by staining T cells for a variety of cytokines. This technique can be useful in diagnosis of a variety of inflammatory conditions and has been considered a significant advance in the field. And so, I am commonly asked to help molecularly profile skin biopsies from patients with inflammatory skin disease in consultation from other institutions.

4. I am also an Assistant Professor of Dermatology and of Pathology at Yale School of Medicine where I train dermatology residents and fellows to both treat patients and develop their research abilities in the field.

5. I graduated with honors from the University of Vermont with a Bachelor of Science in Biology. I then earned both my Ph.D. and Medical Degree from the University of Vermont College of Medicine in 2011 and 2013, respectively.

6. I have a Ph.D. in Cell & Molecular Biology. During my PhD training I focused on developing mouse models of cancer. As part of this work, I intensively studied intracellular signaling pathways including the effects of turning these pathways up and turning the pathways down or off; several of these pathways are regulated by cytokine signaling. I completed five years of postdoctoral training studying basic immunology with world-renowned immunologists. During this time, I focused on the role of cytokine signaling and the JAK-STAT pathway in inflammatory skin diseases and the effect of inhibiting this pathway.

7. I was awarded a Young Investigator Award from both the American Society for Clinical Investigation and the American Academy of Dermatology for this work in inflammatory skin disease, cytokine signaling, and the JAK-STAT pathway. I was also awarded the LEO Foundation award for this work in inflammatory skin disease, cytokine signaling, and the JAK-STAT pathway. I am

also the upcoming recipient of the University of Vermont Alumni Association award (my medical school alma mater) for my leadership in medicine.

8. Each year from 2019 to present, I have been invited to deliver multiple lectures on the use of molecularly targeted therapies in dermatology at the annual American Academy of Dermatology meeting, including in popular plenary sessions. I have also been invited to deliver talks on diagnosis and molecularly targeted treatment of inflammatory skin diseases at the American Society of Dermatopathology, Society for Investigative Dermatology, European Academy of Dermatology and Venerology, World Congress of Dermatology, and Inflammatory Skin Diseases Summit meetings, among others. These lectures often focus on detection and inhibition of cytokine activity, including IL-15 in skin disease.

9. I have published articles in Nature, the New England Journal of Medicine, Lancet, the Journal of the American Medical Association, Cancer Cell, Nature Genetics, Science Translational Medicine, the Journal of Experimental Medicine, the Journal of the American Academy of Dermatology, the Journal of Investigative Dermatology, the British Journal of Dermatology, the Journal of the European Academy of Dermatology and Venerology, the Journal of Cutaneous Pathology, the Journal of Allergy and Clinical Immunology, Pigment Cell & Melanoma Research, and others.

10. I have served as reviewer for the following journals: Nature Communications, Science Immunology, Journal of the American Academy of Dermatology (JAAD), JAAD Case Reports, The Journal of Investigative Dermatology, Journal of the European Academy of Dermatology and Venerology (JEADV), JAMA Dermatology, British Journal of Dermatology, Pediatric Dermatology, Dermatologic Therapy, American Journal of Clinical Dermatology, International Journal of Dermatology, Therapeutic Advances in Musculoskeletal Diseases, Journal of Clinical Medicine, Arthritis Care and Research, British Medical Journal Case Reports, British Journal of Cancer, BMC Medical Genomics, Tumor Biology, Clinical Medicine Insights: Oncology, and Therapeutic Advances in Chronic Diseases. I am usually invited to review articles that deal with molecularly targeted evaluation and therapy of inflammatory skin diseases, including on vitiligo and on IL-15.

11. I have served on the editorial board of the Journal of the American Academy of Dermatology. I founded, organize, and moderate Global Dermatology Talks, a biweekly virtual lecture series in dermatology with the objectives of providing financially equitable and open access to the latest dermatologic information, providing a forum for investigators from traditionally underrepresented geographic locations to share their work, and to support junior investigators sharing their work.

12. I am an active member of the following organizations: American Academy of Dermatology, American Society of Dermatopathology, Society for Investigative Dermatology, and the International Cytokine and Interferon Society.

13. I have been invited to present Grand Rounds at Harvard Medical School, the University of Washington, New York University, University of California Irvine, Yale University, and the Hospital for Special Surgery, among others. I am generally asked to speak about cytokine targeted therapy in dermatology, including targeting of IL-15.

14. I have authored >120 publications including numerous articles on the use of cytokine inhibitors to treat inflammatory skin diseases including vitiligo. I have written some of the most highly cited reviews on the use of cytokine targeted therapy for dermatologic indications (including for the treatment of vitiligo), for example my review article “JAK Inhibitors in Dermatology: the Promise of a New Drug Class” (EX1021) was published in 2017 and has been cited > 400 times. I have an h-index of 38 and an i10-index of 55.

15. My laboratory discovered the utility of IL-15 inhibition in the treatment in an inflammatory skin condition called erythema multiforme (“Treatment of Persistent Erythema Multiforme with Janus Kinase Inhibition and Role of Interferon Gamma and Interleukin 15 in its Pathogenesis”). My laboratory has also described the role of IL-15 in other inflammatory skin diseases and the role its inhibition plays

in response to therapy (in journal articles titled, “Inhibition of type 1 immunity with tofacitinib is associated with improvement in longstanding sarcoidosis,” and “Treatment of granuloma annulare and suppression of proinflammatory cytokine activity with tofacitinib.”).

16. I have served as a principal investigator on 5 past or active clinical trials evaluating cytokine targeted therapies in dermatology. This work includes translational and mechanism-based immunology where the levels and activity of cytokines, including IL-15, are assessed before and during treatment.

17. I have experience in manipulating cytokine signaling and binding affinity through directed evolution or engineering. I led a team at Yale that designed a novel cancer therapy based on engineering of IL-18 to enhance its potency through modification of its ability to bind IL-18 binding protein (BP), an inhibitor of IL-18, while preserving its ability to bind to the IL-18 receptor. This engineered IL-18 compound is currently in clinical trials.

18. A copy of my curriculum vitae is provided as Exhibit 2006.

III. Legal Standards

19. The opinions I express in this declaration involve the application of my technical knowledge and experience to evaluating certain prior art with respect to the '505 patent. In preparing this declaration, certain patent law concepts have been

explained to me by legal counsel, including the legal standard for interpreting claims, as well as those for assessing written description, enablement, and obviousness.

20. I understand that patentability must be analyzed from the perspective of “*a person of ordinary skill in the art*” (“POSA”) in the same field as the challenged patent as of the “effective filing date” of the claims. I understand that a POSA is a hypothetical individual presumed to know the relevant art as of the “effective filing date” of the claims and has the same level of skill as the ordinary practitioner of the art at issue.

21. I understand that the Patent Trial and Appeal Board (“PTAB”) interprets claims based on their ordinary meaning as understood by a POSA at the time of the “effective filing date” in light of the claim language, patent specification, and prosecution history.

22. I understand that the “*effective filing date*” is evaluated on a claim by claim basis and that it is (1) the actual filing date of the patent or the application containing a claim to the invention; or (2) the filing date of the earliest priority application that provides “*written description*” and “*enables*” the subject matter of the claim.

23. I understand that a patent claim is not entitled to a filing date of a priority application as its “effective filing date” if the disclosure in the priority application *lacks written description* support for the claim, that is, if the claim is not

sufficiently supported by the disclosure in the earlier filed application. I understand that the basic inquiry for written description is whether the specification describes the claimed subject matter such that a POSA would understand that the inventor actually invented what is claimed.

24. I understand that a number of factors are to be considered in evaluating the written description requirement, including: (a) the existing knowledge in the particular field; (b) the extent and content of the prior art; (c) the maturity of the science or technology; and (d) the predictability of the aspect at issue. I have been instructed that a sufficient description of a genus requires the disclosure of either a representative number of species or structural features common to the genus so that one of skill in the art can visualize or recognize the members of the genus.

25. I understand that a patent claim also cannot benefit from the filing date of an application if the disclosure in the application *lacks enablement*, that is, if the patent specification does not enable a POSA to make and use the full scope of the claimed subject matter without undue experimentation.

26. I understand that each claim of a patent must be enabled such that, at the effective filing date of the patent, one of ordinary skill in the art could practice the invention without undue experimentation. I understand that the factors I may consider in determining whether a disclosure would require undue experimentation, known as the “*Wands* factors,” include (1) the quantity of experimentation necessary,

(2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. I further understand that enablement is not precluded where a reasonable amount of routine experimentation is required to practice a claimed invention.

27. I understand that a patent claim is unpatentable for *obviousness* if any subject matter within the scope of the claim would have been obvious to a POSA as of the effective filing date. I understand this entails considering (a) the scope and content of the prior art, (b) the differences between the prior art and the claimed invention, (c) the level of ordinary skill in the art, and (d) any secondary considerations of non-obviousness, such as unexpected results, commercial success of products or processes using the invention, long-felt need for the invention, failure of others to make the invention, industry acceptance of the invention, and copying of the invention by others.

28. I further understand that a claim may be obvious based on multiple references combined with one another, as well as based on the knowledge and skill of a POSA. I also understand there must have been a *motivation or other reason* that would have prompted a POSA to combine the features of the prior art. I also understand that a POSA must have reasonably expected that the combination will

work; that is, obviousness requires a “*reasonable expectation of success*” in achieving the claimed subject matter.

IV. Background and State of the Art

A. Standard of Care for Treating Vitiligo

29. Vitiligo is an autoimmune disease of the skin affecting about 1% of the population characterized by depigmentation (complete loss of melanin pigment), resulting in light patches of skin. EX2052 (Frisoli 2017), 1. As of April 2017, treatments in clinical use included topical steroids and calcineurin inhibitors, phototherapy, oral immunosuppressive medications (including prednisone), and surgical procedures. EX2052 (Frisoli 2017), 1-2. Topical steroids and calcineurin inhibitors were used to target localized areas of the skin where the immune infiltrate causing depigmentation was located. EX2052 (Frisoli 2017), 1.

30. For patients with more widespread disease or disease that was active and expanding with the appearance of new lesions, systemic immunosuppressive therapies (e.g., prednisone) were often utilized. Phototherapy was often an adjunctive therapy to these approaches and works by stimulating pigment-producing cells (melanocytes) to repopulate the depigmented skin. EX2052 (Frisoli 2017), 1. Even with these approaches, repigmentation was often unsatisfactory, if it occurred at all.

1. The Focus of Vitiligo Treatment Was on Interferon- γ (IFN- γ)

31. As of 2017, targeted therapies for vitiligo were also emerging. In particular, inhibition of the interferon (IFN)- γ -CXCL10 cytokine-chemokine axis was known to be a key driver of depigmentation in vitiligo and recognized as a promising pathway for development of novel, targeted immunotherapies. EX1020 (Rashighi 2014). A goal for emerging treatment strategies was to reverse established disease through repigmentation, rather than simply halting the depigmentation. EX1020 (Rashighi 2014), 7.

32. Janus kinase (JAK) inhibitors were viewed as a promising therapeutic strategy for and had shown efficacy in vitiligo, as I had explained in 2017. EX1021 (Damsky 2017). For example, oral administration of tofacitinib (a pan-Janus kinase inhibitor [JAK1/3>2]) and ruxolitinib (JAK1/2 inhibitor) showed repigmentation of skin in patients with vitiligo. EX2053 (Rodrigues 2017), 9; EX1021 (Damsky 2017), 5. Treatment with the JAK inhibitor ruxolitinib, however, was found to not be durable, as repigmentation regressed after discontinuing treatment. EX1032 (Harris 2016).

2. Vitiligo Treatment Goals

33. The need for improved vitiligo treatment options was consistent with day-to-day clinical dermatologic practice. Repigmentation in vitiligo, even with the traditional therapies discussed above (as well as JAK inhibitors), was viewed as

tenuous. Ongoing therapy was viewed as necessary to maintain the treatment effect. EX1032 (Harris 2016), Fig. 1 (showing vitiligo recurrence after treatment cessation). In fact, at the time, there were no FDA approved therapies for vitiligo repigmentation. EX2054 (Rodrigues 2017b), 2. The only FDA approved therapy for vitiligo at all was monobenzyl ether of hydroquinone, a depigmenting agent which causes depigmentation of any remaining pigmented skin in patients with widespread vitiligo (and thus evening out the skin tone). EX2054 (Rodrigues 2017b), 10.

34. By April 2017 and even by 2019, there was “no consistent, long-term, durable therapy for vitiligo for all patients....” EX2055 (Relke 2019), 1. As one dermatology expert, Dr. Seneschal, noted, “[m]ost vitiligo experts describe JAK inhibitors as the most promising new treatments in clinical testing for vitiligo. But they’re not a cure: ‘When you stop the drugs, the disease recurs rapidly.’” EX2056 (Dappled Dilemma), 10. Effective and safe long-term treatments that durably reverse vitiligo were thus greatly needed.

35. For instance, numerous groups emphasized these treatment needs for vitiligo. Birlea *et al.* states that the “long-term goal [for vitiligo] is to design pharmacological compounds that can specifically activate melanocyte precursors in the hair follicle in order to obtain faster, better, and durable repigmentation.” EX2057 (Birlea 2017), Abstract. Parsad *et al.* further states that “[t]here are two main goals of any vitiligo treatment; first is to stop the arrest of further depigmentation

and second is to induce repigmentation.... In order to achieve the ultimate goal of total stability and complete repigmentation, there is a need to define a roadmap and roadblocks.” EX2058 (Parsad 2013), 1; EX2055 (Relke 2019), 1 (There was “no consistent, long-term, durable therapy for vitiligo for all patients....”); EX2059 (Lei 2021), 1 (The “overall goal of vitiligo treatment is to halt disease progression, induce repigmentation by stimulating melanocyte differentiation and proliferation, and use maintenance therapy to prevent depigmentation of repigmented lesions.”); EX2060 (Rashighi 2017), 14 (“[T]here are 3 goals to consider during the treatment of vitiligo: 1) reducing melanocyte stress, 2) suppressing autoimmune targeting of melanocytes, and 3) promoting melanocyte regeneration.”).

3. Vitiligo is Distinct From and Treated Differently Than Alopecia Areata

36. Vitiligo and alopecia areata are both autoimmune diseases but are very different in numerous respects that are significant. EX1008 (Harris 2013), 1; EX1019 (Rork), 5.

a) Cellular Differences

37. First, the cell types targeted and effect of the immune response in vitiligo and alopecia areata are fundamentally different.

38. Melanocytes—the target of the immune response in vitiligo—are melanin pigment producing cells that reside along the base of the epidermis (upper layer of the skin). Under normal circumstances, melanocytes are spaced as

individual cells at regular intervals throughout the skin and transfer melanin pigment to other skin cells resulting in skin tone (pigmentation) (**Figure 1**). In vitiligo, the immune response specifically targets melanocytes, destroying them, and resulting in permanent depletion of these melanocytes in the interfollicular epidermis (the epidermis in between hair follicles where they normally reside). EX1020 (Rashighi 2014), 1. Even if the inflammation is removed, the depigmentation persists. EX2061 (Oh 2011), 2; EX2038 (Cavalie 2015), 4.

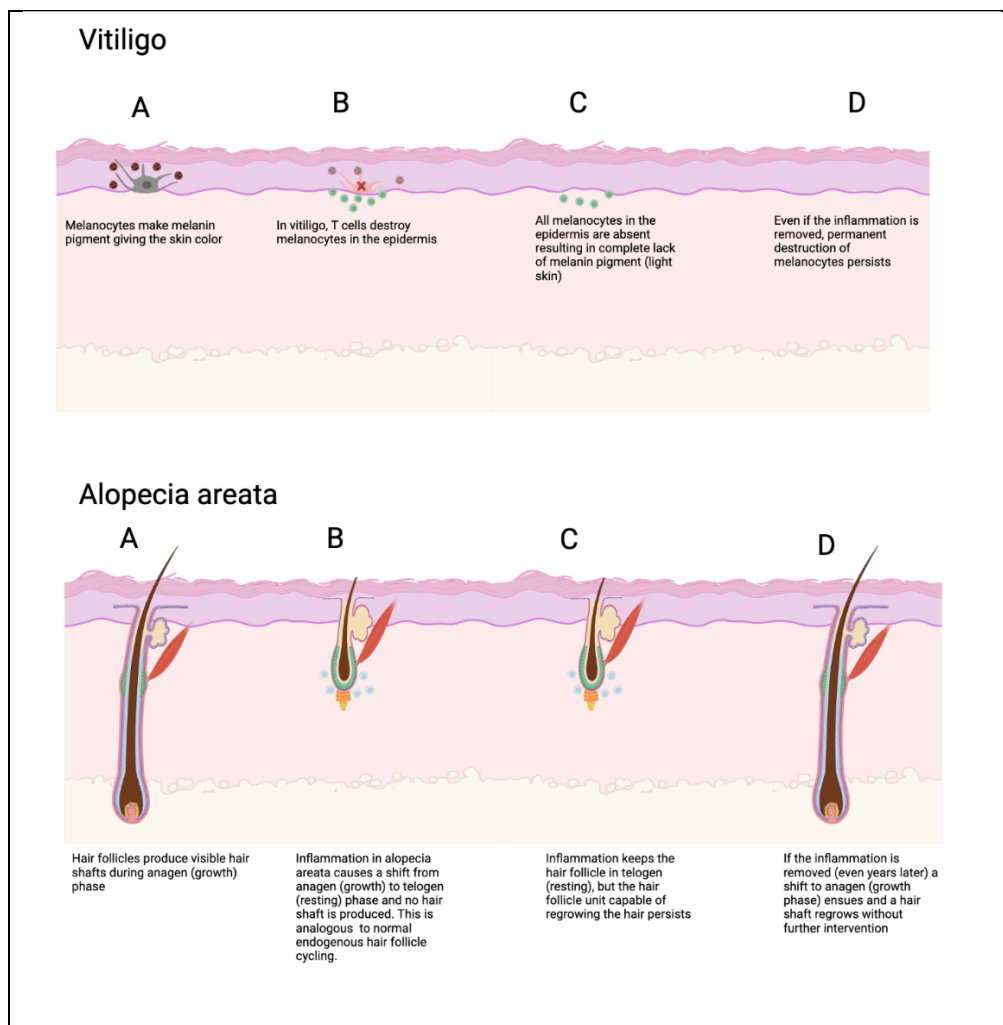


Figure 1. Summary of Vitiligo and Alopecia Areata

39. In alopecia areata, the cells targeted by the immune response are groups of follicular epithelial cells called keratinocytes that exist in the deepest portion of the hair follicle which is termed the “bulb.” Hair follicles are located in the lower “dermis” and/or “subcutaneous fat” layers of the skin whereas melanocytes (targeted in vitiligo) are in the top “epidermis” layer. Bulb keratinocytes can be likened to bricks in a wall and together form the structure of the hair follicle and also produce the hair shaft, which is the visible portion of hair (**Figure 1**). Hair follicles naturally “cycle,” that is there is a period of growth (anagen), shedding (catagen), and rest (telogen). EX2063 (Stenn & Plaus 2001), 3.

40. In contrast to vitiligo, the immune response in alopecia areata does not result in permanent destruction of these hair follicle components. Rather, it induces a shift from anagen (growth) to catagen (shedding) phase and ultimately telogen (resting) phase, which results in the hair shaft falling out, clinically manifesting as alopecia (hair loss). Thus, in contrast to vitiligo where the melanocytes in the epidermis are destroyed, all the components required to regrow the hair are preserved in alopecia areata. If the inflammation is removed (even years later), the hair follicles will re-enter anagen and hair shafts will regrow. EX1019 (Rork 2016). 2; EX2064 (Harries 2010), 3 (“Importantly [in AA], follicles are not destroyed by this inflammatory process, so hair can potentially regrow even after many years.”).

41. Moreover, hair follicles are “immune privileged” sites that protect against alopecia areata. Immune privileged sites use unique regulatory mechanisms to protect themselves from immune responses, including T cell responses.¹ And so, the immune response against hair follicles (immune privileged site) is fundamentally different than the immune response in the epidermis (non-immune privileged site where melanocytes that pigment the skin reside). Mechanisms of maintaining immune privileged status in the hair follicle include reduced MHC class I molecule expression (required for antigen presentation and thus recognition by disease causing T cells), unique properties of T resident memory cell populations (EX2065 (Bertolini 2020), 1, 3 (Table 1)), minimal antigen presenting cells with reduced MHC class II expression (also required for disease causing antigen recognition), and constitutive production of immune suppressive molecules such as TGF- β . EX1031 (Gilhar 2016). The loss of immune privilege that creates a feed forward loop is unique to alopecia areata and is not known to have any known parallel in vitiligo. EX1007 (Xing), 6. Therefore, the effects of modulation of the immune response, even using similar means, could not be reasonably expected to have the equivalent effects in vitiligo (epidermis, non-immune privileged) and alopecia areata (hair follicle, immune privileged).

¹ The eye and the brain are also immune privileged sites, for example.

42. Second, vitiligo is a disease caused by T resident memory (Trm) cells and generally spares the hair follicle. T resident memory cells reside in the interfollicular epidermis (the epidermis in between hair follicles) and are known to be heterogeneous. As *Harris* explains, these T cells recognize a melanocyte-specific differentiation antigen (PMEL) in mouse and human skin that specifically targets the epidermis but spares the hair. EX1006 (Harris), 2, 6. In contrast, a specific subset of T cells that express NKG2D are present in AA and infiltrate the epithelial layers of the hair follicle, which overexpress NKG2D ligands. EX1007 (Xing), 1. As of 2017, a POSA would understand that the properties and cytokine response of the NKG2D T cells in the hair follicle in AA and Trm cells in the interfollicular epidermis in vitiligo were different and not extrapolatable between one another.

43. Moreover, the Trm cells that cause inflammation of the interfollicular epidermis in different diseases are not even the same. For example, the Trm causing disease in vitiligo and psoriasis (another common inflammatory skin disease of the interfollicular epidermis) are also different. EX1027 (Cheuk 2017). CD49a is a cell surface maker that is expressed by some (~15%), but not all T cells in the skin; thus, marking a very specific subset of T resident memory cells in the skin. EX2066 (Purwar 2011). Functionally, CD49a is a molecule that helps T cells cross the dermal-epidermal junction of the interfollicular epidermis, so not only does it serve as a marker of these T resident memory cells, but it is also important in their function.

In 2017, it was established that CD49a was a key marker of disease-causing T resident memory cells in vitiligo, but not in psoriasis (illustrating the complexity in T cell biology even among inflammatory diseases of the interfollicular epidermis, let alone those of the hair follicle). EX1027 (Cheuk). CD49a expression was not known to be present on or associated with the T cells mediating alopecia areata.

44. It was also known at the time that characteristics of T resident memory cells are fundamentally different in the interfollicular epidermis (e.g., vitiligo) compared to the hair follicle (e.g., alopecia areata). EX2067 (Rodriguez 2014), 5, 8; EX2039 (Adachi 2015), 2-3. Thus, with CD49a as a specific-example and general characteristics of T resident memory cells more broadly, it is incorrect to equate the immune response, and thus the effect of perturbing it with a medication, in alopecia areata and vitiligo.

b) Diagnostic Differences

45. These important distinctions between vitiligo and alopecia areata also form a cornerstone in histopathologic diagnosis of these two different disorders. When skin pathologists, including me, examine biopsy tissue to diagnose vitiligo, they look for a complete loss of melanocytes (and of melanin pigment) in the epidermis to confirm the diagnosis. In contrast, when pathologists examine biopsy tissue to diagnose alopecia areata, they expect to see a normal number of hair follicles, with increased numbers of follicles in the catagen and telogen phase, and

in fact, would not diagnose alopecia areata if hair follicles had been completely lost. The melanocytes and melanin pigment are unaffected in alopecia areata.

46. Further, the magnitude of inflammation observed histologically in alopecia areata and vitiligo is very different. In vitiligo, especially in long-standing lesions, minimal inflammation is typically observed. In contrast, alopecia areata is typically highly inflammatory when biopsies of affected tissue are examined.

c) Treatment Differences

47. The distinction between permanent cell depletion in the epidermis (in vitiligo) versus alteration in hair cycling dynamics, but preservation of components required to regrow hair in alopecia areata (e.g., non-permanent) is an important fundamental difference between these diseases. If the immune response in alopecia areata is suppressed, normal hair cycling ensues and spontaneous hair regrowth occurs. Regrowth may occur even after many years, if the inflammation is removed. EX2068 (Liu 2016). In contrast, if the immune response in vitiligo is suppressed, it is too late—the melanocytes in the epidermis have already been destroyed. And so, the clinical expectation when the immune response is removed in these two diseases is fundamentally divergent. That is to say, the effect of turning the immune response off in one disease does not predict what will happen when the immune response is turned off in the other disease.

48. Accordingly, a POSA would not extrapolate treatment of vitiligo with alopecia areata or vice versa. Take the specific example of immunomodulatory therapy with diphenylcyclopropenone (DPCP). DPCP is used treat alopecia areata through its ability to reprogram the immune response and stop destruction of the hair follicle by T cells. In contrast, in vitiligo, this exact same compound can actually *cause* melanocyte death leading to vitiligo. EX2061 (Oh 2011); EX2069 (Nilforoushzadeh 2012). Thus, the same immunomodulatory strategy was known to have *opposite* effects in these two diseases and illustrates the danger of assuming a therapeutic intervention in one will lead to the same result in both diseases.

49. Harris et al. reported another example illustrating the differences in the immunology of alopecia areata and vitiligo for the JAK inhibitor ruxolitinib. EX1032 (Harris 2016). In this report, a patient with both vitiligo and alopecia areata was treated with oral ruxolitinib (a JAK1/2 inhibitor) for 20 weeks. EX1032 (Harris 2016), 1. Improvement in the vitiligo and alopecia areata were both noted on therapy. *Id.* However, “Twelve weeks after discontinuing ruxolitinib, while his hair regrowth was maintained, much of the regained pigment had regressed.” EX1032 (Harris 2016), 1. That is, durable improvement in the alopecia areata was achieved, but durable improvement in the vitiligo (pigment) was not achieved.

50. Another treatment difference is based on mobilizing permanently destroyed melanocytes in vitiligo back into the interfollicular epidermis in order to

achieve repigmentation. In clinical practice, the only established method to reliably do this with medical ultraviolet light treatment, generally narrowband ultraviolet B (nbUVB). Ultraviolet light is thought to coax the melanocyte stem cells out of the hair follicle bulge and back into the intrafollicular epidermis. If the immune response is suppressed, melanocytes may be able to persist in the interfollicular epidermis and repigment the skin and so phototherapy is considered to be an essential supplement to existing medical therapy in optimizing therapeutic response. EX2070 (Liu 2017). In contrast, phototherapy is not required for hair regrowth in alopecia areata.

51. A summary of the differences between vitiligo and alopecia areata is shown in the table below.

Differences	Vitiligo	Alopecia Areata (AA)
Cellular Differences		
Immune response target	Epidermal melanocytes	Bulb keratinocytes
Immune privilege	No known protection	Protective against AA
Mechanism	Autoreactive CD8 ⁺ Trm cells destroy epidermal melanocytes	Autoreactive CD8 ⁺ T cells disrupt hair follicles
Location	Superficial layer of skin	Deeper within the skin, in and around the hair follicle bulb
T cells	PMEL CD8 ⁺ / Trm	CD8 ⁺ NKGD2 ⁺
CD49a	Marker of driver T-cells	No known association
Antigenic drivers	Known (e.g. PMEL)	Not known
Mouse strain used to study	C57bl/6	C3H/HeJ
Diagnostic Differences		
Clinical appearance	Depigmentation of the skin	Non-scarring hair loss

Biopsy features	Loss of melanocytes	Normal number of hair follicles
Lesional features	Minimally inflammatory	Highly inflammatory
Treatment Differences		
Treatment strategies	Repigment skin from a natural reservoir of melanocyte stem cells	Stimulate hair regrowth
Treatment considerations	Age, overall health, where it appears on the body	Age, amount of hair loss, location of hair loss
Treatments	Topical therapies, UVB	Intra-lesional steroids

B. Classic Research Paradigms in Dermatological and Autoimmune Diseases

52. Basic and translational research approaches for discovering and testing new treatment strategies for autoimmune and dermatological conditions, including vitiligo, follow similar principles in many aspects. When investigating a new disease, researchers often begin by collecting samples and comparing diseased tissue from affected patients with normal tissue from unaffected patients. Measuring levels of gene expression, such as cytokine levels, across all detectable expressed genes is the backbone of such investigation. Certain genes, such as cytokines, are typically overexpressed, while other genes may be under expressed when comparing diseased tissue to control normal tissue and begin to give insight into the pathogenic mechanisms of the disease at hand.

53. Once a particular target (or group of targets) is identified, the targets are then functionally evaluated for their potential role in mediating disease. That is to say, just because a particular gene is overexpressed, it does not mean that inhibiting

it will result in improvement of the disease. Strategies to do so include inhibiting the target or sometimes overexpressing the target and measuring the effect on the disease severity. Animal models, particularly mouse models, are fundamental for testing the functional consequences of inhibiting a particular target in this respect. EX2071 (Blumberg 2012), 2-3. Validation of a particular target for autoimmune and skin diseases in mouse models is necessary before moving onto preclinical studies in humans. This is illustrated in the figures below. I understand that Forte's expert, Dr. Abbas, confirmed this classic research approach that still applies today. EX2007 (Abbas Dep. Tr.), 65:21-67:20. By April 2017, this classic research paradigm was reflected in discoveries that RA, psoriasis, celiac disease, and alopecia areata, among others, can each be treated by inhibition of certain cytokine pathways. *See, e.g.*, EX1007 (Xing); EX2012 (Yokoyama); EX2072 (van der Fits 2009); EX1022 (Waldmann 2004).

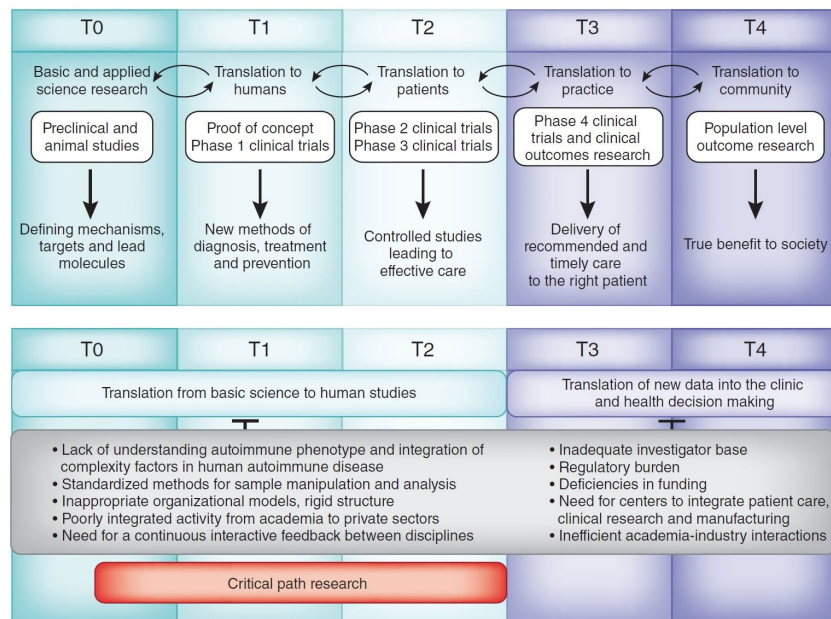


Figure 2. Excerpt of Fig. 2 of EX2071 (Blumberg 2012)

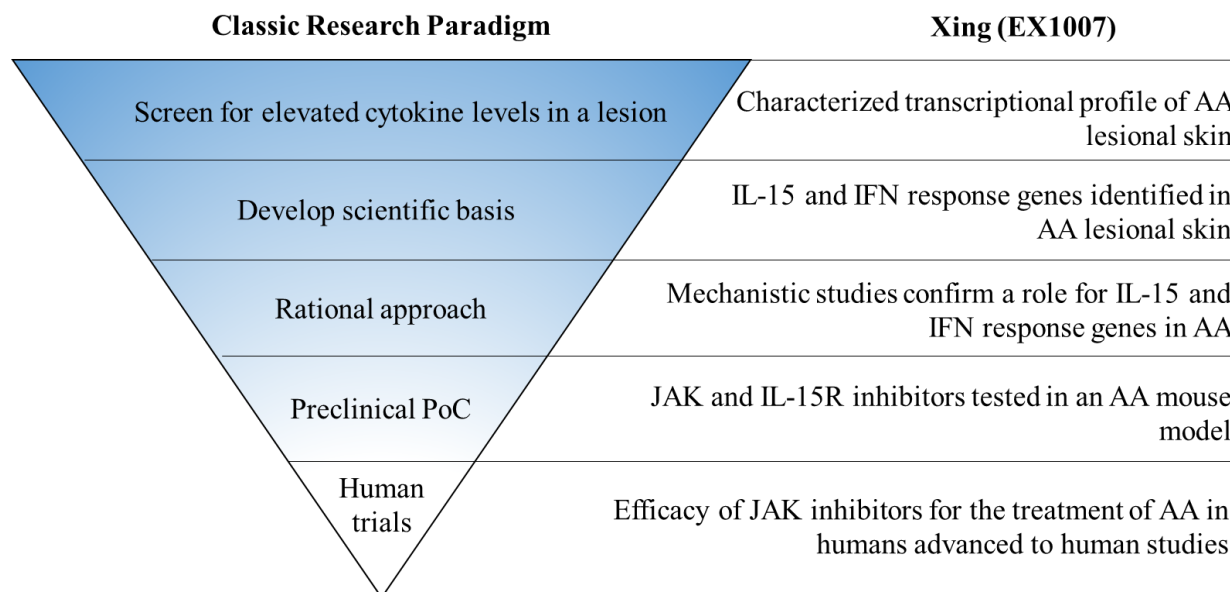
54. For example, as Waldmann explained in 2004, “[o]ur emerging understanding of the IL-15/IL-15R system is providing the scientific basis for the development of rational approaches for the IL-15-targeted treatment of autoimmune diseases, disorders associated with the retrovirus HTLV-1 and also selected leukemias and lymphomas.” EX1022 (Waldmann 2004), 3.

55. Braegelmann further explained that “most targeted drugs aim at specific inflammatory pathways that are typically upregulated in individual diseases or in the respective family of immune type-related disorders.” EX2073 (Braegelmann 2021), 5. There are numerous examples of cytokine blocking therapy that have been used to treat autoimmune and skin conditions in the art, three of which I describe in more detail below.

1. JAK Inhibitors for Alopecia Areata and Other Dermatological Diseases

56. A classic example of blocking cytokine signaling to treat dermatologic diseases is shown by Janus Kinase (JAK) inhibitors. A number of groups identified the Janus-kinase–signal transducer and activator of transcription (JAK-STAT) pathway as drivers of inflammatory dermatoses and potential therapeutic targets. EX1021 (Damsky 2017), 1. For instance, *Xing* used a mouse model (C3H/HeJ) that develops spontaneous AA and characterized the transcription profile of lesional skin biopsies from alopecic mice. EX1007 (Xing), 1-2; EX2035 (Xing Suppl. Data), 17-18. *Xing* observed three gene expression signatures in lesional skin: IFN response genes, several cytotoxic T lymphocyte-specific transcripts, and cytokines and their receptors, including IL-2 and IL-15. EX1007 (Xing), 2; EX2035 (Xing Suppl. Data), 17-19.

57. *Xing* used this information as guide for potential therapeutic strategies. Using the AA mouse model, *Xing* administered blocking antibodies to IL-2, IL-15R β , as well as JAK inhibitors to test whether inhibition of these signaling pathways would be therapeutically effective for AA *in vivo*. EX1007 (Xing), 4-6. *Xing* established that the JAK inhibitor tofacitinib could durably reverse disease and suggested future clinical evaluation of this compound for treating humans with AA, as summarized in the diagram below. EX1007 (Xing), 6.



58. In addition to AA, a 2015 report from Craiglow and King describes the first use of oral tofacitinib (JAK1/2>3 inhibitor) to successfully treat a patient with vitiligo. EX1033 (Craiglow 2015), 2 (“We propose that because interferon gamma signal transduction occurs through JAK1/2, the use of the JAK1/3 inhibitor tofacitinib effectively leads to blockade of interferon gamma signaling and downstream CXCL10 expression, thus giving rise to repigmentation in vitiligo.”) Likewise, *Harris* provides another example of the classic research approach for evaluating JAK inhibitors to block IFN- γ for treating vitiligo. EX1006 (Harris). Prior to April 2017, tofacitinib and other JAK inhibitors were being explored for their efficacy and safety in vitiligo. EX1033 (Craiglow 2015), 1.

59. Preclinical studies have been crucial in establishing the clinical importance of JAK inhibitors to treat AA and vitiligo, among other dermatoses, including atopic dermatitis and psoriasis. EX1021 (Damsky 2017), 6. JAK

inhibitors, including ruxolitinib and others, are now FDA approved for multiple dermatologic indications including AA and vitiligo and several others are in clinical trials. EX1021 (Damsky 2017), 2. A topical JAK inhibitor cream, Opzelura (ruxolitinib 1.5%), is now FDA-approved for treating vitiligo.

2. IL-2 Inhibitors for Immunotherapy

60. Another example is IL-2 and how it was discovered to have dual roles that could be exploited for therapeutic applications in humans. IL-2 was first discovered to play an essential pro-inflammatory role by the promoting the proliferation and activation of T cells. EX2042 (Abbas 2018), 1. However, it was subsequently discovered that IL-2 also had a second and opposing function: maintaining anti-inflammatory regulatory T cells that instead dampen immune responses. EX2042 (Abbas 2018), 1. The mechanisms underlying IL-2 signaling and potential therapeutic strategies have emerged on the foundation of basic research including the use of mouse models. For instance, Dr. Abbas explains that “[d]efinitive proof of the importance of IL-2 and its signaling pathway... has come from mice....” EX2042 (Abbas 2018), 1. Dr. Abbas further states that “our understanding of IL-2 is a remarkable example of how basic research, mostly in experimental models, informs therapeutic strategies in humans.” EX2074 (Abbas 2020), 5; EX2002 (Abbas Textbook), 69-70, 100-103.

61. Given IL-2's prominent alternative role in suppressing immune activation through regulatory T cells (EX2075 (Chinen 2016)), researchers tested the effect of low-dose IL-2 and anti-IL-2 blocking antibodies (e.g., anti-CD25) in treating various autoimmune diseases. EX2074 (Abbas 2020), 5. These agents have been shown effective for controlling inflammatory reactions in these settings. EX2074 (Abbas 2020), 5; EX2076 (van den Hoogen). Researchers are now moving to the next phase of cytokine therapy by testing specific modifications to IL-2 that modify its affinity for its receptors to control autoimmune diseases and for controlling transplanted organ rejection. EX2074 (Abbas 2020), 5.

3. IL-23 and IL-17 Inhibitors for Psoriasis

62. The development of treatment for psoriasis and identification of key molecular targets for treatment in this disease is another prototypical example of the classic research paradigm. Circa 2008, the upregulation of IL-17 and IL-23 cytokines in psoriasis began to crystallize through the analysis of lesional psoriatic skin compared to healthy controls without psoriasis. Specifically, it was noted that levels of IL-17 and IL-23 were upregulated in the skin of patients with psoriasis relative to controls, raising the possibility that targeting these cytokines could be an effective approach to treat this disease. From here, mouse models were employed to functionally evaluate the role of these cytokines in psoriasis (just because they are overexpressed, it does not necessarily mean that inhibiting them will lead to disease

improvement). Multiple mouse models of psoriasis, including induction of psoriasis via injection of IL-23 into the skin of mice, were used to functionally evaluate the role of these cytokines in disease and were key to providing support for further clinical development.

63. Researchers showed using a mouse model of psoriasis that disease development was almost completely blocked when IL-23 or IL-17 signaling was abrogated. EX2072 (van der Fits 2009). This proof of action in mouse models led to clinical testing of both IL-17 and IL-23 inhibitors in psoriasis which were subsequently found to be effective and ultimately led to the FDA approval of 3 current IL-17 and 3 current IL-23 inhibitors.

C. IL-15 Signaling and Its Relevance to Human Disease

64. First identified in 1994, IL-15 is a well-known cytokine involved in the survival and proliferation of CD8⁺ T and natural killer (NK) cells. EX2002 (Abbas Textbook), 106. Since then, the IL-15 signaling mechanisms and potential clinical utility as a therapeutic target have been extensively studied. EX2010 (Fehniger 2001), 1. For instance, IL-15 signaling had been implicated in several autoimmune diseases including rheumatoid arthritis (RA), multiple sclerosis, ulcerative colitis, celiac disease, and psoriasis. EX1022, 1 (Waldmann 2004); EX2010 (Fehniger 2001), 10-13. By 2004, the “emerging understanding of the IL-15/IL-15R system” had provided the “scientific basis for the development of rationale approaches for

the IL-15-targeted treatment of autoimmune diseases.” EX1022 (Waldmann 2004), 3. And by 2008, preclinical data “overwhelmingly suggest[ed]” an important role of IL-15 in cancer therapy in which it was ranked the #1 agent with high potential for use in treating cancer. EX2011 (Cheever 2008), 4.

65. By April 2017, the efficacy of blocking IL-15 signaling for treating certain autoimmune conditions was well established. EX1011 (’830 Pat.), 4:25-34 (disclosing several autoimmune diseases for treatment with anti-CD122 antibodies). For instance, Waldmann described that “therapeutic strategies that inhibit the actions of IL-15 might prove to be of value in the treatment of such T-cell-mediated autoimmune inflammatory diseases,” including RA where a humanized antibody (Mik β 1) specific for IL-15R β (CD122) was in Phase I/II clinical trials. EX1016 (Waldmann 2006), 6; *see also* EX1018 (Villadsen 2003), Abstract (the “results obtained with this IL-15-specific mAb support an important role for IL-15 in the pathogenesis of psoriasis”). It had also been demonstrated that “blockade of IL-15 signaling with an antibody (TM- β 1) that binds to murine CD122 leads to a reversal of autoimmune intestinal damage.” EX2012 (Yokoyama 2009); EX2009 (Forte Interrogatory Response), 6-7. Despite decades of IL-15 research, by April 2017, there was no established connection between blocking IL-15 signaling and the treatment of vitiligo.

1. IL-15 Signaling Biology

66. IL-15 is a part of a family of cytokines that share a common cytokine receptor γ -chain (also known as CD132), further containing a unique β -chain receptor subunit shared with IL-2, termed IL-15R β (also known as IL-2R β or CD122). EX1015 (Jabril 2015), 1; EX1016 (Waldmann 2006), 1. The receptor for IL-15 is heterotrimeric meaning that it also has a third receptor subunit- α IL-15R α (also known as CD215). EX1016 (Waldmann 2006), 1-2; EX1018 (Villadsen 2003), 10 (“[t]he α -chain is crucial for binding of IL-15, whereas the β - and γ - chains are essential for signaling processes”). Despite some shared receptor components, signaling through IL-15 was recognized as having distinct and well-defined functions compared to other cytokines including IL-2. EX1016 (Waldmann 2006), 4.

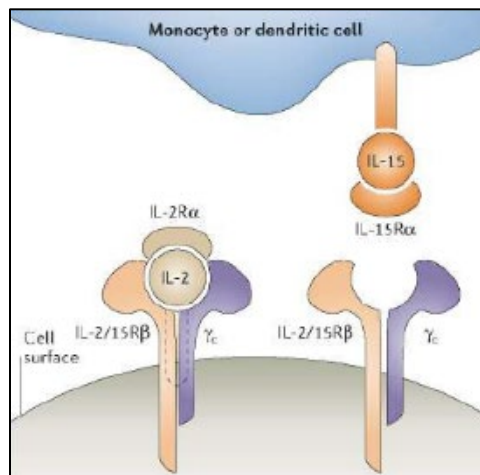


Figure 2. IL-2 and IL-15 signaling (Fig. 2 of EX1016)

67. By 2017, IL-15 was understood to function predominantly via a *trans*-presentation where the IL-15R α subunit presents IL-15 to neighboring cells that express IL-15R β and γ . EX1011 ('830 Pat.), 2:46-48; EX1016 (Waldmann 2006), 3-4, Fig. 2; EX1015 (Jabri 2015), 1-2, Fig. 1; Pet., 11-12 (*trans*-presentation common for IL-15, not IL-2); EX2007 (Abbas Dep. Tr.), 69:21-70:9. In essence, IL-15

signaling is dependent on the combination of the ligand and all three receptor subunits, and blockade of any of these four components (IL-15, IL-15R α , IL-15R β , γ c) inhibits IL-15 signaling. EX2007 (Abbas Dep. Tr.). 70:10-71:5; EX1002, ¶77; EX1011 ('830 Pat.), 22:17-38 (anti-CD122 antibodies suppressed cell growth “mediated by the trans-presentation of IL-15”).

2. IL-15 and IL-15R Inhibition Research

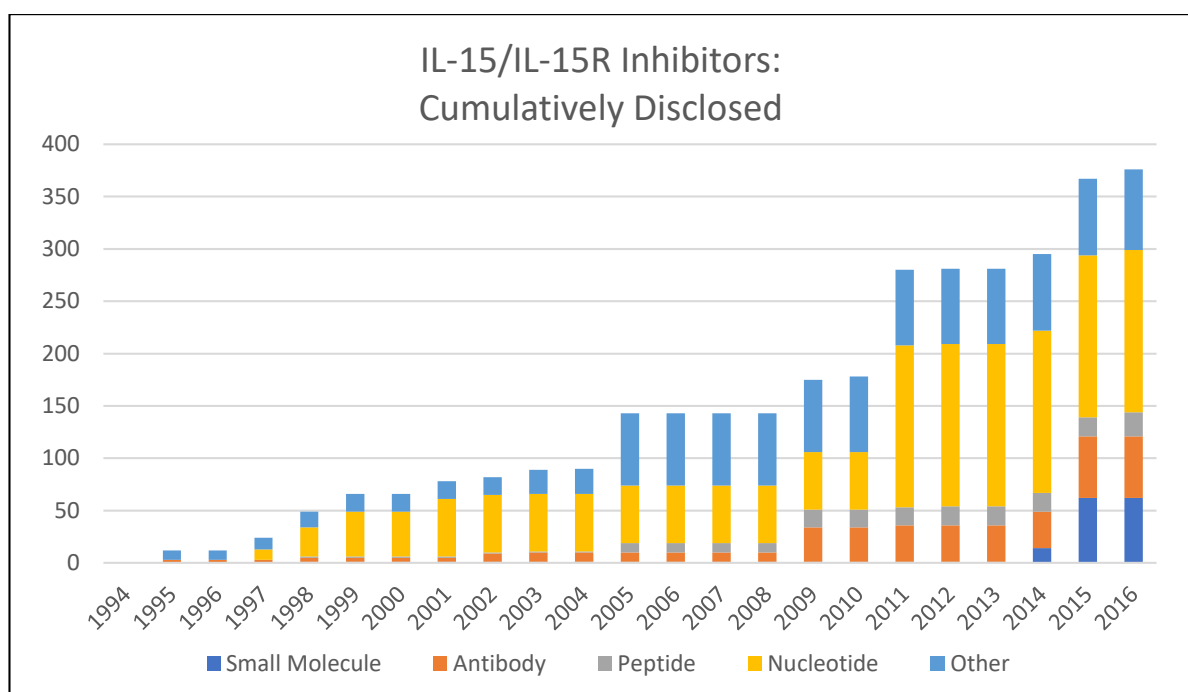
a) Known IL-15 and IL-15R Inhibitors

68. By 2017, interleukin 15 (IL-15) had been well characterized, which was unsurprising since IL-15 was first described in 1994. EX2077 (Grabstein 1994). Even by 2006, a “wide range” of inhibitors of the IL-15/IL-15R system were “readily available and [had] been successfully tested at the in vivo level.” EX2078 (Budagian 2006), 16 (“[A] wide range of well-targeted and relatively selective agonistic or antagonistic pharmacological interventions in IL-15/15R signaling are readily available and have been successfully tested at the in vivo level.”).

69. “The search for small chemical molecules fitting in the IL-15 specific receptor domain was carried out on the basis of the model of the [IL-15R α - IL-15] complex structure, elaborated on the basis of the crystal structure of the complex fragment (2Z3Q code of Protein Data Bank).” EX2013 (WO2014191822), 4.

70. By April 2017, by my estimation over 375 IL-15/IL-15R inhibitors were known (at least 119 cytokine and 257 receptor), including at least 62 small

molecules, 59 antibodies, 23 peptides, 155 nucleotides, and 77 others directed against inhibiting IL-15 and IL-15R. *See Appendix A*; EX2013; EX2014; EX2015; EX2017; EX2019; EX2024; EX2025; EX2027; EX2028; EX2029; EX2030; EX2031; EX2032; EX2049; EX2050; EX2051; EX2085; EX2087; EX2088; EX2102; EX2103; EX2104; EX2105; EX2106; EX2107; EX2108; EX2109; EX2110, EX2111, EX2112; EX2113; EX2114.



71. Exemplary IL-15 and IL-15R inhibitors known in the art were described in the '505 patent. EX1001, 2:49-53; 7:33-40 (citing EX2013 (WO2014191822) (small molecule inhibitor of the IL-15 receptor alpha chain, e.g., benzoic acid derivatives)); 7:40-44 (citing EX2015 (US20160235762)(small molecule inhibitor of IL-15-induced cellular responses, e.g., cefazolin)); 7:44-47

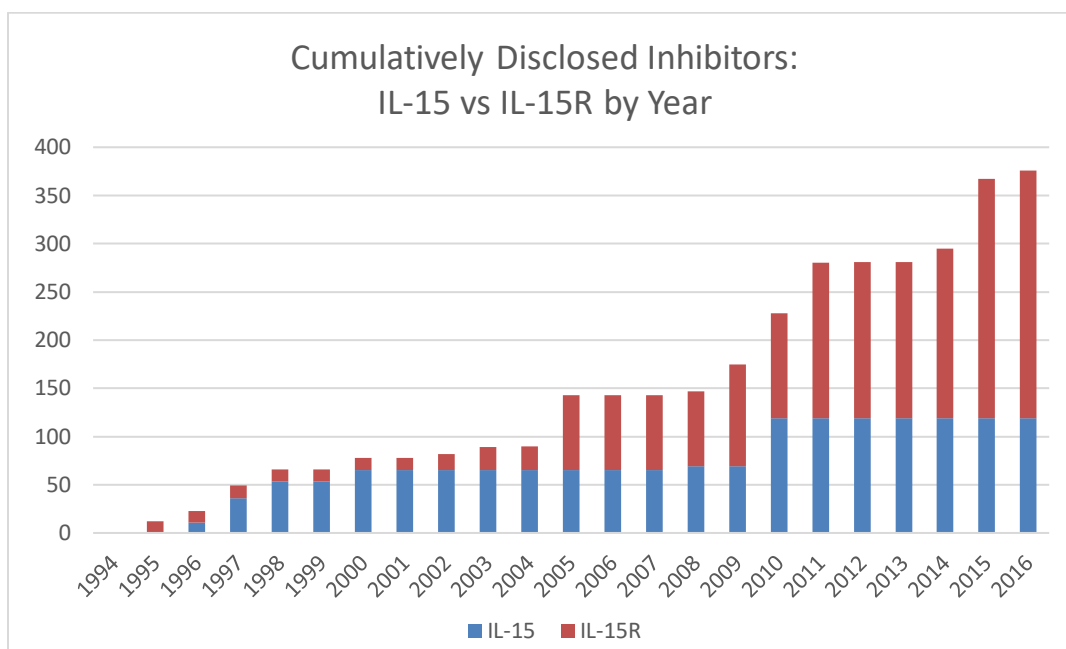
(citing EX2017 (Ruchatz 1998) (soluble IL-15 receptor alpha chain which binds IL-15 and antagonizes the IL-15)); 7:47-51 (citing EX2018 (Kim 1998) (antagonistic mutant IL-15/Fc-gamma 2a fusion protein which competitively inhibits binding of IL-15 to the IL-15 receptor)); 7:51-54 (citing EX2019 (US7,736,638) (peptide that binds the IL-15 receptor alpha chain and inhibits IL-15)); 7:54-58 (citing EX1011 ('830 Pat.) (antibody which specifically binds the IL-2/IL-15 receptor beta subunit)); 7:60-64 (citing EX2022 (Wilson and Arkin 2010)(small molecules (e.g., Ro26-4550, SP4206, ABT-737, Nutlin-2, and compound 3)); 7:64-8:3 (citing EX2021 (Epron 2012) (antibody that specifically binds the IL-15 receptor alpha subunit)); 8:3-6 (citing EX2020 (WO03017935) (antibody that specifically binds the IL-15)); 8:25-37 (nucleic acids that target IL-15, IL-15 receptor alpha subunit, IL-15 receptor beta subunit (CD122), or IL-15 gamma subunit mRNAs). For example, U.S. Patent No. 9,028,830 (EX1011), referenced in the patent (EX1001, 2:49-53)² discloses hundreds of monoclonal antibodies that bind to CD122 for the treatment of “autoimmune disease, such as, for example, sclerosis, rheumatoid arthritis, systemic

² I understand that each reference cited in the '505 patent was incorporated by reference (EX1001, 2:49-53), which I understand from counsel meant that the disclosure of each incorporated reference is considered part of the '505 patent.

lupus erythematosus, diabetes, psoriasis, celiac disease or uveitis,” among others.

EX1011 ('830 Pat.), 4:28-34.

72. Besides the specific inhibitors identified in the '505 patent, hundreds of other inhibitors of IL-15 and IL-15R were known prior to April 2017. For example, US Patent No. 5,844,099, filed in 1993, was the first patent to describe IL-15 soluble receptors that function as antagonists for IL-15. Likewise, US Patent No. 5,591,630, claiming a priority date of 1994, was the first patent claiming antibodies directed against IL-15R. Thus, IL-15 inhibitors were first, followed quickly by IL-15 receptor inhibitors, resulting in a field full of both IL-15 and IL-15R inhibitors.



73. IL-15 signaling and its biologic activity was also well-studied for its ability to turn on immune responses as an anti-cancer therapy. That is, IL-15 or IL-15 derivatives administered to patients with cancer to induce an antitumor immune

response and regression of the tumor. In fact, in a 2008 article IL-15 was ranked #1 of all therapies (cytokine and non-cytokine based) as having the greatest potential for use in cancer immunotherapy by the National Cancer Institute as discussed in an article entitled “Twelve immunotherapy drugs that could cure cancers.” EX2011 (Cheever 2008), Table 1.

74. This known class of inhibitors was taught for use in several different diseases, though it had not been shown to be useful for treating vitiligo. *See, e.g.* EX2015 (US20160235762) (for treatment of rheumatoid arthritis, psoriasis, inflammatory bowel disease, sarcoidosis, T-cell leukemias, or transplant rejection); EX2014 (WO2014191823) (for treatment of rheumatoid arthritis); EX2041 (US20090123414) (for treatment of rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, psoriasis, and Crohn diseases); EX1011 (US9028830) (for treatment of systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, diabetes, psoriasis, celiac disease or uveitis); EX2047 (US5591630) (for treatment of graft rejection); EX2048 (US9428573) (for treatment of cancer or viral infection); EX2049 (US8431524) (for treatment of rheumatoid arthritis and prostate cancer); EX2050 (WO2000002582) (for treatment of inflammatory bowel diseases); EX2051 (US8163879) (for treatment of neoplasia, including cancer, or viral infection).

75. Additional examples of IL-15 and IL-15R inhibitors being taught for therapeutic use are listed in **Appendix A**.

3. Rational Development of IL-15 and IL-15R Inhibitors

76. Based on the well-developed knowledge of both IL-15 and the IL-15 receptor, including their known sequences and crystal structures, rational drug design techniques had also been employed to generate modulators of IL-15 or IL-15R. The structural basis of IL-15-IL-15R signaling, including mechanisms for both cis and trans signaling, was well known. EX1015 (Jabri), Fig 1. Indeed by 2017, cytokine engineering to modulate biologic activity of IL-15 was well-underway and development of multiple IL-15R antagonists and IL-15 “superagonists,” had occurred through engineering efforts that leveraged the well delineated signaling biology of IL-15. EX2018 (Kim 1998); EX2079 (Robinson 2017).

77. The crystal structure of IL-15-IL-15R α had been solved by 2007 implying methods for inhibiting this interaction therapeutically. EX2080 (Chirifu 2007). For example, computer screening of known compounds for IL-15R inhibition is described in US 2016/0235762, filed September 29, 2014, based on knowledge of the IL-15R crystallographic structure.

The identification of a chemical compound which will fit in the IL-15R α receptor was facilitated due to the evaluation of the receptor domain structure, which is of key importance while binding to IL-15 (Wei X. et al., J. Immunol. 167, 277-82 (2001)). The search for small

chemical molecules fitting in the IL-15 specific receptor domain was carried out on the basis of the model of the [IL-15R α -IL-15] complex structure, elaborated on the basis of the crystal structure of the complex fragment (2Z3Q code of Protein Data Bank). ...

US 2016/0235762, ¶[0027].

78. In a 2004 review article entitled “Targeting the interleukin-15/interleukin-15 receptor system in inflammatory autoimmune diseases,” Dr. Waldmann writes a “series of therapeutic agents that inhibit IL-15 action have been introduced, including the soluble IL-15 receptor (IL-15R) α chain, mutant IL-15, and antibodies directed against the IL-15 cytokine and against the IL-2R/IL-15R β subunit used by IL-2 and IL-15.” EX1022 (Waldmann 2004), Abstract. He also explained that “disorders involving interleukin-15 (IL-15) have been shown in such autoimmune diseases as RA, multiple sclerosis, ulcerative colitis, celiac syndrome, psoriasis, sarcoidosis...” and therefore an “array of therapeutic strategies are therefore being developed to target IL-15, its receptor subunit or its signaling elements to provide effective therapy for such autoimmune diseases.” EX1022 (Waldmann 2004), 1.

79. A POSA would have also recognized that, while there were many different possible variants of inhibitors already known, they all worked as intended to block IL-15 signaling and varied only in potency or selectivity. The claimed

inhibitors would still be understood to treat vitiligo based on inhibiting IL-15-mediated signaling, as first described in the '505 patent's disclosure.

4. Inferring Activity from Known Antagonists Was Common, But None Had Been Recognized for Vitiligo

80. By April 2017, it was recognized that inhibiting IL-15 signaling would have beneficial therapeutic effects based on proof-of-concept (PoC) models. For instance, by 2003, IL-15 signaling was recognized as playing “a pivotal role” in disease pathogenesis of RA, and those skilled in the art saw therapeutic potential “in other inflammatory diseases, like psoriasis, which has many similar features.” EX1018, 2. The CD122 inhibitor (Hu-Mik β 1) had moved to Phase I clinical trials for leukemia (EX1012), while the therapeutic potential for other IL-15 signaling inhibitors had expanded to numerous disease indications, including multiple sclerosis, RA, lupus, diabetes, allergies, asthma, and graft versus host disease. EX1011 ('830 Pat.), 4:35-34.

81. Moreover, newly identified inhibitors of IL-15 signaling were understood to have the similar or improved therapeutic effects already established in PoC models based on their common property of inhibiting IL-15 signaling and without the need for specific testing. For example, WO2015/181394 (EX2024) discloses a genus and more than 50 species of small molecule IL-2/IL-15R antagonists without testing in any animal model.

82. The disclosed antagonists were taught to be useful for the treatment of autoimmune diseases because “[c]ytokine targeting is now established as a feasible method for treating such chronic inflammatory diseases and this is best exemplified by the blockade of tumor necrosis factor (TNF) α in rheumatoid arthritis (RA), psoriasis and Crohn’s diseases...” EX2024 (WO2015181394), 1; *see also* EX2026 (Feldmann 2003); EX2025 (WO2015/044761), 1-2 (“Significant involvement of IL-15 in the development of the pathogeneses of the aforementioned afflictions suggests that targeting this cytokine signaling pathway can reduce or eliminate the occurrence of IL-15-related disorders.... always resulted in the alleviation of the disease symptoms.”). EX2027 (WO ’818), 5-6 (“antibodies against human IL-15 and IL-15R have been described that are able to inhibit the biological pathways that are associated with IL-15 mediated signaling”); EX2019 (US 7,736,638), 2:1-6 (“this suggest[s] that IL-15 inhibition could have a therapeutic potential on the disease treatment as well as other auto-immune and inflammatory diseases”); EX2028 (US 10,202,433), 1:18-29 (similar); EX2029 (US 2002/0082230), [0009] (similar).

83. While the existing knowledge of inhibitors of IL-15 and the IL-15 receptor was advanced by 2017, their ability to treat vitiligo had not yet been discovered. This is an important distinction that Forte’s declarants fail to recognize in their declarations.

D. The Asserted Ground 3 References

1. *Harris* (EX1006)

84. *Harris* discloses “an adoptive transfer mouse model of vitiligo using melanocyte-specific CD8⁺ T cells, which recapitulates the human condition by inducing epidermal depigmentation while sparing the hair.” EX1006 (*Harris*), Abstract. *Harris* describes that prior studies support “a direct role for cytotoxic T lymphocytes in melanocyte destruction in human vitiligo.” EX1006 (*Harris*), 1. *Harris* concludes that its mouse model “suggests a therapeutic potential” for the approach of “antibody-mediated neutralization of IFN- γ to prevent CD8⁺ T-cell accumulation in the skin as well as depigmentation.” EX1006 (*Harris*), 2.

85. Those in the art recognized the significance of the *Harris* vitiligo mouse model. EX2033 (*Antonelli* 2015), 2 (*Harris*’s mouse model exhibits a gene expression profile “similar to human vitiligo”); EX1020 (*Rashighi* 2014), 3. Indeed, the *Harris* mouse model was considered superior to existing models of vitiligo, which have black hair but light skin owing to the few melanocytes found in the upper layer of the skin. EX1006 (*Harris*), 1.

86. It was extremely common in the art for researchers to rely on animal models such as the *Harris* mouse model to support the therapeutic use of cytokine inhibitors. For instance, *Hechinger et al.* found a “cytokine that was shown to be critical in a humanized mouse model and that may have relevance for human

GVHD” using the known BALB/c mouse strain. EX1030 (Hechinger), 4; *see also* EX2009 (Forte Interrogatory Response), 11 (relying on BALB/c mice). As I discuss below, Forte likewise relies on the Harris mouse model—including the patent’s own data—to publicize the use of its untested IL-15R inhibitor to treat vitiligo. *See* Section VII.

87. In his declaration, Dr. Abbas asserts that the *Harris* model is not representative of “a complicated autoimmune disease such as vitiligo”. EX1002, ¶36. I disagree. Aside from vague assertions that vitiligo in a human patient is “more complicated” and “immune systems of these different species are not identical,” (EX1002, ¶¶62-63). Dr. Abbas ignores the 10 hallmarks of human vitiligo recapitulated by the models as delineated below.

88. Dr. Abbas also asserts that the *Harris* model is “not representative of natural or spontaneous vitiligo.” EX1002, ¶62. Yet he fails to name a single hallmark of spontaneous or natural vitiligo that is not recapitulated by the model. The *Harris* model was and is viewed as the primary preclinical *in vivo* model which does capture the natural and spontaneous nature of vitiligo. EX2036 (Manga 2016), 3-4; EX2033 (Antonelli 2015), 2; EX2007 (Abbas Dep. Tr.), 52:6-10. For instance, *Harris* shows induction of vitiligo in the mice requires a combination of events, including 1) transfer of melanocyte causing T cells and 2) administering an agent to “boost” the natural T cell response against melanocytes. EX1006 (Harris), 7. Further,

depigmentation generally took 4-5 weeks to occur. EX1006 (Harris), 2. The latency suggests that in vivo proliferation, homing, and differentiation into effector cytotoxic T cells is occurring and mimicking natural vitiligo. This latency and stochasticity in phenotype suggests a natural or spontaneous component to the model, and to me argues that the model does indeed recapitulate natural or spontaneous vitiligo.

89. Summarized below is a list of common features of the *Harris* mouse model and human vitiligo:

- Melanocyte-specific T cells drive skin depigmentation.
- Both involve T cell recognition and reaction against common melanocyte-specific antigens that lead to melanocyte death and depletion in the epidermis.
- Both have T cells that exhibit a T resident memory phenotype and express CD122/IL-15R β .
- IFN- γ is key driver in disease pathogenesis and levels of IFN- γ correlate with depigmentation.
- Both have a predominant site of depigmentation in the interfollicular epidermis.
- Both have pigment retained within the hair follicles of vitiligo lesions.
- Both have a predilection for involvement of acral sites (ears, hands, feet), the face, and genitalia.

- Both involve disease progression from patchy areas of depigmentation to confluent areas of depigmentation, a sign of active vitiligo.
- Both include no visible clinical evidence of skin inflammation.

2. *Xing* (EX1007)

90. *Xing* is unrelated to vitiligo, studying alopecia areata (“AA”), a common autoimmune disease involving a different mechanism that affects the hair follicles, resulting in hair loss. EX1007 (*Xing*), 1. *Xing* used a different mouse model to evaluate the mechanism of AA, finding that a specific subset of CD8⁺ T cells (CD8⁺NKG2D⁺) that infiltrate the hair follicle are also implicated in AA. EX1007 (*Xing*), 1. In particular, *Xing* discloses that transferring cytotoxic CD8⁺ T cells from mice experiencing AA to healthy recipient mice induced AA in the healthy mice. EX1007 (*Xing*), 2.

91. *Xing* further discloses that administering one type of IL-15 receptor antibodies “prevented AA in grafted mice [and] blocked the accumulation of CD8⁺NKG2D⁺ T cells in the skin.” EX1007 (*Xing*), 4. But *Xing* also reported that neither IL-2 nor other types of IL-15 receptor “blocking antibodies given alone were able to reverse established AA.” EX1007 (*Xing*), 4.

92. *Xing* further discloses treating AA by administering other classes of inhibitors, “which signal downstream of a wide range of cell surface receptors.”

EX1007 (Xing), 4-5. For example, both systemically and topically administering JAK inhibitors resulted in hair regrowth in AA mice. EX1007 (Xing), 6.

93. Other studies reflected that reversal of disease with a durable treatment effect was the ultimate, but elusive objective for vitiligo as well as other inflammatory skin diseases. For example, in work by *Xing* and colleagues the effect of treating alopecia areata (AA) with JAK inhibitors and by inhibition of individual cytokines including IL-2 and IL-15R were evaluated in the C3H/HeJ mouse model of alopecia areata. While it was observed that treatment with JAK inhibitors was able to induce durable hair regrowth (persisting 2-3 months after treatment discontinuation), blockade of individual cytokines IL-2 and IL-15R β was not “able to reverse established AA.” EX1007 (Xing), 6. Following this observation, *Xing* only evaluated JAK inhibitors in and only suggested JAK inhibitors for human clinical use. EX1007 (Xing).

V. Level of Ordinary Skill in the Art

94. I agree with Drs. Abbas’s and Plott’s definition of a person of ordinary skill in the art with one modification. EX1002, ¶¶39-40; EX1004, ¶¶31-32. A POSA having experience “researching cytokine signaling pathways” would have been familiar with well-known inhibitors of IL-15 and IL-15R as described in the ’505 patent and recognized in the art as of April 2017. See ¶99, below; **App’x A**.

VI. The '505 Patent

A. The Claims

95. The '505 patent contains one independent and four dependent claims, all directed to methods of treating a subject who has a vitiligo lesion by administering a therapeutically effective amount of an inhibitor of IL-15 or the IL-15 receptor.

96. For instance, independent claim 1 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.

EX1001, 44:13-17.

97. Additionally, dependent claims 2-5 further require that:

- the inhibitor is a small molecular inhibitor, an antibody, a peptide inhibitor, or an inhibitory nucleic acid targeting IL-15 or IL-15R (claim 2);
- the inhibitor is administered to the lesion (claim 3);
- the inhibitor is administered to the epidermis within the lesion (claim 4); and
- the inhibitor is administered by subcutaneous or intradermal administration, or a microneedle array (claim 5).

B. The Specification

98. The '505 patent describes exemplary inhibitors of IL-15 and the IL-15 receptor, which a POSA would have recognized cover a range of chemical structures representative of all classes of inhibitors of IL-15 and IL-15 receptor. The reason that IL-15/IL-15R inhibitors span a diverse range of chemical structures is that the structure of the IL-15-IL-15R complex accommodates such diversity. In particular, a POSA would have understood that the complex could be targeted and IL-15 signaling could be inhibited in a variety of ways, e.g., by targeting any of the alpha, beta, and/or gamma subunits or the IL-15 cytokine itself using a variety of different strategies. A POSA would understand, however, that these IL-15 and IL-15 receptor inhibitors share the common property of inhibiting IL-15 signaling and would be useful for treatment of diseases where the mechanisms had been shown effective, as the '505 patent does for vitiligo.

99. More specifically, the '505 patent discloses inhibitors of IL-15 and IL-15R across nine inhibitor classes (small molecule inhibitors of the IL-15 receptor alpha chain; small molecule inhibitors of IL-15 induced cellular responses; soluble IL-15 receptor alpha chains; IL-15/Fc-gamma 2a fusion proteins; peptide inhibitors of the IL-15 receptor alpha chain; anti-IL-15 antibodies; anti-IL15 receptor antibodies, including those that bind to the IL-2/IL-15 receptor beta, gamma, and alpha subunits; small molecule inhibitors of CD122; and inhibitory nucleic acids

targeting IL-15 or IL-15R) and 20 specific inhibitors across these classes. EX1001, 7:33-40 (citing EX2013 (WO2014191822) (small molecule inhibitor of the IL-15 receptor alpha chain, e.g., benzoic acid derivatives)); 7:40-44 (citing EX2015 (US20160235762) (small molecule inhibitor of IL-15-induced cellular responses, e.g., cefazolin)); 7:44-47 (citing EX2017 (Ruchatz 1998) (soluble IL-15 receptor alpha chain which binds IL-15 and antagonizes the IL-15)); 7:47-51 (citing EX2018 (Kim 1998) (antagonistic mutant IL-15/Fc-gamma 2a fusion protein which competitively inhibits binding of IL-15 to the IL-15 receptor)); 7:51-54 (citing EX2019 (US7,736,638)(peptide that binds the IL-15 receptor alpha chain and inhibits IL-15)); 7:54-58 (citing EX1011 ('830 Pat.) (antibody which specifically binds the IL-2/IL-15 receptor beta subunit)); 7:60-64 (citing EX2022 (Wilson and Arkin 2010) (small molecules (e.g., Ro26-4550, SP4206, ABT-737, Nutlin-2, and compound 3)); 7:64-8:3 (citing EX2021 (Epron 2012) (antibody that specifically binds the IL-15 receptor alpha subunit)); 8:3-6 (citing EX2020 (WO03017935) (antibody that specifically binds the IL-15)); 8:25-37 (nucleic acids that target IL-15, IL-15 receptor alpha subunit, IL-15 receptor beta subunit (CD122), or IL-15 gamma subunit mRNAs). Each of those disclosed inhibitors could be used according to the claimed methods.

100. While IL-15/IL-15R inhibitors were well understood to a POSA, prior to what's disclosed in the '505 patent it was not known that this well-developed class

of inhibitors could also be effectively used to treat subjects with vitiligo lesions. The inventors demonstrated this discovery through six examples, extensive data, and 52 figures. EX1001, 30:53-37:17.

101. For instance, Example 1 discloses the experimental determination that *human* patients with vitiligo lesions have CD8⁺ T cells that show an antigen-specific Trm phenotype and express IL-15R. EX1001, 30:53-31:12, Figs. 1A-1E. There, the inventors described the results of biopsies from vitiligo patients having both active and stable disease, identifying melanocyte antigen-specific T cells in their blood and skin fluid. EX1001, 30:53-31:12, Figs. 1A-1E. The inventors describe finding increased numbers of melanocyte antigen-specific Trm cells in lesional fluid that express high levels of IL-15R β /CD122 in patients with both active and stable vitiligo, while melanocyte antigen specific T cells were not found in the skin of healthy controls without vitiligo. The level of IL-15R β /CD122 expression was particularly high on the melanocyte-specific T cells compared to other T cells. Further the levels of IL-15R α was higher on keratinocytes in lesional vitiligo. EX1001, 30:53-31:12, Figs. 1A-1E. A POSA, reading Example 1, would understand the role of IL-15 and its receptor subunits in the development of vitiligo lesions.

102. Examples 2, 3, and 4 establish the functional role of Trm in vitiligo using a reliable *in vivo* mouse model of vitiligo previously described by *Harris* (EX1006). EX1001, 5:40-47, 28:55-57, 31:14-32:67; EX1006 (Harris).

103. Example 2 demonstrates that only melanocyte-specific T cells establish themselves as Trm in the epidermis where autoantigen is expressed compared to control cells which do not. EX1001, 3:22-31, 31:14-43, Figs. 2A-2G (Fig. 2G below showing that only T cells, called PMEL, establish long-lived epidermal cells compared to the foreign OVA antigen OT-1). Example 3 reports that self-reactive Trm in vitiligo maintain IFN- γ expression up to 30 weeks post-vitiligo induction, indicating that “Trm are long-lived and maintain effector function for long periods.” EX1001, 31:45-32:35, Figs. 3A-D. Example 4 further reports that inhibiting the egress and recirculation of T cells from the lymph nodes using the S1P1 inhibitor FTY720 results in “rapid reversal of disease,” indicating that “recirculating memory T cells contribute[s] to sustained melanocyte killing during the maintenance of vitiligo....” EX1001, 3:46-56, 32:37-67, Figs. 4A-4G (Fig. 4E below showing an increase in pigmentation with FTY720 compared to the PBS vehicle control).

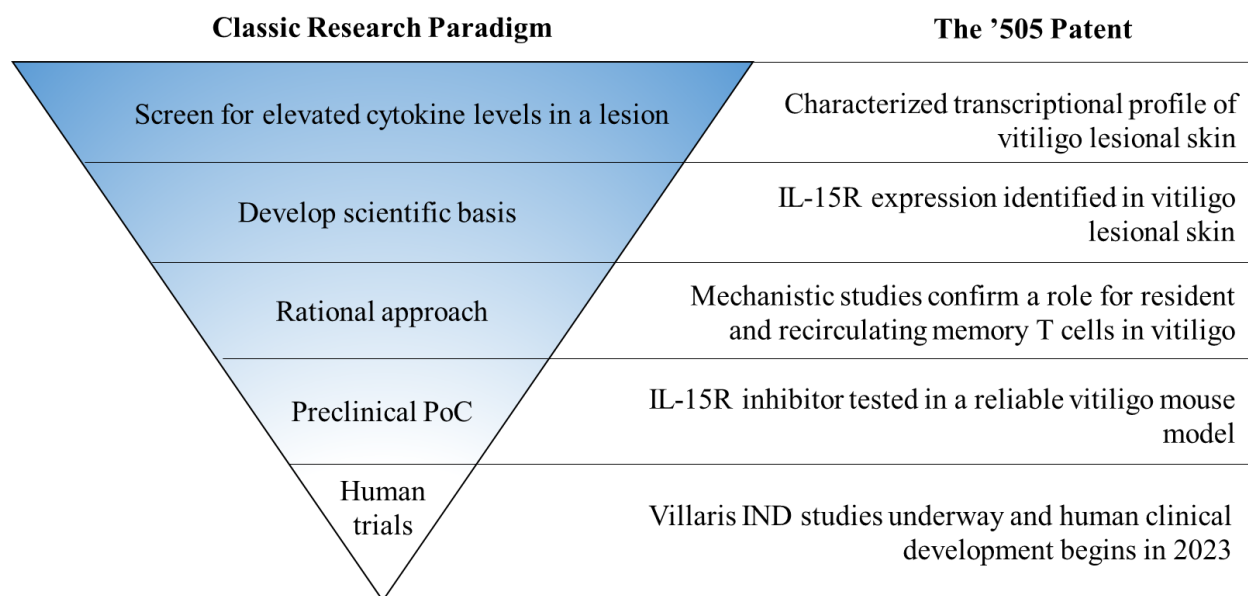
104. Further, Example 5 describes in vivo efficacy using the Harris 2012 (EX1006) mouse model for the treatment of vitiligo. EX1001, 33:1-34:45. The inventors report the finding that blocking the IL-15 signaling pathway with an anti-mouse IL-15R β /CD122 antibody (a commercial antibody known as ChMBC7) significantly repigments mice after either 2, 4 or 8 weeks of treatment compared to controls and further provides a durable vitiligo treatment effect (*e.g.*, repigmentation persisted even after treatment was stopped). EX1001, 33:1-34:45, Figs. 5, 6A-6I.

The '505 patent describes the finding that as opposed to IL-15 inhibitors, previous non-IL-15/IL-15R “[e]xisting treatments for vitiligo are not durable, as the disease returns at the site of treatment after discontinuation.” EX1001, 33:5-6. After administering the IL-15R β /CD122 antibody for 2 or 4 weeks and then stopping treatment, repigmentation was maintained even after treatment was stopped for 8-10 weeks. EX1001, 33:36-34:45, Figs. 7A-7C, 8A-8E. A POSA, reading Example 5, would understand the significance of blocking the IL-15 pathway, and that this mechanism offered greater success at treating vitiligo than existing vitiligo treatments that targeted different mechanisms.

105. Lastly, Example 6 describes a method to sample lesional skin and reliably capture markers of inflammation to assess disease activity and offer a new, targeted treatment strategy for the treatment of human vitiligo. EX1001, 34:47-37:18, Figs. 9A-9F (extraction of blister fluid), 10A-10C (detection of lesional skin), 11A-11C (detection of active lesional skin), 12A-12B (measuring of gene expression).

106. Taken together, these examples teach a POSA (i) the IL-15 / IL-15R pathway is critical in the development of human vitiligo lesions, and (ii) that by blocking the IL-15 pathway, IL-15 and IL-15R inhibitors, exemplified with an inhibitor of IL-15R, provide therapeutically effective treatment of vitiligo lesions. *See e.g.*, EX1001, 6:16-21 (“targeting IL-15 signaling through antibody treatment

even after the generation of Trm in the tissue was effective at clearing these cells from the epidermis, indicating that IL-15 signaling is required for maintenance of these cells”); *id.*, 33:64-66 (data “suggests that targeting IL-15 in the skin in vitiligo, unlike existing therapies, could provide a durable treatment option”). This classic research approach is summarized in the diagram below.³



VII. Forte’s Reliance on Proof-of-Concept Studies and Results from the ‘505 Patent

107. I understand that Forte is developing “FB-102,” an anti-CD122 inhibitor in the same class of inhibitors as the ChMB7 antibody disclosed in the ‘505

³ Clinical development is expected for Auremolimab, an anti-CD122 antibody developed by Villarix and acquired by Incyte, as a treatment of vitiligo. EX2101 (Incyte Press Release).

patent. Forte's press releases and investor presentations relied on established proof of concept studies for extrapolating therapeutic efficacy of its anti-CD122 antibody tested in GvHD to other autoimmune diseases, such as vitiligo, celiac disease, alopecia areata, Type I diabetes, and solid organ transplant. EX2003 (Press Release), 1 ("Published preclinical PoC data also support the therapeutic potential of anti-CD122 in multiple autoimmune diseases including vitiligo, celiac disease, alopecia areata, Type 1 diabetes, and solid organ transplant."); EX2004 (Investor Presentation), 26 ("Mechanism of FB-102 also shows activity in vitiligo and alopecia areata"), 33.

108. I also considered Forte's interrogatory response (EX1036). EX2009. As reflected in Forte's responses, Forte relies on the same approach for inferring therapeutic activity for FB-102 based on knowing it to be an IL-15 signaling inhibitor and knowing from published proof of concept studies that inhibition of IL-15 signaling has therapeutic activity for vitiligo. *See* Sections IV.C.3. and IV.C.4. For example, it relies on EX2046 (Richmond 2018), EX2012 (Yoyokama), EX1007 (Xing), and other animal models for vitiligo, celiac disease, alopecia areata, and other diseases.

109. Particularly relevant here is Forte's reliance on the Richmond 2018 reference, which republished the '505 patent's data, to attribute vitiligo therapeutic activity to FB-102, as I will now further explain. Specifically, I understand that the

Richmond 2018 publication relied upon by Forte corresponds to the invention claimed in the '505 patent and discloses its same mouse model data with ChMB7, consistent with common practice for scientific researchers to file a patent application and then publish those results in a scientific publication.⁴

110. Forte's reliance on the *Harris* vitiligo model and results with ChMBC7 is *inconsistent* with the positions of Drs. Abbas and Plott that the patent does not describe or enable the use of other inhibitors or the treatment of humans. *See* EX2009 (Forte Interrogatory Response) (relying on Richmond 2018 mouse model also described in the '505 patent to understand FB-102 would be effective in treating vitiligo). And, while I recognize that Forte's statements reflecting the understanding that cytokine signaling inhibitors share common therapeutic utility based on their common mechanisms of inhibiting cytokine signaling are not prior art, they are reflective of the understanding of a POSA which had not changed in this regard from 2017 to 2018 or to the present.

VIII. Ground 1: The Disclosure in the '505 Patent Describes the Claimed Invention

111. In my opinion, the '505 patent specification, when read by a POSA, describes to those skilled in the art that the inventors were in possession of the

⁴ Here, the provisional application for the '505 patent was filed on April 24, 2017, and Richmond 2018 published the following year in 2018.

claimed invention. At the time of invention in 2017, a POSA would have understood from reading the specification that the inventors discovered the class-wide effect of IL-15 signaling inhibition for the treatment of vitiligo. Petitioner and its declarants Drs. Abbas and Plott contend that the '505 patent fails to describe the full scope of the claimed method of treating vitiligo by administering any inhibitor of IL-15 or the IL-15 receptor. Pet., 25; EX1004, ¶53; EX1002, ¶61. For the reasons discussed below, I disagree. There is sufficient support for the methods recited in claims 1-5, both with respect to the individual claim elements as well as the full scope of the claims as a whole.

112. Forte correctly recognizes “the inventors [of the '505 patent] were not the first to use a mouse CD122 antibody to deplete CD8⁺ effector T cell in the skin to treat autoimmune disease patches in mice.” A POSA would be well aware that, as I describe above (IV.C.2.), hundreds of IL-15 signaling inhibitors were known and studied for the treatment of other diseases, including the treatment of autoimmune disease in mice. This is important background to the discovery reported in the '505 patent by the inventors, which was the first to demonstrate the use of this known class of existing compounds was effective to treat vitiligo. That is, the key feature of the claimed method that differentiates it from the prior art is the new application of IL-15 signaling inhibitors—for the treatment of vitiligo; a POSA would appreciate

the rest of the information necessary to understand the claimed method was known in the art and that the '505 patent shows possession of its full scope.

A. The '505 Patent Describes Inhibitors of IL-15 and the IL-15 Receptor

1. Inhibitors of IL-15 and the IL-15 Receptor Were Known, Including Their Structure/Function Correlation

113. By 2017, as reported in the art and based on my personal experience at the time, the IL-15 signaling pathway had been extensively studied and was a well-developed research area since its discovery in 1994. EX2082 (Mishra 2014), 1. EX2021 (Epron 2012), 7 (“IL-15 has been extensively studied....”); EX2083 (Lu 2002), 1 (“Among the various factors that seem to control the expansion and viability of antigen-activated T lymphocytes, IL-2 and IL-15 are perhaps the most extensively studied.”).

114. Because of this extensive research surrounding the IL-15 signaling pathway, a POSA would have been well aware that “Interleukin-15 (IL-15) is a pro-inflammatory cytokine involved in the development, survival, proliferation and activation of multiple lymphocyte lineages... utilize[ing] three distinct receptor chains in at least two different combinations to signal and exert its effects on the immune system.” EX2082 (Mishra 2014), 1.

115. A POSA would have understood “[t]he binding of IL-15 to its receptor complex activates an ‘immune-enhancing’ signaling cascade in natural killer cells and subsets of T cells.” EX2082 (Mishra 2014), 1.

116. It was also understood that four structural components were involved in IL-15 signal activation: the IL-15 cytokine, IL-15R α (CD215), IL-15R β (CD122), and γ c (CD132). EX1015, 2 (“Once IL-15 is secreted out of the cell, it binds to either the membrane bound or the soluble form of IL-15R α and is presented in trans to and bound by the IL-2R $\beta\gamma$ complex expressed on nearby effector cells in order to initiate cellular activation”). As depicted below, in the dominant *trans*-presentation the IL-15 cytokine is presented with high-affinity by the IL-15R α receptor to the dimeric IL-15R $\beta\gamma$. Consistent with Dr. Abbas’s explanation, a POSA would have understood that because all four elements are required for IL-15 signaling, IL-15 signaling would be inhibited by blocking any one of the (1) IL-15 cytokine, (2) the IL-15R α receptor, (3) the IL-15R β receptor, or (4) the gamma chain (γ c) receptor. EX2007 (Abbas Dep. Tr.), 70:6-71:5.

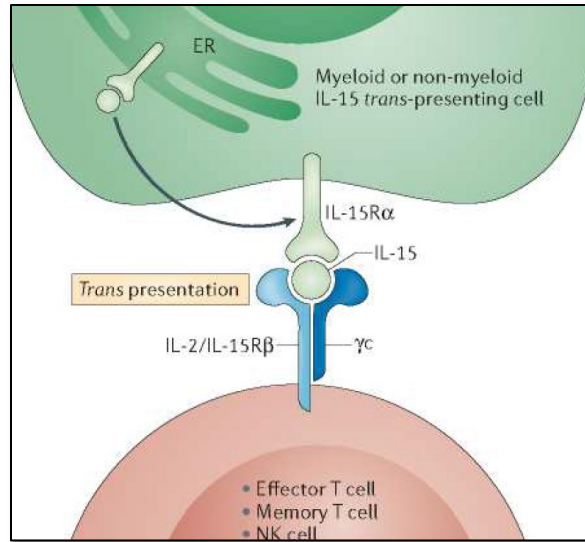


Figure 3. Excerpt of Fig. 1 of Jabri (EX1015)

117. A POSA would also appreciate that while *trans*-presentation is the dominant IL-15 signaling pathway *in vivo*, the same structural components are involved in less common *cis*-presentation (lower affinity), which involves binding of IL-15 to IL-15Rβ (CD122) and γc (CD132) on the target cell with variable involvement of IL-15Rα (CD215), also on the target cell. EX1015 (Jabri 2015), 1-2, Fig. 1 (“the main mechanism by which IL-15 interacts with its receptor *in vivo* is trans-presentation”); EX1001, 31:6-10; EX2007 (Abbas Dep. Tr.), 69:9-71:5; EX1016 (Waldmann 2006), 3-4, Fig. 2. Thus, a POSA would have understood that just like *trans*-presentation, for *cis*-presentation, inhibition of any one of IL-15 cytokine, IL-15Rα (CD215), IL-15Rβ (CD122), and γc (CD132) would still inhibit the IL-15 signaling pathway.

118. The class of IL-15 and IL-15 receptor inhibitors was well known. *See* Section IV.D.2.a), above. Some of the first recognized inhibitors of IL-15 were described in 1995. *See* Section IV.C.2, above. In the over two decades since, hundreds of other inhibitors were characterized and studied for diseases involving the IL-15 signaling pathway. *See* **Appendix A** (IL-15/IL-15R chart).

119. The inventors of the '505 patent recognized the well-developed class of IL-15 and IL-15 receptor inhibitors, describing nine different classes of inhibitors with an exemplary subset of 20 exemplary compounds. EX1001, 2:49-53; 7:33-40 (citing EX2013 (WO2014191822) (small molecule inhibitor of the IL-15 receptor alpha chain, e.g., benzoic acid derivatives)); 7:40-44 (citing EX2015 (US20160235762) (small molecule inhibitor of IL-15-induced cellular responses, e.g., cefazolin)); 7:44-47 (citing EX2017 (Ruchatz 1998) (soluble IL-15 receptor alpha chain which binds IL-15 and antagonizes the IL-15)); 7:47-51 (citing EX2018 (Kim 1998) (antagonistic mutant IL-15/Fc-gamma 2a fusion protein which competitively inhibits binding of IL-15 to the IL-15 receptor)); 7:51-54 (citing EX2019 (US7,736,638) (peptide that binds the IL-15 receptor alpha chain and inhibits IL-15)); 7:54-58 (citing EX1011 (U.S. Pat. No. 9,028,830) (antibody which specifically binds the IL-2/IL-15 receptor beta subunit)); 7:60-64 (citing EX2022 (Wilson and Arkin 2010) (small molecules (e.g., Ro26-4550, SP4206, ABT-737, Nutlin-2, and compound 3)); 7:64-8:3 (citing EX2021 (Epron 2012) (antibody that

specifically binds the IL-15 receptor alpha subunit)); 8:3-6 (citing EX2020 (WO03017935) (antibody that specifically binds the IL-15)); 8:25-37 (nucleic acids that target IL-15, IL-15 receptor alpha subunit, IL-15 receptor beta subunit (CD122), or IL-15 gamma subunit mRNAs). Especially with the background knowledge discussed above regarding the use of IL-15 signaling inhibition to treat other diseases (*see* Section IV.C., above), a POSA reading this diverse sampling of exemplary IL-15 and IL-15 receptor inhibitors would have understood the inventors were describing a class-wide effect that would extend to the hundreds of other known inhibitors. *See* **Appendix A** (IL-15/IL-15R chart).

120. With respect to antibodies that block IL-15 signaling, it would have made no difference to a POSA whether an “Fc-intact version” of the ChMBC7 antibody was tested in the ’505 patent (EX1002, ¶78), because both Fc-intact and Fc-diminished antibodies were known and routinely used in the art as of 2017. *See, e.g.,* EX1011 (’830 Pat.), 20:53-21:52 (describing generation of CD122-Fc antibodies which a POSA would understand are intact); EX2085 (US 10,301,384), 10:31-56 (discussing effects of FC-modified regions). Regardless, as I discuss above, blocking IL-15 signaling is the key discovery recognized by the inventors to treat vitiligo, as opposed to the specific molecule used to block the pathway. A POSA would understand that it does not matter if the inhibitor is an antibody (Fc-intact or

Fc-diminished), a fragment, a small molecule, or other compound, as they were all expected to block the signaling pathway.

121. A POSA would not just recognize that hundreds of IL-15 and IL-15 receptor inhibitors (small molecules, peptides, antibodies, nucleic acids, and others) were known, but would also appreciate structural features conferring their function. That is, a POSA would know the chemical structures and nucleotide sequences for the hundreds of known inhibitors (**Appendix A** (IL-15/IL-15R chart)) and would appreciate the common chemical elements and their structural and functional relationship. *See, e.g.*, EX2019 (US7736638), 2:14-18 (“Asp56 in the IL-15 molecule is important in the binding to the receptor β subunit and Gln156 is important in the binding to receptor γ subunit”); EX2049 (US8431524), 2:30-40 (same); EX2028 (US10202433), 1:39-43 (“two sequences of the IL-15 molecule for binding to IL15-Ralpha... comprise amino acids 44 to 52 and 64 to 68 in the mature protein, and they also described muteins that could act as agonists or antagonists of IL-15”); EX2015 (US20160235762) (“small chemical molecules fitting in the IL-15 specific receptor domain was carried out on the basis of the model of the [IL-15Ra-IL-15] complex structure, elaborated on the basis of the crystal structure of the complex fragment”)

122. IL-15 signaling inhibitors known in the art (i.e. those exemplified in the patent and those described in **Appendix A**), were known to block IL-15 signaling

through either direct or indirect inhibition. For instance, small molecule and antibody inhibitors were known to block IL-15 signaling by binding IL-15 cytokines or the IL-15 receptor subunits directly. *See, e.g.*, EX1011 ('830 Pat.); EX2086 (US5844099); EX2047 (US5591630). Likewise, oligonucleotides were known to bind mRNA encoding the IL-15 cytokine or IL-15 receptor subunits to prevent protein synthesis, thereby inhibiting IL-15 signaling. *See, e.g.*, EX2030 (US5985663); EX2087 (US2003/0013668); EX2088 (WO2012061536).

123. A POSA would not view literature addressing a particular IL-15 or IL-15 receptor inhibitor or its use to elucidate the mechanisms of action of a disease in isolation. That is, a POSA would not view a reference teaching use of a particular inhibitor for a disease as only relevant to that particular inhibitor. Instead, a POSA would have a wide-ranging breadth of knowledge about the IL-15 signaling pathway, informed by the decades of research and publications on the topic and appreciate the well-characterized pathway and mechanisms for IL-15 or IL-15 receptor inhibition. EX2082 (Mishra 2014), 1. EX2021 (Epron 2012), 7; EX2083 (Lu 2002), 1.

124. In view of the decades of research surrounding the IL-15 signaling pathway, a POSA would understand that results of inhibition of IL-15 demonstrated with one inhibitor would be common to other inhibitors of the IL-15 signaling pathway. For example, as explained above, a POSA would appreciate that blocking any one of the IL-15 cytokine, IL-15R α (CD215), IL-15R β (CD122), and γ c

(CD132) would be functionally representative of blocking any of the others to inhibit the IL-15 pathway. EX1001, 31:6-10; EX2007 (Abbas Dep. Tr.), 69:9-71:5. Indeed, this is reflected in the prior art literature as well as the more recent disclosure from Forte, where therapeutic activity of new IL-15 signaling inhibitors is understood based on their mechanism of action (blocking IL-15 signaling) without the need for testing in the given disease model. *See* Section IV.C.3., IV.C.4, and VII., above.

125. Thus, a POSA would have understood that the therapeutic effects of blocking IL-15 signaling to treat vitiligo demonstrated in the '505 patent with one inhibitor of IL-15 or the IL-15 receptor would be a class-wide effect among IL-15 or the IL-15 receptor inhibitors.

2. Demonstration in the '505 Patent of Treating Vitiligo by Inhibition of CD122 Was Representative of a Class-Wide Effect

126. The ChMBC7 antibody used in the specification was described as inhibiting the IL-15 signaling pathway by binding CD122 (IL-15R β). EX1001, 33:16-23.

127. Because it was understood that the IL-15 cytokine, IL-15R α (CD215), IL-15R β (CD122), and γ_c (CD132) were all necessary for IL-15 signal activation, a POSA would understand the treatment of vitiligo demonstrated in the '505 patent with ChMBC7 to be representative of not only other CD122 (IL-15R β) inhibitors, but also IL-15 signaling pathway inhibitors, generally. EX1015, Fig. 1.

128. This follows from ChMBC7's activity in inhibiting the predominant *trans*-presentation of IL-15 signaling, as any other IL-15 or IL-15R would also necessarily inhibit this signaling. And because IL-15 *cis* and *trans*-presentation involve the same components for signal activation, only differing in whether receptor subunits are expressed on the same cell, a POSA would also understand ChMBC7's activity would be representative of inhibiting *cis*-presentation of IL-15 as well. EX1015, 1-2, Fig. 1; EX1001, 31:6-10; EX2007 (Abbas Dep. Tr.), 69:9-71:5.

129. As the inventors of the '505 patent discovered and described in the specification, the IL-15 signaling pathway is a critical component to vitiligo pathogenesis. EX1001, 30:53-31:12. Based on this, a POSA would have understood the demonstrated efficacy of ChMBC7 for the treatment of vitiligo in the '505 patent as describing the class-wide effect for inhibitors of IL-15 and the IL-15 receptor for the treatment of vitiligo.

130. My conclusion in this regard is consistent with the understanding that IL-15 inhibitors will share common therapeutic effects based on their mechanisms of action, as reflected in the prior art for other disease (*see* Section IV.C.4.) and in the more recent disclosures of Forte for vitiligo specifically and other IL-15 mediated disease (*see* Section VII.).

131. While Dr. Abbas agrees that CD122 inhibitors were commercially available and some were already in clinical development (EX2007 (Abbas Dep. Tr.), 71:25-72:11), Dr. Abbas asserts “[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.” EX1002 , ¶70. I disagree that this is relevant. Reflecting that the structure of an individual inhibitor is not necessary for a POSA to understand the significance of a mechanistic proof of concept, it was common practice for literature to refer to inhibitor by name (in this case the specific antibody clone used, ChMBC7) without a structure or sequence. *See, e.g.*, EX1018 (Villadsen 2003) (disclosing 146BE7 and 404E4 by codename without sequences); EX2089 (Bernard 2004) (disclosing L45D, L45E, Q48K, V49D, S51D, L52D, E64K, N56K, L66D, L66E, I67D, I67E, and I68D by codename without sequences); EX2084 (Mitra 2015) (disclosing IL-2-H9-RET and IL2-H9-RETR by codename without sequences). Forte does the same with reference to its “FB-102” antibody and was able to rely on the patent’s data as republished in Richmond 2018 (EX2046) which also does not provide the structure of FB-102. *See* Section VII.

132. A POSA would not need to know the sequence of ChMBC7 to understand the ’505 patent fully described the claimed invention. What would have been important to a POSA would be the understanding that ChMBC7 inhibited the

IL-15 receptor and thus that the experimental data was representative of IL-15 signaling inhibition.

133. Dr. Abbas wrongly contends the use of ChMBC7 described in the '505 patent does not demonstrate a "class wide effect" for vitiligo treatment for IL-15/IL-15R antibodies. EX1002 (Abbas Decl.), ¶67. Citing EX1013 (DeGottardi), he concludes that 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." *Id.* I disagree. The data in DeGottardi et al. supports the studies in the '505 patent examples. In DeGottardi, it is shown that IL-15 inhibition results in long-lasting depletion of memory T cells in "tissue T_{EM}", however, remained significantly reduced," but circulating T_{EM} returned over time and were not durably depleted. EX1013 (DeGottardi), Abstract. Indeed, the '505 patent inventors observed that when IL-15 signaling was blocked using short-term administration of ChMBC7 (2 weeks) and resulted in durable repigmentation, over time (analyzed 10 weeks after treatment), there was a depletion of Trm cells in the skin (tissue). But importantly, there was not a similar depletion in memory T cells in the spleen and lymph node. EX1001, 33:42-45. This result suggested the effect on pathogenic T cells in skin (tissue) is key to the observed phenotype, while effective depletion of T cells in other central sites is less relevant. This reinforces that there is no reasonable basis to extrapolate the effects of pathogenic T cells in other sites,

unconnected to vitiligo, to the treatment of vitiligo caused by the effects of pathogenic T cells in the epidermis. Further in the DeGottardi study, the authors are not examining disease-causing T cells. In fact, this could be viewed as an advantage when considering treating patients with IL-15 blockade in that background T memory cells, unrelated to a disease process, do come back to some extent and imply a disease-specific effect on overactivated T memory cells in vitiligo, which *Harris* establishes upregulate the IL-15R.

134. Soluble/secreted IL-15 can also signal in *cis*-presentation via the lower affinity IL-15R $\beta\gamma$ (CD122/CD132) receptor complex, with variable contribution from IL-15R α . Given that CD122 is one of two key receptor components in this signaling complex, a POSA would understand the treatment of vitiligo inhibition demonstrated in the '505 patent with an anti-CD122 antibody (exemplified by the '505 patent inventors through the use of ChMBC7 antibody) to be representative of a class wide effect, including inhibition of *cis* IL-15 signaling.

B. The '505 Patent Describes Treating the Claimed Subjects

135. As discussed above (IV.B.2.), a POSA would have understood the value of pre-clinical proof of concept models (such as the Harris mouse model) and rely on such models to understand what to expect in treatment of other species. EX1022, 3; EX1007, 1; EX2007 (Abbas Dep. Tr.), 65:21-67:20. Moreover, as discussed above, the *Harris* mouse model used in the '505 patent to demonstrate efficacy in

treating vitiligo, shares the key attributes of and recapitulates human vitiligo. *See* Section IV.D.1, above. It was and remains the primary proof of concept model for vitiligo treatment and was relied upon as representative of human disease. EX2033 (Antonelli 2015), 2; EX1001 ('055 patent), 5:43-45 (the *Harris* mouse model “mirrors human disease”); section IV.D.1, above.

136. Indeed, as discussed above (VIII.B), Forte itself demonstrated how it is common practice for a POSA to have an understanding about human treatment from pre-clinical proof of concept model data. EX2009 (Forte Interrogatory Response).

C. The '505 Patent Describes the Subject Matter Recited in the Dependent Claims

137. As discussed above (VI.A.), the dependent claims of the '505 patent describe the same treatment of vitiligo by blocking the IL-15 pathway, but additionally require the inhibitor is a small molecular inhibitor, an antibody, a peptide inhibitor, or an inhibitory nucleic acid targeting IL-15 or IL-15R (claim 2); the inhibitor is administered to the lesion (claim 3); the inhibitor is administered to the epidermis within the lesion (claim 4); and the inhibitor is administered by subcutaneous or intradermal administration, or a microneedle array (claim 5).

138. In my opinion, the '505 patent specification, when read by a POSA, describes to those skilled in the art that the inventors were in possession of each of these claimed features.

139. For instance, the requirement recited in claim 2 that the inhibitor be a small molecule inhibitor, antibody, peptide inhibitor, and inhibitory nucleic acid is explicitly described within a list of representative inhibitors of each type. EX1001, 7:33-40 (citing EX2013 (WO2014191822) (small molecule inhibitor of the IL-15 receptor alpha chain, e.g., benzoic acid derivatives)); 7:40-44 (citing EX2015 (US20160235762) (small molecule inhibitor of IL-15-induced cellular responses, e.g., cefazolin)); 7:44-47 (citing EX2017 (Ruchatz 1998) (soluble IL-15 receptor alpha chain which binds IL-15 and antagonizes the IL-15)); 7:47-51 (citing EX2018 (Kim 1998) (antagonistic mutant IL-15/Fc-gamma 2a fusion protein which competitively inhibits binding of IL-15 to the IL-15 receptor)); 7:51-54 (citing EX2019 (US7,736,638) (peptide that binds the IL-15 receptor alpha chain and inhibits IL-15)); 7:54-58 (citing EX1011 ('830 Pat.) (antibody which specifically binds the IL-2/IL-15 receptor beta subunit)); 7:60-64 (citing EX2022 (Wilson and Arkin 2010) (small molecules (e.g., Ro26-4550, SP4206, ABT-737, Nutlin-2, and compound 3)); 7:64-8:3 (citing EX2021 (Epron 2012) (antibody that specifically binds the IL-15 receptor alpha subunit)); 8:3-6 (citing EX2020 (WO03017935) (antibody that specifically binds the IL-15)); 8:25-37 (nucleic acids that target IL-15, IL-15 receptor alpha subunit, IL-15 receptor beta subunit (CD122), or IL-15 gamma subunit mRNAs), 9:3-21. Moreover, a POSA would be aware of a breadth of literature describing hundreds of inhibitors across these categories. **Appendix A**

(IL-15/IL-15R chart); *see, e.g.*, EX2024 (WO2015181394) (disclosing small molecule inhibitors); EX2032 (US 9,133,244) (disclosing peptide inhibitors); EX2031 (US 7,153,507) (disclosing antibodies); EX2030 (US 5,985,663) (disclosing inhibitory nucleic acids). As discussed above, the '505 patent's demonstrated efficacy in treating vitiligo by inhibiting IL-15 signaling would have been understood to be representative of inhibiting IL-15 signaling by each of these classes of inhibitors.

140. Likewise, the methods of administration required by claims 3-5 were explicitly described in the specification and a POSA would appreciate that each was common practice and well known in the art. EX1001, 2:9-11; 20:30-54.

IX. Ground 2: Claims 1-5 Are Enabled

141. In my opinion, the '505 patent specification, when read by a POSA, enables those skilled in the art to practice each of the claims 1-5. At the time of invention in 2017, a POSA had a wealth of information about cytokine signaling pathways and experience treating autoimmune and dermatological diseases, including vitiligo. A POSA would also have been familiar with well-known inhibitors of IL-15 and IL-15R as described in the '505 patent and recognized in the art. The '505 patent further provides extensive data characterizing the role of IL-15 signaling in vitiligo and demonstrating a highly effective and durable treatment strategy for vitiligo through blockade of this signaling pathway. Indeed, nowhere do

Forte's experts identify any inhibitor of IL-15 signaling that would not work to treat a subject's vitiligo lesion.

142. The claimed method of treating vitiligo is based on basic research and reliable animal models that guide the translational process, as is standard for developing targeted therapies for autoimmune and dermatological diseases. As I discuss above, there were numerous examples of cytokine therapies, including inhibitors of IL-17 and IL-23, JAK-STAT signaling, and IL-2 that were shown to be effective in humans based on validation in preclinical models. *See* Section IV.B.1-IV.B.3. above. Given that the inventors of the '505 patent employed this classic approach for developing translational therapy, it is my opinion that a POSA would have been able to practice the claimed method with IL-15 and IL-15R inhibitors without undue experimentation consistent with how pre-clinical models had been relied upon in other autoimmune diseases. A POSA would also have understood the *Harris* vitiligo model to have faithfully recapitulated key pathogenic features of human vitiligo such that its results would have enabled treating human subjects without undue experimentation.⁵

⁵ To be clear, while my opinion is that the '505 patent enables the claimed method including in human subjects, I recognize that *actually* treating human subjects in practice is necessarily limited by demonstration of an acceptable balance of safety

143. A POSA would have considered the research approach disclosed in the '505 patent analogous to pre-clinical research in *Xing* (EX1007), among others. *See* Section IV.B; *see also* EX2012 (Yokoyama); EX2072 (van der Fits 2009); EX1030 (Hechinger). Both here and in *Xing*, the scientists started with a particular disease (vitiligo and alopecia areata) and characterized the transcriptional profile of the disease in human samples and an established mouse model (*Harris* model and C3H/HeJ). Potential therapeutic targets, including the cytokines IFN- γ and IL-15, were then identified and assessed using known inhibitors to block the pathway. The agents that demonstrated success in the mouse models (inhibitors of IL-15 signaling and JAK inhibitor) were then selected to move forward for future clinical evaluation. In both cases, the pre-clinical results enable treatment with other inhibitors of the same pathway (IL-15 or JAK) and in human subjects. *Xing* (EX1007) demonstrated how this type of pre-clinical data was relied upon to enable treating human disease, as it reports actually proceeding to human clinical use based on its pre-clinical mouse

and efficacy as required under FDA regulations and consistent with proper patient care. For example, in my practice, I would not administer a new therapy to a patient without sufficient knowledge of its balance of safety and efficacy even if I expected it to provide some therapeutic benefit.

model research. *See* EX1021, 3-4 (by 2017, human clinical trials were underway for evaluating JAK inhibitors in AA).

A. Analysis of Claim 1

144. Claim 1 is directed to a novel method of treating vitiligo using a known class of inhibitors having the specific function of blocking IL-15 signaling. This approach for targeting a cytokine signaling pathway for other autoimmune diseases was recognized through the art, where pre-clinical proof of concept models demonstrated therapeutic success for a range of autoimmune conditions as well, including AA (*Xing*), celiac disease (Yokoyama), and psoriasis (van der Fits 2009), and others. *See* Section IV.B. Once the role of a signaling pathway had been established in a particular disease, POSAs understood that inhibitors of the pathway shared common therapeutic effects resulting from their common inhibition of that pathway. In this context, a POSA would have understood the '505 patent to demonstrate with mechanistic and preclinical data that inhibiting IL-15 signaling was effective to treat vitiligo and to enable treating vitiligo with an IL-15 or IL-15R inhibitor.

145. Especially in the context of this standard practice in the art, the *Harris* mouse model relied upon in the specification is sufficient to enable the scope of treatment subjects, as I describe in more detail below. *See also* Section IV.D.1 (listing common features of the *Harris* mouse model and human vitiligo). It was common

for those skilled in the art, including Forte more recently, to rely on animal models like the *Harris* model (the same one used in the patent specification) for understanding therapeutic utility.

146. I discuss the enablement of claim 1 under the *Wands* factors below.

1. *Wands* Factors Analysis

**a) Nature of the Invention and Breadth of the Claims
(*Wands* Factors 4 and 8)**

147. The '505 patent claims are tailored to identifying and administering an inhibitor of IL-15 or the IL-15 receptor to a subject who has a vitiligo lesion for treating the subject's vitiligo. The claimed invention is based on the discovery that IL-15 signaling is fundamental to vitiligo pathophysiology and it can be treated with compounds that inhibit IL-15 signaling. In this regard, the nature of the invention is a specific application of cytokine inhibition treatments well-known in the art for treating other autoimmune diseases. *See* Section IV.C.2. The claims are also narrow based on their specificity to treating a single disease (vitiligo) by inhibiting a specific cytokine pathway (IL-15).

148. As discussed in more detail above, the '505 patent specification demonstrates that autoreactive T cells within lesions of human vitiligo patients express IL-15R β /CD122. EX1001 ('055 Pat.), 30:53-31:12 (Example 1). Using an established mouse model for vitiligo and a CD122 antibody, the inventors demonstrated that inhibiting the interaction of IL-15 to autoreactive Trm in the skin

(termed “PMEL”) is effective to treat vitiligo. EX1001 (’055 Pat.), 33:1-67 (Example 5). As also discussed above, while an important advance for the treatment of vitiligo, the demonstrated efficacy is consistent with treatment effects demonstrated by blocking relevant cytokines in other disease conditions. *See* Section IV.C.3-IV.C.4. In this regard, the nature of the invention is a specific application of well-established science.

149. The breadth of the claims is narrow, in that they are directed to treating a single disease (vitiligo) using inhibitors of a specific cytokine (IL-15) pathway. *See* Section IV.C.2. In my opinion, that the claimed subjects would encompass different species, including humans, does not make them broader than the ’505 patent’s enabling disclosure. That there is potentially some variability, e.g., between patients or even species, is always true in translational medicine and does not make the claims “broad” relative to the patent’s enabling disclosures. To the contrary, a POSA would have understood that the *Harris* mouse model used in the ’505 patent faithfully recapitulates key elements of vitiligo disease, including in humans. *See* Section IV.C.3.; EX2033 (Antonelli 2015); EX1001 (’055 patent), 5:43-45 (the *Harris* mouse model “mirrors human disease”). Indeed, it had been relied upon in the prior art and more recently by Forte. *See* Section VII. Nothing in the Petition or declarations show that it was not representative, other than speculation.

150. And while the claims cover inhibiting IL-15 signaling with different inhibitors and in different ways, this is again the application of signaling mechanisms and inhibitors that had already been characterized and which were well known. *See Appendix A.*

151. Forte's declarants argue that the claims encompass administration to any subject, including humans having "natural or spontaneous vitiligo" and species with different immune systems. EX1002, ¶85; EX1004, ¶60. These variabilities, however, exist in almost all translational research processes for autoimmune and dermatological diseases, and are within a narrow range such that a POSA would reasonably understand the claimed treatment methods to work. To suggest that somehow the *Harris* vitiligo model is different than any other relied-upon pre-clinical mouse model that forms the bedrock of translational science is unfounded. To the contrary, a POSA would recognize the vast amount of work performed by *Harris* and colleagues to ensure the model was as biologically representative of human vitiligo as possible. Again, I understand that Forte's development of FB-102 for vitiligo rests on the same model and data as in the '505 patent. *See* Section VII.

152. For instance, as I discuss above, the *Harris* mouse model was considered a reliable model that recapitulates vitiligo in humans. *See* Section IV.C.3. and IV.D.1, above; EX2033 (Antonelli 2015), 2 (Harris's mouse model exhibits a gene expression profile "similar to human vitiligo"); EX1020 (Rashighi 2014), 3.

Drs. Abbas and Plott have not identified any specific key features that are exemplified in the pathogenesis of human vitiligo that are not in the Harris vitiligo mouse model other than hypothetical ones. *E.g.*, EX1002, ¶62 (“The ’505 patent merely invites a POSA to undertake a research project in treating natural or spontaneous vitiligo outside the mouse model.”).

153. I also disagree with Dr. Abbas’s assertion that the “’505 patent’s cytokine blocking experiments in mice are not representative of the effects of cytokine blocking in humans....” EX1002, ¶85. With regard to being “representative” *of treating vitiligo*, the mechanism taught in the patent to be effective to treat vitiligo is based on inhibiting IL-15 signaling via inhibition of IL-15 or its receptor subunits will inhibit the IL-15 pathway. *See* EX1001, 6:16-21. The patent’s PoC with ChMBC7 does this—treating vitiligo by inhibiting IL-15 signaling—and is representative of treating vitiligo with inhibitors of IL-15 or IL-15R as recited in the claims. EX1001, 33:1-67.

154. This was consistent with the “emerging understanding” already by 2004 “of the IL-15/IL-15R system [] providing the scientific basis for the development of rational approaches for the IL-15-targeted treatment of autoimmune diseases....” EX1022 (Waldmann 2004), 3. That is, the novel aspect of treating vitiligo as described in the patent is based on inhibiting IL-15 signaling, not the specific inhibitor used in the patent examples nor the underlying rationale of using IL-15-

targeted treatment of other autoimmune diseases. This is also consistent with the recognized therapeutic effects for inhibiting the action of other cytokines and in other diseases.

155. Dr. Abbas also contends “inhibiting CD122 can inhibit IL-2 signaling, IL-15 signaling, or both, in a variety of combinations each having different sets of biological consequences.” EX1002, ¶86. As of April 2017, however, it was recognized that IL-15 is much more potent at generating CD8⁺ Trm pools than IL-2 signaling in skin tissue (EX2039 (Adachi 2015)), and IL-15 is required for the generation of CD8⁺ Trm in viral models of mice (EX2040 (Mackay 2013)). Accordingly, based on the patent’s examples demonstrating that vitiligo lesions express IL-15R β /CD122 (Example 1) and blocking IL-15 signaling with a CD122 inhibitor results in a reduction of Trm (Example 5), a POSA would understand that the demonstrated vitiligo treatment effect results from inhibiting IL-15 (not IL-2) signaling and thus be enabled to treat vitiligo by inhibiting IL-15 signaling.

156. Another way to look at this is to examine the well-known differing effects of IL-2 and IL-15. IL-2 signaling is important for activation induced-cell death (AICD) as well as maintenance of T regulatory cells, an anti-inflammatory T cell population. A POSA, understanding the field as a whole, would have recognized that IL-15 is not known to significantly be involved in these anti-inflammatory processes. EX1001, 6:3-21. In this light, a POSA would have understood that the

driving effect of ChMBC7 on treating vitiligo demonstrated in the '505 patent was reducing autoimmunity via inhibition of IL-15 signaling.

**b) State of the Art, Level of Skill, and Predictability
(Wands Factors 5-7)**

157. Regarding the state of the art, which encompasses treatment of vitiligo, cytokine signaling pathways, and inhibitors of IL-15 signaling, the principles underlying the invention were well established. As a discuss above, IL-15 was a textbook cytokine (EX2002 (Abbas Textbook), 106) and inhibitors of IL-15 signaling were well-known. *See Appendix A.* Moreover, rational drug design models were readily available that would facilitate a POSA to develop new inhibitors of IL-15 signaling through the use chemical modifications or combinations thereof, based on their known structures and function. *E.g.*, EX1022 (Waldmann 2004), 3.

158. Key principles underlying the method of treating vitiligo claimed in the '505 patent were also largely understood. Previous work by van den Boorn et al. and others had demonstrated that CD8⁺ T cells were involved in killing melanocytes and leading to depigmented spots on the skin in vitiligo. EX2037 (van den Boorn 2009). Other studies implicated a role for IL-15 signaling in the generation of Trm in some autoimmune diseases, but not vitiligo specifically. EX1017 (Mackay 2015). What had not been shown prior to the '505 patent was that inhibition of IL-15 signaling was sufficient to treat vitiligo.

159. Drs. Abbas and Plott argue that the “state of knowledge about inhibiting cytokine signaling to treat autoimmune diseases such as vitiligo was low and the field itself was highly unpredictable.” EX1004 (Plott Decl.), ¶59; EX1002 (Abbas Decl.), ¶84 (“treating vitiligo... [was] very complex and unpredictable”). Leaving aside their comment about vitiligo specifically, I strongly disagree that “state of knowledge about inhibiting cytokine signaling to treat autoimmune diseases... was low and the field itself was highly unpredictable.” As discussed above, the state of the art for using cytokine signaling to treat autoimmune diseases was well established and already in clinical use long before 2017. *See* section IV.C.4. It was also predictable that compounds commonly inhibiting a given cytokine pathway will have common therapeutic effects based on that mechanism of action. *See* section IV.C.3. The only point with which I agree is that knowledge was limited and unpredictability was high when trying to extrapolate between different autoimmune diseases. That is, as I further discuss in the context of obviousness in Section X. below, a POSA could not have reasonably expected a treatment effective in alopecia areata, for example, to be effective in vitiligo. Further, as described above, the claims are tailored to administering an inhibitor of IL-15 signaling, which was already shown by the inventors to treat vitiligo. A POSA would have understood the claimed treatment methods to effectively treat a subject’s vitiligo lesion particularly because “experimental models,” including mouse models, were known to “inform[]

therapeutic strategies in humans.” EX2074 (Abbas 2020), 5 and the Harris model would have been known to be highly accurate.

160. Next, regarding the relative skill of those in the art, the level of skill was high. *See* Section V., above. The combination of the credentials and experiences of a POSA would have a high technical aptitude that would allow a POSA to understand the teachings of the ’505 patent in concert with their own knowledge of vitiligo, cytokine signaling, and translational research. This knowledge would include extensive information about inhibitors of IL-15 signaling that was provided in decades of prior art publications and used in the art, as discussed above. *See, e.g.*, Section IV.C.2.a). This means that a POSA would have sufficient skill to apply and modify the disclosed experiments to achieve the claimed method of treating a subject’s vitiligo lesions, including in humans, even if not expressly exemplified in a working example in the ’505 patent. Indeed, this level of skill is reflected in the large number of prior art references attributing therapeutic efficacy to newly developed inhibitors without necessarily even testing in a disease model (*see* section V.) as well as Forte’s later reliance on the same data in in the patent to support the development of FB-102 for vitiligo (*see* section VII.).

161. Next, regarding predictability of the art, I considered every step recited in and necessary to practice claim 1 of the ’505 patent. The first step of “identifying

a subject in need of treatment” is simple and would have been predictable to a POSA based on the known diagnostic features of vitiligo. *See* Section IV.A.2., above.

162. The second step of “administering a therapeutically effective amount of an inhibitor of IL-15 or the IL-15 receptor” would also have been predictable for a POSA to follow based on the known class of inhibitors of IL-15 signaling, the ’505 patent’s guidance, and a POSA’s knowledge of therapeutically effective doses for vitiligo. As I discuss above, inhibitors of IL-15 signaling were well-developed and understood, meaning administering a known inhibitor of IL-15 and blocking its signaling was predictable. *See* Sections IV.C.2.a), VIII.A.1.-VIII.A.2., above. In addition, Forte’s declarants admit that determining a therapeutically effective dose is “a routine matter and would have involved conducting dose ranging studies known in the art.” EX1002 (Abbas Decl.), ¶103. I agree that while experimental dosing studies would be required for human therapeutic use, it would not require undue experimentation to determine a therapeutically effective dose for any given inhibitor and mode of administration.

163. A POSA would not need to “synthesize and screen” new inhibitors of IL-15 signaling to practice the claimed method. As discussed, inhibitors of IL-15 signaling were already commercially available and in clinical use with hundreds known in total. *See* sections IV.C.2.a), VIII.A.1.-VIII.A.2 above. Even if a POSA were to “synthesize and screen” new inhibitors of IL-15 signaling as Dr. Abbas

contends, I disagree that it would be an “iterative, trial-and-error process.” EX1002 (Abbas Decl.), ¶91. As I discuss above, the art taught and demonstrated that a POSA could readily employ rational antibody drug design or other standard protein drug design techniques to engineer or modify inhibitors of IL-15 signaling to improve its therapeutic potential. EX2079 (Robinson 2017); EX2015 (US 2016/0235762), ¶[0027]. For instance, various approaches have been developed to improve the *in vivo* half-life and efficacy of IL-15, largely by generating IL-15/IL-15R α conjugates (“super-agonists”). EX2079 (Robinson 2017), 1, 5. These “super-agonists” have been shown to be “significantly more potent than native IL-15 in both *in vitro* and *in vivo* studies,” and several are in human clinical development (ALT-803). EX2079 (Robinson 2017), 5-6, 8.

**c) Guidance and Working Examples in the Specification
(Wands Factors 2 & 3)**

164. Drs. Abbas and Plott rely on their view that “the ’505 patent provides only a single example of treating depigmentation lesions” as their basis for asserting that the ’505 patent provides “no” or “little guidance.” EX1002 (Abbas Decl.), ¶88-89; EX1004 (Plott Decl.), ¶58. I disagree. In my opinion, the ’505 patent provides sufficient direction, guidance, and experimental data to allow a POSA to perform the claimed methods without undue experimentation.

165. The '505 patent specification provides detailed experiments supporting the claimed methods, including six examples, extensive data, and 52 total number of figures. I discuss each of these examples in more detail in Section VI.B above.

166. The inventors demonstrate that targeting IL-15 signaling is effective for treating a subject's vitiligo lesion. EX1001, 6:22-29; *see* Section VI.B, above. For instance, the inventors show, among other things, that both human and mouse Trm express the CD122/IL-15R β subunit of the IL-15 receptor (EX1001, Example 1) and targeting IL-15 signaling with an anti-CD122 antibody inhibits Trm production and treatment results in long-term depletion of pathogenic Trm cells from skin lesions (EX1001, Example 5). The inventors demonstrated that short-term treatment with an anti-CD122 antibody provides durable repigmentation when administered systemically or locally in the skin in reliable animal model. *E.g.*, EX1001, Example 5. Examples 2-4 and 6 provide further evidence of the signaling mechanisms and diagnostic implications of targeting IL-15 for the treatment of vitiligo.

167. The '505 patent specification also discloses a list of exemplary IL-15 and IL-15R inhibitors from various classes such as small molecule inhibitors, antibodies, and nucleic acid inhibitors. EX1001, 7:33-8:37. Further, the specification provides guidance for diagnosing (EX1001, 23:60-35) and administering a therapeutically effective amount of the inhibitor, and also describes how to

determine useful doses for administration to animals and humans (EX1001, 23:8-59).

168. I disagree with Dr. Abbas's contentions that the 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." EX1002 (Abbas Decl.), ¶88. The *Harris* mouse model was (and remains) the "gold standard" model of vitiligo and has been shown to recapitulate human disease pathology, as I describe above. *See* Section IV.D.1.

169. The ChMBC7 antibody tested in the patent's examples would also have been recognized by POSAs as enabling of treatment with other claimed inhibitors. Knowledge of its specific structure would not have been necessary. As I explain throughout, the structures and functions of IL-15/IL-15R inhibitors were known, and a POSA would have understood that inhibitors would have common therapeutic effects based on their common mechanism of inhibiting IL-15 signaling. This is consistent with the prior art (*See* Section IV.C.2.a), VIII.A.1.-VIII.A.2) and Forte's reliance on an established mechanism for inferring therapeutic activity for its FB-102 product (e.g., blockade of IL-15 signaling is inferred therapeutic for vitiligo based on the '505 patent's results). *See* Section VII.

170. Accordingly, based on the patent's guidance and detailed experimental data, a POSA would understand targeting IL-15 signaling as an effective and durable

treatment strategy for a subject having a vitiligo lesion. A POSA would also know the doses, administration routes, and administration sites to select for the claimed methods, which are all routine pharmaceutical procedures. EX1001, 23: 43-45.

**d) Quantity of Experimentation Necessary (*Wands*
Factor 1)**

171. In my opinion, only routine experimentation was necessary to perform the methods recited in claims 1-5 in light of the '505 patent's teachings, the prior art, and a POSA's knowledge. In evaluating the quantification of experimentation necessary, I considered that a POSA, at the time of invention, would have been able to identify a subject in need of treatment and administer a therapeutically effective amount of an inhibitor of IL-15 or the IL-15 receptor to treat the subject's vitiligo lesion. My opinion applies regardless of whether the treated subject is a mouse or human, and whether the inhibitor of IL-15 signaling was a commercial, otherwise known, or newly developed inhibitor. I have already addressed much of my reasoning in this regard in the context of *Wands* Factors 5-7, above, and provide the following additional opinions.

172. Forte and its declarants ignore the inventors' fundamental discovery that inhibition of IL-15 signaling is effective to treat vitiligo and distort the nature of the invention. They also ignore the hundreds of IL-15 signaling inhibitors known in the art and making new inhibitors was routine, such that no more than routine experimentation is needed to practice the claimed method.

173. As discussed above with respect to written description support for the claims, there were hundreds of known inhibitors of IL-15 or IL-15R. *See Appendix A.* Forte's declarants ignore that rational drug design approaches and high throughput screening techniques were available for developing improved inhibitors of IL-15 signaling. For instance, by 2017, several new and improved inhibitors of IL-15/IL-15R had been developed, particularly given that IL-15 signaling was well understood and POSAs recognized particular structural features that could be targeted for enhancing existing IL-15 and IL-15R inhibitors. EX2079 (Robinson 2017).

174. Therefore, no experimentation would have been required to obtain an IL-15 / IL-15R inhibitor as these were well-known, including commercial. Even to make new ones, the art provided specific guidance for their rational design. To be clear, however, identifying a new compound is not required to practice the claimed method. Rather, only *the use of* IL-15/IL-15R inhibitors—where the '505 patent teaches the mechanism by which IL-15/IL-15R inhibitors deplete autoreactive Trm and how this effectively treats vitiligo—is required and hundreds of these were known.

175. A POSA could have also readily administered the claimed inhibitor to a subject using standard routes of administration and dosages to achieve repigmentation and further preventing a subject's vitiligo lesion to return as detailed

in the '505 patent. This would have required only confirmatory experimentation given that the inventors demonstrated targeting IL-15 as a strategy to clear disease-causing Trm cells from the tissue, resulting in a long-lasting, durable response to treatment, and that the art was advanced for the use of cytokine inhibitors, including IL-15, to treat other autoimmune diseases. *See* IV.C.2., IV.C.4.

176. In addition, the patent's disclosure confirms that formulating an appropriate dosage and dosage route were standard pharmaceutical procedures (EX1001, 23:8-59) that a POSA could readily apply for practicing the claimed methods. It follows that the total experimentation necessary for performing the claimed methods was simply following standard procedures known in the art for administering a known (or alternatively new) inhibitor against a known signaling pathway using routine pharmaceutical methods.

177. Dr. Abbas's declaration confirms that a POSA would have known how to carry out the claimed invention for effectively treating vitiligo. For instance, Dr. Abbas states that "at least some inhibitors of IL-15 were known to treat vitiligo." EX1002 (Abbas Decl.), ¶¶54-60. His analysis is based on the underlying mechanism that inhibition of IL-15 signaling was known to deplete Trm CD8⁺ T cells. *E.g.*, EX1002 (Abbas Decl.), ¶59 ("neutralizing antibodies to IL-15 or its cytokine-specific receptor IL-15R α could deplete Trm CD8⁺ T cells"). He further argues that certain inhibitors of Jak1 or Jak3 were reported to treat vitiligo based on their

signaling via IL-15. EX1002 (Abbas Decl.), ¶¶60. But none of the papers Dr. Abbas cites discloses actual treatment of vitiligo using an inhibitor of IL-15 signaling. EX1002 (Abbas Decl.) ¶¶59 (citing EX1006 (Harris), EX1007 (Xing), EX1032 (Harris 2016), EX1033 (Craiglow)).

178. Prior testimony from Forte’s Declarants also support the importance of animal models in developing therapeutic strategies for autoimmune or dermatological diseases. For instance, Dr. Abbas describes that “IL-2 is a remarkable example of how basic research, mostly in experimental models, informs therapeutic strategies in humans.” EX2074 (Abbas 2020), 5. Prior work by Dr. Plott also shows that he oversaw the development of posaconazole (trade name Noxafil) during his time at Schering, which was based on animal studies for determining that administration of posaconazole “in human subjects would be a therapeutically effective dosage regimen.” EX2090 (Nomeir 2000), 1.

179. Dr. Abbas suggests that “a POSA would have to synthesize and screen each new candidate compound through an iterative, trial-and-error process” because “different means of IL-15 or IL-15R inhibition could provide disparate results depending on which ligand or subunit was targeted.” EX1002 (Abbas Decl.), ¶¶81, 90. Dr. Abbas’s assessment ignores both the state of the art and the patent’s specification describing known inhibitors of IL-15 and IL-15R that were recognized as effective agents for blocking IL-15 signaling. As evident from **Appendix A**, the

art disclosed hundreds of inhibitors of IL-15 and IL-15R and POSA's were continuously working to develop improved inhibitors, which were known to inhibit this pathway. *E.g.*, EX2079 (Robinson 2017); EX2018 (Kim 1998). Beyond this predictable effect of blocking IL-15 signaling for which no experimentation is required, any "disparate results," such as those concerning safety, potency, or binding strength, may be relevant to the balance of safety and efficacy, determining an optimal treatment, and FDA considerations but do not seem relevant to whether a POSA could practice the claimed invention without undue experimentation.

180. Even if a POSA was seeking a new inhibitor or desired adjustments to a known inhibitor, a POSA would not go about screening each and every possible compound. Rather, a POSA would use high-throughput and well-established methodology to design a suitable or improved equivalent, which could be performed even as quickly as a matter of days to weeks, depending on the method employed. *See e.g.*, EX2015 (US 2016/023/5762), [0027]. Once an inhibitor was selected, a POSA would simply follow the procedures described in the patent for administering the agent and reasonably expect success in treating a subject having a vitiligo lesion.

B. Analysis of Claims 2-5

181. For similar reasons as I describe above, I disagree with Forte's arguments against claim 2. In fact, each of the categories of inhibitors recited in claim 2 are specifically exemplified in the patent and known in the prior art. EX1001,

7:33-40 (citing EX2013 (WO2014191822) (small molecule inhibitor of the IL-15 receptor alpha chain, e.g., benzoic acid derivatives)); 7:40-44 (citing EX2015 (US20160235762) (small molecule inhibitor of IL-15-induced cellular responses, e.g., cefazolin)); 7:44-47 (citing EX2017 (Ruchatz 1998) (soluble IL-15 receptor alpha chain which binds IL-15 and antagonizes the IL-15)); 7:47-51 (citing EX2018 (Kim 1998) (antagonistic mutant IL-15/Fc-gamma 2a fusion protein which competitively inhibits binding of IL-15 to the IL-15 receptor)); 7:51-54 (citing EX2019 (US7,736,638) (peptide that binds the IL-15 receptor alpha chain and inhibits IL-15)); 7:54-58 (citing EX1011 ('830 Pat.) (antibody which specifically binds the IL-2/IL-15 receptor beta subunit)); 7:60-64 (citing EX2022 (Wilson and Arkin 2010) (small molecules (e.g., Ro26-4550, SP4206, ABT-737, Nutlin-2, and compound 3)); 7:64-8:3 (citing EX2021 (Epron 2012) (antibody that specifically binds the IL-15 receptor alpha subunit)); 8:3-6 (citing EX2020 (WO03017935) (antibody that specifically binds the IL-15)); 8:25-37 (nucleic acids that target IL-15, IL-15 receptor alpha subunit, IL-15 receptor beta subunit (CD122), or IL-15 gamma subunit mRNAs), 9:3-21; *see also* EX2024 (WO2015181394) (disclosing small molecule inhibitors); EX2032 (US 9,133,244) (disclosing peptide inhibitors); EX2031 (US 7,153,507) (disclosing antibodies); EX2030 (US 5,985,663) (disclosing inhibitory nucleic acids).

182. Regarding claims 3-5, the methods of administration required by those claims are enabled by the specification, and a POSA would appreciate that each was common practice, as Forte's own declarants acknowledge. EX1001, 2:9-11; 20:30-54; EX1004 (Plott Decl.), ¶29 ("Each of these modes of administration were routine and common in the field of vitiligo treatment at the time.").

X. Claims 1-5 Would Not Have Been Obvious Over *Harris* and *Xing*

183. Drs. Abbas and Plott contend that a POSA would have been motivated to use "Xing's CD122 antibody (i.e., TM-β1) in the Harris mouse model of vitiligo because Harris expressly suggests that preventing autoreactive CD8⁺ T cell accumulation in the skin has therapeutic potential for treating vitiligo." EX1002 (Abbas Decl.), ¶99; *see also* EX1004, ¶34. Dr. Abbas also asserts that "applying Xing's antibody to Harris's mouse model is further supported by additional references such as Cheuk... teaching that [Trm cells] are activated by IL-15 in vitiligo, that JAK/STAT inhibition downstream of CD122 reversed vitiligo lesions." EX1002 (Abbas Decl.), ¶104. I disagree. They have not shown that a POSA would have been motivated to make this proposed combination with a reasonable expectation of success to treat vitiligo.

184. In my opinion, as discussed further below, a POSA seeking to treat vitiligo lesions would not have been motivated to combine the distinct teachings of *Xing* (focused on treatment of AA) and *Harris* (focused on treatment of vitiligo) with

a reasonable expectation of success in treating vitiligo at least due to all of the differences between these diseases delineated above. Nor would a POSA have been motivated to pursue an inhibitor of IL-15 signaling generally or *Xing*'s anti-CD122 antibody specifically in *Harris* or otherwise in vitiligo with a reasonable expectation of success given the art's focus on targeting the IFN- γ response. Indeed, neither Petitioner nor its declarants provide a sufficient basis for a POSA to have had a reasonable expectation of successfully treating vitiligo with an IL-15 signaling.

A. Prior to the '505 Patent, a POSA Would Not Have Been Motivated to Use an Inhibitor of IL-15 or IL-15R To Treat Vitiligo

185. *Xing* only addresses inhibitors of IL-15 or IL-15R in the context of AA and provides no motivation for their use for vitiligo. A POSA would understand that *Xing* is on AA and its tests with an IL15R inhibitor are limited to use in the C3H/HeJ mice such that their findings cannot be extrapolated to vitiligo. EX1007 (*Xing*), 1. In this regard, I am familiar with the C3H/HeJ mouse strain used in *Xing* from the literature as well as from my own research, and to my knowledge it has not been used as a model for vitiligo or reported to develop vitiligo. Certainly Drs. Abbas and Plott do not show that the C3H/HeJ mouse was ever used as a model for vitiligo or that it has ever been reported to develop vitiligo.

186. Moreover, *Xing* dissuades a POSA from selecting an inhibitor of IL-15 signaling. *Xing* focused on an IFN- γ activation signature in humans and C3H/HeJ mice. *Xing* reported that only JAK inhibitors (downstream inhibitors of IFN

signaling), and not IL-2 or IL-15 signaling inhibitors, (1) eliminated the IFN- γ signature and (2) both prevented development of and reversed AA. EX1007 (Xing), 1, 6. Based on these results, *Xing* selectively progressed JAK inhibitors for AA. In view of these reported distinctions, the POSA reading *Xing* would not have been motivated to pursue an IL-15 signaling inhibitor (e.g., anti-CD122 antibody) in the first place.

1. Insufficient Evidence for Why a POSA Would Have Modified *Harris* in view of *Xing*

187. I disagree with Dr. Abbas's assertion that a POSA would have been motivated to treat mice vitiligo lesions with a CD122 antibody "to reduce the autoreactive Trm cells in the skin that cause the melanocyte destruction in the mouse model." EX1002 (Abbas Decl.), ¶101. Forte and its declarants oversimplify the mouse model used in *Xing* and ignore key differences in the subset and specificity of CD8⁺ T cells disclosed in *Harris* and *Xing*. In my opinion, a POSA would not have relied on *Xing* as a guide for potential vitiligo treatment in *Harris* or otherwise.

188. *Xing* relies on the C3H/HeJ mouse model, which "spontaneously develops alopecia and recapitulates many (but not all) pathologic features of human AA." EX1007 (Xing), 1. This particular mouse model was well-known and its use dates back to 1963. EX2034 (Sundberg), 1. By 2017, the C3H/HeJ mouse model had been used to study diseases including mammary tumors, epilepsy, atherosclerosis, and obesity. EX2091 (Frankel 2014); EX2092 (Moy 2007); EX2093 (Shi 2002);

EX2094 (West 1992). But there is no evidence that the C3H/HeJ mouse model has been used to study vitiligo, let alone suggest that this model can even develop vitiligo. That the C3H/HeJ mouse model has not been shown to develop vitiligo is significant in the context of Forte's obviousness allegations. If one was to assume, as Drs. Abbas and Plott do, sufficient common disease pathologies such that one could extrapolate effects seen in the C3H/HeJ mouse to the *Harris* vitiligo model, one would have expected that the autoimmune response in C3H/HeJ mouse causing AA would also have been widely reported to also cause vitiligo. It has not.

189. *Xing* induced AA in normal-haired C3H/HeJ mice by either injecting CD8⁺NKG2D⁺ T cells from C3H/HeJ AA mice into the skin of normal-haired C3H/HeJ mice or surgically transferring AA skin to a normal-haired mouse. EX1007 (*Xing*), 8. CD8⁺NKG2D⁺ T cells were injected specifically because this subset of cytotoxic T cells play a role in infiltrating around the hair follicle which overexpresses several proteins including ligands of NKG2D which had been previously shown to be upregulated in hair follicles of patients with alopecia areata and also suggested to be particularly important in AA pathogenesis based on genome wide association studies. *E.g.*, EX1007 (*Xing*), 1; EX1008 (*Harris* 2013), 1. As hair follicles are not the target of attack in vitiligo, NKG2D ligands in hair follicles would not be relevant to the epidermal depigmentation that occurs in vitiligo. *E.g.*, EX1008 (*Harris* 2013), 2 (table 1). Further, as discussed below, NKG2D⁺CD8⁺ T cells have

unique properties such that a POSA would not be able to reasonably expect other CD8⁺ T cells to have the same properties or behavior in response to cytokine signaling.

190. *Harris*, on the other hand, used a different type of CD8⁺ T cells specifically targeting both mouse and human PMEL, a melanocyte-specific differentiation antigen.⁶ EX1006 (*Harris*), 1, 2; EX1023 (*Agarwal*), 2. These PMEL CD8⁺ T cells differentiate into cytotoxic T cells that infiltrate skin where they mediate destruction of melanocytes causing depigmentation. By contrast, as Dr. Abbas recognized, the CD8⁺NKG2D⁺ T cells in *Xing* had no known antigen specificity and were “unlikely” to be PMEL-specific. EX2007 (*Abbas Dep. Tr.*), 45:4-25.

191. *Xing* also provides no evidence of reducing IL-15 expression in the upper layers of the skin where melanocytes reside. Figure 2h of *Xing* at most shows that an anti-IL-15R β antibody reduced the frequency of CD8⁺NKGD2⁺ T cells in the *skin affected by AA*, as indicated by the immunohistochemical staining in Fig. 2i focusing on skin around the hair follicle. EX1007, 3 (Fig. 2h and 2i); *see also*

⁶ Given that the T cells recognize PMEL from mouse and human, they would be expected to respond in a similar fashion when exposed to this melanocyte antigen in the mouse or the human.

EX2035 (Xing Suppl.), 11-12, 17, 28 (discussing throughout analyses of AA skin from mice and immunostaining from treated mice around the hair follicle).

192. Forte and its declarants also fail to address the differences in the disease models with respect to *preventing* accumulation of CD8⁺NKG2D⁺ T cells for AA and *depleting* existing PMEL CD8⁺ T cells for vitiligo. *Xing* describes that the anti-IL-15R β antibody “prevented” AA in grafted mice and “blocked the accumulation of CD8⁺NKG2D⁺ T cells,” but does not disclose “***depleting*** CD8⁺ T cells.” See EX1007, 4; EX1004, ¶34. This is consistent with *Xing* further differentiating between “interventions aimed at either preventing or reversing disease” and concludes that the anti-IL-15R β antibody (unlike JAK inhibitors) was ***not “able to reverse established AA.”*** EX1007 (Xing), 4. *Xing*, however, does not disclose “***depleting*** CD8⁺ T cells” with an IL-15R inhibitor as Dr. Plott contends. See EX1004 (Plott Decl.), ¶34. Depletion of CD8⁺ T cells was only observed with JAK inhibitors in *Xing*. EX1007 (Xing), 7. This distinction is significant as the ’505 patent inventors were the first to identify that IL-15 is required for the maintenance of circulating PMEL populations and Trm CD8⁺ T cells.⁷ EX1001, 32:56-67. Nothing in *Xing* is

⁷ The pathology of the *Harris* mouse model (EX1006) involved established vitiligo based on an excess of CD8⁺ already in the skin that needed to be depleted for an effective treatment. In *Harris*, CD8⁺ cells were injected systemically, cell homing

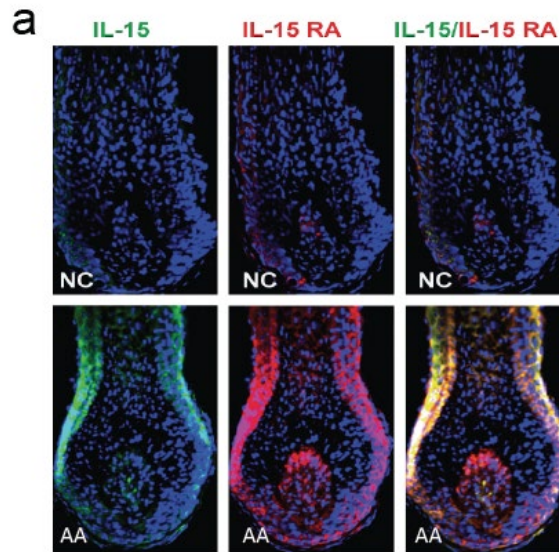
based on treating vitiligo resulting from CD8⁺ T cells already present in the skin. Moreover, nothing in Forte's oversimplified analysis addresses why a POSA would have been motivated to use *Xing's* CD122 antibody—that only prevented accumulation of CD8⁺NKG2D⁺ T cells in skin around the hair follicles and failed to reverse established AA—in the Harris model for vitiligo based on excess PMEL CD8⁺ T cells in the skin epidermal layer where melanocytes reside.

193. Neither Dr. Abbas nor Dr. Plott provide any evidence that the *Harris* PMEL CD8⁺ T cells express NKG2D. Nor would a POSA have assumed that cytokine signaling regulation of CD8⁺NKG2D⁺ T cells is representative of regulation PMEL CD8⁺ T cells. Thus, a POSA would not have relied on targeting

occurred, and the T cells accumulated to form established disease (vitiligo). EX1006 (Harris), 7. Further, “[c]onsistent with human disease, IFN- γ expression was elevated within the depigmenting skin of mice with vitiligo, and was expressed from autoreactive CD8⁺ T cells... This expression... was maintained throughout the course of disease.” EX1006 (Harris), 4; *see also* EX1023 (Agarwal), 5-7, Fig. 5 (using simvastatin in the *Harris* mouse model to reverse vitiligo established over 12 weeks post induction).

IL-15 signaling in *Xing*'s CD8+NKG2D⁺ T cells for AA as a guide for treating vitiligo in *Harris*'s PMEL-specific CD8⁺ T cells.

194. Moreover, vitiligo and AA affect different anatomic structures within the skin, which is a complex organ. *See* Section IV.A.2, above. T cells react along and into the basal layer of the epidermis in vitiligo while T cells in AA collect around the hair follicle bulb, which is deep within the dermis and/or subcutis (depending on the hair cycle stage). None of *Xing*'s reported data provides any indication of IL-15 expression or CD8⁺ T cell accumulation specifically in the melanocyte-containing epidermis layer. Instead, *Xing* focuses on the genes involved in the collapse of immune privilege in the hair follicle, including IL-15 and IFN- γ , but this does not provide any guidance for whether these genes are involved in vitiligo pathogenesis. *See* EX1007 (*Xing*), 6; EX2035 (*Xing* Suppl. Data), 20-21 (Supplementary Figure 5A showing IL-15 expression in the hair follicle deep within the skin (nowhere near the interfollicular epidermis) is reproduced below).



195. For at least these reasons, a POSA would not have been motivated to rely on *Xing's* C3H/HeJ mouse to suggest the immune interactions in or treatment of vitiligo generally or the *Harris* model specifically.

2. There Was No Known Link Between IL-15 Signaling and Vitiligo Treatment

196. As of 2017, the primary focus of vitiligo treatment was on targeting IFN- γ and its signaling response. *E.g.*, EX1006 (Harris), 6 (“clinical significance of the treatment response to IFN- γ neutralization here lies in its potential use as a new therapy for vitiligo”); EX1021, 5 (“Vitiligo is mediated by targeted destruction of melanocytes by CD8⁺ T cells, with IFN- γ playing a central role in disease pathogenesis.”); EX1023, 1 (“We hypothesized that targeting IFN- γ signaling might be an effective new treatment strategy.”); EX2007 (Abbas Dep. Tr.), 50:16-51:20 (discussing EX1023); EX1033, 2 (“Interferon-gamma induced expression of C-X-C

motif chemokine 10 (CXCL10) in keratinocytes is an important mediator of depigmentation in vitiligo.”). As a result, JAK inhibitors targeting the IFN- γ response were being considered for the treatment of vitiligo. EX1021 (Damsky 2017), 5.

197. Neither Dr. Abbas nor Dr. Plott provides any reason for why a POSA would have selected *Xing*’s CD122 inhibitor for use in vitiligo in the context of the vitiligo research focusing on IFN- γ . Indeed, they show no established connection before the ’505 patent between inhibiting IL-15 signaling and treating vitiligo and Dr. Abbas was unaware of any such experiments. EX2007 (Abbas Dep. Tr.), 52:6-10. Forte and its declarants instead rely on references that at most describe IL-15 signaling inhibition for the treatment of *other* autoimmune conditions, with the notable exception of vitiligo. *E.g.*, EX1011, 4:25-34; EX1012, 1; EX1031, 4-7; *see also* EX2012 (Yokoyama), 1.

198. Even if a POSA were guided to *Xing*’s alopecia mouse model to suggest treatment for vitiligo, *Xing* would have dissuaded a POSA from pursuing an CD122 antibody since it failed to show any reversal of alopecia areata; indeed the goal for vitiligo treatment was reversal of disease and durable repigmentation. EX1007 (*Xing*), 4 (“Notably, none of these blocking antibodies [including an anti-IL-15R β antibody] given alone was able to reverse established AA....”); *see* Sections IV.A.1, X.C.1. Even for alopecia treatment, *Xing* appears to have discontinued the study of

the anti-IL-15R β antibody in favor of JAK inhibitors that had shown durable reversal of alopecia. EX1007 (Xing), 6 (“suggest[ing] future clinical evaluation of [ruxolitinib] or other JAK protein kinase inhibitors”). To the extent considered relevant to vitiligo, *Xing*’s results with an CD122 antibody for AA would have been considered a failure given the field’s goals for durable vitiligo reversal, and in fact would have been viewed by a POSA as teaching against this strategy, as discussed further below. EX1007 (Xing), 6; *see also* EX1020 (Rashighi 2014) (“cytokines that drive vitiligo pathogenesis have not been well defined, although they are not likely shared with [psoriasis or related autoimmune] diseases because biological treatments for psoriasis have been ineffective for vitiligo (20-22)”).

199. A POSA would not have expected that targeting IL-15R β would have a stronger effect (reversal of disease through repigmentation) in a different disease (vitiligo). Reversal of alopecia areata in *Xing* was only noted with the use of JAK inhibitors which inhibit multiple cytokines including interferon gamma and thus are inherently different than IL-15 specific blockade. EX1007 (Xing), 6. Given the broad inhibitory function of JAK inhibitors and *Xing*’s findings, a POSA would have been directed away from IL-15 inhibition (which could not reverse alopecia areata in *Xing*) and towards JAK inhibition (which could).

200. This is especially true given *Xing*’s observation that IFN- γ is responsible for the collapse of immunity privilege in the hair follicle, whereas IL-15

is produced as a result, suggesting it is a secondary signal EX1007 (Xing), 6. Indeed, a POSA would not have been motivated to pursue IL-15 inhibition to treat AA (let alone vitiligo) based on this prevailing hypothesis and the observation in *Xing* that IL-15 inhibition cannot reverse established AA. That is to say, once the feed forward loop leading to AA is established, IL-15 inhibition is no longer sufficient to break the loop and lead to hair regrowth. Accordingly, *Xing* would have taught a POSA away from IL-15 inhibition and towards JAK inhibition in AA.

201. In fact, based on the results of *Xing*, IL-15 specific inhibition was not pursued in alopecia areata. Suggesting that a POSA would be motivated to pursue inhibition of IL-15 in vitiligo (an entirely different disease) based on the results of *Xing* is incorrect.

B. Prior to the '505 Patent, a POSA Would Not Have Reasonably Expected Success in Treating Vitiligo with an Inhibitor of IL-15 or IL-15R

202. Even if a POSA were motivated to use *Xing*'s CD122 antibody in *Harris*'s vitiligo mouse model (which I do not agree with), there would have been no reasonable expectation of successfully treating vitiligo.

203. As I discuss above, Forte and its declarants provide insufficient evidence to establish why a POSA would rely on *Xing*'s CD122 inhibitor for the treatment of vitiligo when it was *not* “able to reverse established” disease and reports only preventing accumulation of CD8⁺NKG2D⁺ T cells in the skin. *See*

Section X.A. Given that the *Harris* vitiligo mouse model is premised on established disease resulting from excess PMEL CD8⁺ T cells already present in the skin, a POSA could not have reasonably expected that a treatment that merely prevents accumulation of CD8⁺NKG2D⁺ T cells and that was unable to reverse established AA would then be able to treat vitiligo due to excess cytotoxic PMEL CD8⁺ T cells already present in the skin.

204. There was also no basis for extrapolating a reasonable expectation of success to vitiligo treatment from results for therapeutic agents that worked in AA to the limited extent of preventing CD8⁺NKG2D⁺ T cells accumulation and AA induction. To the contrary, one could not have made this extrapolation since the biological mechanisms and differences in the location of the skin are different between the two diseases. In my opinion, a POSA would have been motivated to pursue a JAK inhibitor targeting the IFN- γ response for AA based on *Xing's* hypothesis and observation that IFN- γ leads to the collapse of immune privilege in the hair follicle, but would not have been motivated to pursue IL-15 inhibition for any purpose—and especially not for vitiligo—given that it was found insufficient to break the feed-forward loop and lead to hair regrowth. Drs. Abbas and Plott do not address the distinct features of *Xing* with respect to IFN- γ response and collapse of immune privilege.

205. Reinforcing the *absence* of a reasonable expectation of success that treatment effects seen with AA can be extrapolated to vitiligo, other reports describe treatment differences between AA and vitiligo using the same agent. For instance, Harris 2016 (EX1032) reports the use of a JAK inhibitor (ruxolitinib) in a patient with concurrent vitiligo and AA, where twelve weeks after discontinuing ruxolitinib, “his hair regrowth was maintained” but “much of the regained pigmentation had regressed” and was “not durable.” EX1032, 1.

206. Moreover, IL-15 was known to have a particularly potent effect on NKG2D T cells that was not known and could not have been predicted for the *Harris* PMEL CD8⁺ cells. For instance, IL-15 was also a known activator of NK cells (in addition to T cells) that drives the expression of NKG2D and activates the cytolytic pathway. EX2012 (Yokoyama), 1. In the context of *Xing*, targeting IL-15 was a logical approach especially given that *Xing* showed elevated IL-15 in both human and mouse AA skin. EX1007 (Xing), 2. Forte and its declarants, however, fail to establish any connection between IL-15 and *Harris*’s PMEL CD8⁺ T cells that were not identified as having the NKG2D receptor. This further reduces any expectation of success in relying on *Xing* for vitiligo.

207. In contrast to what had been shown and was expected for CD8⁺NKG2D⁺ T cells in AA, Forte fails to demonstrate that inhibition of IL-15 signaling would be expected to treat vitiligo. EX1007 (Xing), 4; EX2012

(Yokoyama), 1. Forte thus does not establish that there would have been a reasonable expectation of successfully treating PMEL CD8⁺ T cell-dependent vitiligo in *Harris's* PMEL CD8⁺ T cells via IL-15 signaling inhibition based what was taught in *Xing* with respect to CD8⁺NKG2D⁺ T cells.

208. There would also have been no reasonable expectation of success based on *Xing's* C3H/HeJ mouse model for alopecia, which has never been reported to develop vitiligo. To the extent one would have expected that reducing accumulation of CD8⁺NKG2D⁺ T cells observed in *Xing* would be relevant to treating vitiligo, one also would have expected to have also seen widely reported vitiligo for the C3H/HeJ mouse model. This was not the case. In fact, my laboratory has worked very closely with this strain of mice, maintaining 50-100 animals at any one time, and while development of AA is common, we have never seen depigmentation or vitiligo in this strain, even when the immune system is “turned up” using various strategies including immune checkpoint inhibitor blockade with anti-PD-1 and/or anti-CTLA-4. The absence of vitiligo in C3H/HeJ further precludes having a reasonable expectation of success in vitiligo based on effects seen in those mice.

209. Cheuk (EX1027), which focuses on CD49 expression, provides no more of a reasonable expectation of success than *Xing*. Cheuk identifies a distinct population of CD49a⁺ CD8⁺ Trm cells poised for IFN- γ production in the skin. EX1027 (Cheuk), 2. The authors reported that stimulation with IL-2 or IL-15

potentiate cytokine responses in CD8⁺ Trm cells from healthy skin. EX1027 (Cheuk), 6. Only a small portion of the Cheuk reference actually addresses vitiligo, as opposed to normal healthy donor tissue which is the focus of the paper. Indeed, when studying vitiligo tissue, the authors found an increased prevalence of CD49a⁺ CD8⁺ Trm cells in vitiligo lesions. EX1027 (Cheuk), 8. However, unlike similar cells from normal skin from healthy donors, in vitiligo these cells were already producing cytotoxic markers and IFN- γ (Figure 7E and 7H) and did not require exogenous addition of IL-15 to do so. EX1027 (Cheuk), 9.

210. Cheuk further observed differences in CD49a expression in vitiligo (CD49a⁺) versus psoriasis (CD49a⁻) revealing “a functional specification of distinct skin Trm cell subsets in health and disease.” EX1027 (Cheuk), 4. Cheuk notes that “if Trm cells drive these diseases, then vitiligo and psoriasis would be expected to involve the contribution of functionally different subsets.” EX1027 (Cheuk), 2. The same expectation of “functionally different subsets” holds true for other skin and autoimmune diseases, including vitiligo and AA. Rather than supporting an expectation of success, Cheuk emphasizes the structural and functional differences between healthy and distinct immune-mediated skin diseases and further guards against extrapolating from the results from *Xing* to vitiligo. Thus, POSAs would have recognized that the same “functional dichotomy” may hold true for other skin and autoimmune diseases, including vitiligo and AA, such that there would have

been no reasonable expectation to extrapolate treatment effects seen in one disease model to another. EX1027 (Cheuk), 4.

211. Moreover, Cheuk similarly identifies IFN- γ and CD49 as the root and marker of the problem in these two inflammatory skin diseases. EX1027 (Cheuk), 12. As the authors in Cheuk conclude: “Given the role of IL-2 and IL-15 blockade in potentiating both IL-17 and cytotoxic effector functions in Trm cells, blockade of the downstream JAK/STAT pathways represents a promising therapeutic target for skin diseases putatively caused by aberrant Trm cell activation.” EX1027 (Cheuk), 12. As of 2017, a POSA would have noted and agreed with Cheuk that given the multiple JAK-STAT dependent cytokines implicated, JAK inhibition (and not IL-15 specific inhibition) was the most logical approach to pursue.

212. What this means is that by 2017, the effects seen with one autoimmune disease driven by a distinct subset of Trm cells could not be extrapolated to a different autoimmune disease with a functionally different subset of Trm cells. Rather than supporting an expectation of success for extrapolation from AA to vitiligo, Cheuk points in the opposite direction emphasizing the organizational and functional differences between healthy and distinct immune-mediated skin diseases and further precludes any reasonable expectation of success for extrapolating use of IL-15 from *Xing* to *Harris*.

C. The Claimed Methods Fulfilled a Long-Felt But Unmet Need, Providing Unexpected Results, Praised and Copied by Forte

213. As part of an obviousness analysis, I understand that one must also consider objective evidence, such as whether the invention (i) fulfilled a long-felt but unmet need by (ii) yielding unexpected results (iii) that were praised by and (iv) copied by competitors. As discussed below, each of these factors supports the conclusion that a POSA would not find the claimed invention obvious.

1. Long-Felt But Unmet Need

214. As had been recognized in the literature and based on my experience for vitiligo, “[t]he goal of treatment is not only to halt disease progression, but promote repigmentation through melanocyte regeneration, proliferation, and migration.” EX2060 (Rashigi 2017), 12; EX2062 (Regazzetti 2015) (“Halting disease progression and repigmenting the lesional skin represent the two faces of therapeutic challenge in vitiligo.”); Ex. 1004 (Plott), ¶37 (“Optimally, treatment would eliminate existing lesions.”). *See* Section IV.A.2, above.

215. Yet, despite extensive efforts, prior to April 2017 where there was a recognized long felt but unmet need for an effective and durable therapy for vitiligo. Rashighi (2014), 7 (“[S]uccessful treatment strategies should be able to reverse established disease through repigmentation, rather than simply prevent it.”); Relke 2019, 1 (although not prior art, even in 2019 there remained “no consistent, long-term, durable therapy for vitiligo for all patients, *highlighting the unmet need* for

new safe and effective therapies to control this disease.” (emphasis added)); EX2001 (Harris 2015), 2 (“There are currently no FDA-approved treatments for vitiligo, and standard off-label treatments are limited in efficacy.”); EX2098 (Rashighi & Harris 2015, 1 (“[Existing] treatments utilize a non-targeted approach with moderate efficacy, but are used off-label, as they are not Food and Drug Administration (FDA)-approved for use in vitiligo.”); EX2099 (Riding 2019), 15 (“[T]here are no FDA approved treatments for vitiligo.”); EX2100 (Grimes 2005) (“At best, none of these [existing] treatment options have been optimal”).

216. Even JAK inhibitors, such as ruxolitinib, used successfully to treat AA had not been shown to durably reverse disease. EX2060 (Rashighi 2017), 4 (“The treatment response from these inhibitors did not appear to be durable, as patients lost the repigmentation after discontinuing treatment.”); EX2055 (Relke and Gooderham 2019), 6 (“repigmentation is not maintained after discontinuation of JAK inhibitors”); EX2001 (Harris 2015), 1 (“Here we 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... Twelve weeks after discontinuing ruxolitinib, while his hair regrowth was maintained, much of the regained pigment had regressed.”); *see also* EX1007, 4, 6. (neither disease reversal nor durability was achieved using Xing’s an IL-15R inhibitor for AA)

217. Forte highlighted the continued unmet need for durable vitiligo treatment to its investors. EX2004 (SEC Forte Investor Presentation), 33 (“while JAK inhibitors have demonstrated efficacy... there remains a significant unmet need... for treating [] vitiligo”).

2. Unexpected Results

218. A POSA would appreciate the repeated failure by others to develop a durable vitiligo specific therapy. And in particular, a POSA would be aware of cases where a treatment produced durable results for other immune-mediated diseases, but not vitiligo. EX2001 (Harris 2015), 1.

219. In view of these failures by others, a POSA would have been surprised by the results reported in the '505 patent describing durable treatment of vitiligo. Specifically, practicing the claimed method, the data in the patent demonstrates that using an IL-15 signaling pathway inhibitor to treat vitiligo in mice produced sustained durable repigmentation of vitiligo lesions, even after treatment was discontinued. *See* EX1001, 33:24-26 (“After 8 weeks of systemic treatment, we saw significant repigmentation in treated mice compared to controls (FIG. 6A-C).”), Fig. 6C (depicted below showing statistically significant increase in pigmentation of IL-15R β Ab treated animals compared to control), 33:56-64 (after stopping treatment over a 10-week period, “experimental mice treated with intradermal CD122

antibody had significant repigmentation compared to control mice without depletion of PMEL T cells (FIG. 8”).

220. The ’505 patent explains, and a POSA reading the patent would understand, that the results reported are due to inhibition of IL-15 signaling with a therapeutically effective amount of an IL-15 or IL-15R inhibitor generally as opposed to the specific inhibitor used in the example. In this regard, the ’505 patent explains

The present data support targeting this cytokine as a strategy to clear autoreactive memory cells from the tissue, resulting in a long-lasting, durable response to treatment. This is in contrast to existing therapies for inflammation in skin and other tissues, which result in rapid relapse after they are discontinued. Further, targeting IL-15 preferentially affects autoreactive T cells while leaving most endogenous T cell populations intact.

EX1001, 6:22-29, *see also* 6:16-21 (“targeting IL-15 signaling through antibody treatment even after the generation of Trm in the tissue was effective at clearing these cells from the epidermis, indicating that IL-15 signaling is required for maintenance of these cells”); *id.*, 33:64-66 (data “suggests that targeting IL-15 in the skin in vitiligo, unlike existing therapies, could provide a durable treatment option”).

3. Praise by Forte

221. The significance of the claimed method of treating vitiligo with an inhibitor of IL-15 or the IL-15 receptor is also reflected in Forte’s reporting of the

potential commercial value of its CD-122 antibody, specifically its own “FB-102 is more advanced... highlighting significant current value.” EX2004 (SEC Forte Investor Presentation), 27 (“\$70M upfront and \$1.4 billion in milestones”), 26, (FB-102 “has significant intermediate and long term value based on [PO’s] acquisition[.]”).

4. Copying by Forte

222. It is clear that Forte recognized the large unmet need in treating vitiligo and the unexpected results described in the ’505 patent as Forte then copied the claimed method by developing “FB-102, [which] targets CD-122, a subunit of the [] IL-15 receptor,” which Forte advertises as a pipeline candidate for the treatment for vitiligo. EX2045 (Forte Pipeline Website); EX2003 (Forte Press Release), 1 (FB-102 has “therapeutic potential of anti-CD122 in multiple autoimmune diseases anti-CD-122 including in vitiligo.”); EX2004 (Forte 9/1 Investor Presentation), 26 (“FB-102 also shows activity in vitiligo”).

223. As discussed above (VII.B. and IX.A.), a POSA would have understood the ’505 patent described and enabled a POSA to use IL-15 inhibitors for the treatment of vitiligo. A POSA would understand Forte thought so too, as Forte copied exactly the claimed method in developing its own FB-102, and in fact, relies on the same preclinical proof of concept mouse model. EX2009 (Forte Interrogatory Response).

Appendix A

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent Pub. No. 25 2006/0236411 (EX2107)		NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPS CKVTAMKCFLELQVISLESGDASIHDTVENLILA NNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVH IVQMFINTS	Other (Fusion Protein)	13-Oct-03	IL-15R	γc, β	
US Patent Pub. No. 25 2006/0236411 (EX2107)		PKSADKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSGFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	Other (Fusion Protein)	13-Oct-03	IL-15R	γc, β	
US Patent Pub. No. 25 2006/0236411 (EX2107)		PRGPTIKPCPPCKCPAPNLLGGPSSVFIFPPKIKDV LMISLSPIVTCVVVDVSEDDPDVQISWVFNNEV HTAQQTQTHREDYNSTRLVVSALPIQHQQDWMSG KEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVL PPPEEEMTKKQVTLTCMVTDMPEDIYVEWTN NGKTELNYKNTEPVLDSDGSYFMYSKLRVVEKK NWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK	Other (Fusion Protein)	13-Oct-03	IL-15R	γc, β	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent Pub. No. 25 2006/0236411 (EX2107)		NWVNVISDLKKTEDLIQSMHIDATLYTESDVHPS CKVTAMKCFLELQVISLESGDASIHDVTENLIILA NNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFV HIVQMFINTSDPKSADKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYS KLTVDKSRWQQGNVFCFSVMHEALHNHYTQKS LSLSPGK	Other (Fusion Protein)	13-Oct-03	IL-15R	γc, β	
US Patent Pub. No. 25 2006/0236411 (EX2107)		NWVNVISDLKKTEDLIQSMHIDATLYTESDVHPS CKVTAMKCFLELQVISLESGDASIHDVTENLIILA NNSLSSNGVTESGCKECEEELEEKNIKEFLQSFVHI VQMFINTSDPRGPTIKPCPPCKCPAPNLLGGPSV FIFPPKIKDVLMSLSPIVTCVVVDVSEDDPDVQIS WVFVNNVEHTAQTQTHREDYNSTLRVVSALPIQH QDWMSGKEFKCKVNNKDLPAPIERTISKPKGSV RAPQVYVLPPEEEMTKKQVTLCMVTD FMPE DIYVEWTNNGKTELNYKNTEPVLDSGDSYFMYS KLRVEKKNWVERNSYSCSVVHEGLHNHHTTTS FSRTPGK	Other (Fusion Protein)	13-Oct-03	IL-15R	γc, β	
US Patent No. 8,163,879 (EX2051)	46:24	huIL15N72R	Other (Fusion Protein)	5-Feb-10	IL-15R	γc, β	
US Patent No. 8,163,879 (EX2051)	46:44	huIL15D8A	Other (Fusion Protein)	5-Feb-10	IL-15R	γc, β	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 8,163,879 (EX2051)	46:43	huIL15D8N	Other (Fusion Protein)	5-Feb-10	IL-15R	γc, β	
US Patent Pub. No. 2017/0101452 (EX 2106)	16	Pro Lys Glu Phe Leu Glu Arg Phe Val His Leu Val Gln Met Phe Ile His Gln Ser Leu Ser	Peptide	6-Oct-16	IL-15R	γc	Specific sequence of peptide
US Patent No. 9,133,244 (EX2032)	25	Ile Lys Glu Phe Leu Gln Arg Phe Ile His Ile Val Gln Ser Ile Ile Asn Thr Ser	Peptide	17-Jan-12	IL-15R	γc	Specific sequence of peptide
US Patent No. 7,153,507 (EX2031)	2:46	146B7	Antibody	23-Aug-02	IL-15R	γ, β	
US Patent No. 7,153,507 (EX2031)	2:46	146H5	Antibody	23-Aug-02	IL-15R	γ, β	
US Patent No. 7,153,507 (EX2031)	2:46	404E4	Antibody	23-Aug-02	IL-15R	γ, β	
US Patent No. 7,153,507 (EX2031)	2:46	404A8	Antibody	23-Aug-02	IL-15R	γ, β	
US Patent No. 5,795,966 (EX2105)	18	IL-15-Q156C	Other (Mutein)	22-Feb-95	IL-15R	γ, β	
US Patent No. 5,795,966 (EX2105)	18	IL-15-Q156S	Other (Mutein)	22-Feb-95	IL-15R	γ, β	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 5,795,966 (EX2105)	18	IL-15-D56C	Other (Mutein)	22-Feb-95	IL-15R	γ, β	
US Patent No. 5,795,966 (EX2105)	18	IL-15-D56C-Q156C	Other (Mutein)	22-Feb-95	IL-15R	γ, β	
US Patent No. 5,795,966 (EX2105)	18	IL-15-D56C-Q156S	Other (Mutein)	22-Feb-95	IL-15R	γ, β	
US Patent No. 5,795,966 (EX2105)	18	IL-15-D56S	Other (Mutein)	22-Feb-95	IL-15R	γ, β	
US Patent No. 5,795,966 (EX2105)	18	IL-15-D56S-Q156S	Other (Mutein)	22-Feb-95	IL-15R	γ, β	
WO 2015/181394 (EX2024)	4:8-9	N-(2,4-dichlorophenyl)-2-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)sulfonyl)acetamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	4:10-11	2-methyl-4-((4-methyl-5-(methylthio)-4H-1,2,4-triazol-3-yl)methyl)phthalazin-1 (2H)-one	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	4:12-13	N-(adamantan-1 -yl)-2-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1 -yl)methyl)-4H-1,2,4-triazol-3-yl)thio)acetamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	4:14-15	2-methyl-4-((4-methyl-5-(methylsulfinyl)-4H-1,2,4-triazol-3-yl)methyl)phthalazin-1 (2H)-one	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2015/181394 (EX2024)	4:16-17	2-methyl-4-((4-methyl-5-(methylsulfonyl)-4H-1,2,4-triazol-3-yl)methyl)phthalazin-1-one	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	4:18-19	N-(2,4-dichlorophenyl)-2-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)acetamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	4:20-21	N-(2,4-dichlorophenyl)-4-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)butanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	4:22-23	N-(2,4-dichlorophenyl)-6-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)hexanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	4:24-25	N-(2,4-dichlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	4:26-27	N-(2,4-dibromophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	4:28-29	N-(2,4-difluorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent Publication Date (NPL))	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2015/181394 (EX2024)	4:30-31	N-(2,4-dihydroxyphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide;	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:1-2	N-(2-hydroxyphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:3-4	N-(2-hydroxy-4-methoxyphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:5-6	N-(4-azidophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:7-8	N-(adamantan-1-yl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:9-10	N-(2-Chloro-4-methylphenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:11-12	Ethyl 3-(8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamido)benzoate	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2015/181394 (EX2024)	5:15-16	N-(2-chlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula; Duplicate of 5:21-22
WO 2015/181394 (EX2024)	5:17-18	N-(3-chlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:19-20	N-(4-chlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:23-24	11-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)-N-(naphthalen-1-yl)undecanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:25-26	N-(furan-2-ylmethyl)-11-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:27-28	4-((5-(decylthio)-4-methyl-4H-1,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1 (2H)-one	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:29-30	N-(2,4-dichlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)oxy)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2015/181394 (EX2024)	5:31-32	N-(adamantan-1-yl)-2-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	5:33-34	N-(adamantan-1-yl)-4-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	6:1-2	Methyl 2-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzoate	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	6:3-4	N-(2,4-dichlorophenyl)-4-(((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	6:5-6	N-(2,4-dichlorophenyl)-11-(((4-methyl-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	6:7-8	N-(2,4-dichlorophenyl)-11-(((5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)undecanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2015/181394 (EX2024)	6:9-10	N-(2,4-dichlorophenyl)-11 -((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1 -yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	6:11-12	N-(2,4-dichlorophenyl)-11 -((5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1 -yl)methyl)-lo,x3a,4d-iazol-2-yl)thio)undecanamide	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	6:13-14	N-(2,4-dichlorophenyl)-7-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-lyl)methyl)-4H-1,2,4-triazol-3-yl)thio)heptanamide (compound C5)	Small Molecule	1-Jun-15	IL-15R	β	Preferred embodiment of disclosed formula
WO 2015/181394 (EX2024)	16:24-25	ethyl [(E)-3-oxo-l,3-dihydroisobenzofuran-l-ylidene]acetate	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	17:14	ethyl 2-(3-methyl-4-oxo-3,4-dihydrophthalazin-l-yl)acetate	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	18:7-8	N-alkylation of ethyl 2-(3-methyl-4-oxo-3,4-dihydrophthalazin-lyl) acetate	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	19:1-2	2-(3-methyl-4-oxo-3,4- dihydrophthalazin-l-yl)acetohydrazide	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	19:15-16	4-((5-mercapto-4-methyl-4H-l,2,4-triazol-3-yl)methyl)-2-methylphthalazin-1 (2H)-one	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	20:24-25	8-bromo-N-(2,4-dichlorophenyl)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	21:13	8-bromo-N-(2,4-difluorophenyl)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2015/181394 (EX2024)	22:8	8-bromo-N-(adamant-1-yl)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	23:4-5	N-(2,4-dichlorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	23:26-27	N-(2,4-difluorophenyl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	24:19-20	N-(adamantan-1-yl)-8-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)octanamide.	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	25:16-17	N-(2,4-dichlorophenyl)-11-((4-methyl-5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)undecanamide	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	26:02	11-bromo-7V-(2,4-dichlorophenyl)undecanamide	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
WO 2015/181394 (EX2024)	27:22-23	N-(2,4-dichlorophenyl)-11-((5-((3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl)thio)undecanamide (D4)	Small Molecule	1-Jun-15	IL-15R	β	Example preparation of compound of the formula
US Patent No. 9,028,830 (EX1011)	1-4	HuABC2	Antibody	7-Apr-11	IL-15R	β	At least 90% Identical to SEQ ID NO. 41
US Patent No. 9,028,830 (EX1011)	1-4	ABC101	Antibody	7-Apr-11	IL-15R	β	At least 90% Identical to SEQ ID NO. 41

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 10,150,802 (EX2110)	46:24	IL-2-H9-T	Other (Mutein)	21-Oct-16	IL-15R	β	Characterized as IL-2 β , but this is the same subunit as IL-15R β
US Patent No. 10,150,802 (EX2110)	46:24	IL-2-H9-RE	Other (Mutein)	21-Oct-16	IL-15R	β	Characterized as IL-2 β , but this is the same subunit as IL-15R β
US Patent No. 10,150,802 (EX2110)	46:24	IL-2-H9-RET	Other (Mutein)	21-Oct-16	IL-15R	β	Characterized as IL-2 β , but this is the same subunit as IL-15R β
US Patent No. 10,150,802 (EX2110)	46:24	IL-2-H9-RETR	Other (Mutein)	21-Oct-16	IL-15R	β	Characterized as IL-2 β , but this is the same subunit as IL-15R β
US Patent No. 7,736,638 (EX2019)	4:16-17	Lys Val Thr Ala Met Lys Cys Phe Leu Leu	Peptide	16-Sep-05	IL-15R	α -fc	
US Patent No. 7,736,638 (EX2019)	4:16-17	CodeName: Peptide 7	Peptide	16-Sep-05	IL-15R	α -fc	
US Patent No. 10,301,384 (EX2085)	31:55-32:6	huB-E29-I	Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6	huB-E29-2	Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6	huB-E29-3	Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-4		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-5		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-6		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-7		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-8		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-9		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-10		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-11		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-12		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-13		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-14		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-15		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-16		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-17		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-18		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-19		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-22		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-24		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-30		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-31		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region
US Patent No. 10,301,384 (EX2085)	31:55-32:6 huB-E29-34		Antibody	1-Jul-15	IL-15R	α -Fc	95% Identity of Heavy Chain Variable Region and 95% Identity of Light Chain Variable Region

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent Pub. No. 15 2006/0057680 (EX2108)		NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPS CKVTAMKCFLELQVISLES GDASIHD TVENLIILANNSLSSNGNVTESGCKECEELEEKNIK EFLQSFVHIVQMFINTS	Peptide	11-Aug-05	IL-15R	α , β , γ	
US Patent Pub. No. 15 2006/0057680 (EX2108)		NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPS CKVTAMKCFLELQVISLES GD ASIHDTVENLIILANNSLSSNGNVTESGCKECEELE EKNIKEFLDSFVHIVDMFINTS	Peptide	11-Aug-05	IL-15R	α , β , γ	
US Patent Pub. No. 15-16 2006/0057680 (EX2108)		EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRWS VLTVLHQDWLNGKEYKCKV SNKALPAIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK	Peptide	11-Aug-05	IL-15R	α , β , γ	
US Patent Pub. No. 16 2006/0057680 (EX2108)		DPKSADKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKV SNKALPAIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK	Peptide	11-Aug-05	IL-15R	α , β , γ	

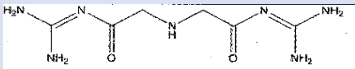
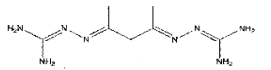
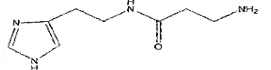
Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent Pub. No. 16-17 2006/0057680 (EX2108)		NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPS CKVTAMKCFLELQVISLESGD ASIHDTVENLIILANNSLSSNGNVTESGCKECEELE EKNIKEFLDSFVHIVDMFINT SDPKSADKTHTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVWDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK	Peptide	11-Aug-05	IL-15R	α , β , γ	
US Patent Pub. No. 17 2006/0057680 (EX2108)		MPMGSLQPLATLYLLGMLVASCLGNWVNVISD LKKIEDLIQSMHIDATLYTESD VHPSCVTAMKCFLELQVISLESGDASIHDTVEN LIILANNSLSSNGNVTESGCK ECEELEEKNIKEFLDSFVHIVDMFINTSDPKSADK THTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYN STYRWSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTL PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK	Peptide	11-Aug-05	IL-15R	α , β , γ	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent Pub. No. 16:28 2005/0123542 (EX2109)		mAb 146B7	Antibody	11-Jun-03	IL-15R	α , β , γ	
US Patent No. 16:46 5,795,966 (EX2105)		M110 [ATCC Accession HB12061]	Antibody	22-Feb-95	IL-15R	α , β , γ	Hybridoma Derived/Deposited with ATCC
US Patent No. 16:46 5,795,966 (EX2105)		M111 [ATCC Accession HB12052]	Antibody	22-Feb-95	IL-15R	α , β , γ	Hybridoma Derived/Deposited with ATCC
US Patent No. 16:46 5,795,966 (EX2105)		M112[ATCC Accession HB12063]	Antibody	22-Feb-95	IL-15R	α , β , γ	Hybridoma Derived/Deposited with ATCC
Ferrari-Lacraz S et al., Targeting IL-15 Receptor-Bearing Cells with an Antagonist Mutant IL-15/Fc Protein Prevents Disease Development and Progression in Murine Collagen-Induced Arthritis, 173(9) J. Immunol. 5818-26 (2004) (EX2114)	5819	CRB-15	Other (Fusion Protein)	27-Apr-04	IL-15R	α , β , γ	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2014/191823 (EX2014)	11		Small Molecule	29-May-14	IL-15R	α	
WO 2014/191823 (EX2014)	11		Small Molecule	29-May-14	IL-15R	α	
WO 2014/191823 (EX2014)	11		Small Molecule	29-May-14	IL-15R	α	
WO 2014/191823 (EX2014)	11		Small Molecule	29-May-14	IL-15R	α	
WO 2014/191822 (EX2013)	10:3	4-([1-(4-Fluorophenyl)-1H-tetrazol-5-yl]-thio)methyl)benzoic acid	Small Molecule	29-May-14	IL-15R	α	Preferred embodiment of disclosed formula
WO 2014/191822 (EX2013)	10:4	Methyl 2,4-dihydroxy-3-methyl benzoate	Small Molecule	29-May-14	IL-15R	α	Preferred embodiment of disclosed formula
WO 2014/191822 (EX2013)	10:5	3,5- bis[(3-Carboxy-1-oxo-2-(E,E)-propen-2-enyl-1-yl)amino]benzoic acid,	Small Molecule	29-May-14	IL-15R	α	Preferred embodiment of disclosed formula
WO 2014/191822 (EX2013)	10:6	4-([2-Carboxybicyclo[2.2.1]heptan)carbonyl]amino}methyl)benzoic acid	Small Molecule	29-May-14	IL-15R	α	Preferred embodiment of disclosed formula
WO 2014/191822 (EX2013)	10:7	4-([2-Carboxycyclohexyl)carbonyl]amino}methyl)benzoic acid	Small Molecule	29-May-14	IL-15R	α	Preferred embodiment of disclosed formula
WO 2014/191822 (EX2013)	10:8	3,5- bis[(4-Carboxyethyl-2-oxo)amino]benzoic acid	Small Molecule	29-May-14	IL-15R	α	Preferred embodiment of disclosed formula
WO 2014/191822 (EX2013)	10:9	Methyl 4-([3-methoxycarboxyethyl)carbonyl]amino}methyl benzoate	Small Molecule	29-May-14	IL-15R	α	Preferred embodiment of disclosed formula
WO 2012/061536 (EX2088)	42	GAGATGAAGACTTGAAAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CACAGGAACCACAGAGATA	Nucleotide	2-Nov-11	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2012/061536 (EX2088)	42	ACATCTGGGTCAAGAGCTA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GAATAGATGTGGTAATGAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CTGGAATACATGTGGTAAT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GGATTCAGGAAGAAGAAAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CAGCAGAGATGAAGACTTG	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	AGGGAAGACACCAGCGTTT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GCTAAAGACGACTGAGAAG	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	TGACATTGTACCTTGATA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	ACTCTGGTTTCAAGCGTAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CCACAGAGATAAGCAGTCA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	AGAGATGAAGACTTGGAAG	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CAGGAGAGACCAAAGGCTT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GACCAGCAGCAGAGATGAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	TAGGTAAAGACGACTGAGA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GTGTGAGCTGCCTGGAATA	Nucleotide	2-Nov-11	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2012/061536 (EX2088)	42	ACCCAAAGCTCTCTGTCAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	TACCTCAAGTCAAGGCAAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GAAAAGTGACATACCCAAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GAAGGATTCAGGAAGAAGA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GGCCACAACAGCAGCTATT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GCAGTAGAGATGAAGACTT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CCAGCTAAGTCCGGAGTGA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GCTCTCACCACCTATGAAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CTAAAGACGACTGAGAAGA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	AGTGTGAGCTGCCTGGAAT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	AAGGATTCAGGAAGAAGAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GAGATAAGCAGTCATGAGT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GGCCAGCGTTGAAATGGAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GGGACCAGCAGCAGAGATG	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	AGCTAAAGACGACTGAGAA	Nucleotide	2-Nov-11	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2012/061536 (EX2088)	42	CAAAGCTCTCTGTCAATTA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GCTTCATCTCCCAGCTCAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CCACAGGAACCAACAGAGAT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CAGCTAAGTCCGGAGTGAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CAGCAGGATCTCACGGACT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GACCAAAGGCTTCTGAGCA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GAAGAAAACCTCAACTCAGT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GCATGCTACCTCAAGTCAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CACAGAGAAAAGTGACATA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CATTGTACCTTGATATAAAC	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CAGCTGATGCCTTCAAAAT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	ACAGGAACCCACAGAGATAA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	GCAGAGATGAAGACTTGGA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	TGAAGGAGCCTCTCTGCTT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	ACCAAAGGCTTCTGAGCAG	Nucleotide	2-Nov-11	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2012/061536 (EX2088)	42	AGGCTTCTGAGCAGGATTT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	CCCAAAGCTCTCTGTCAAT	Nucleotide	2-Nov-11	IL-15R	α	
WO 2012/061536 (EX2088)	42	TCTCCCAGCTCAAACAACA	Nucleotide	2-Nov-11	IL-15R	α	
WO 2010/037818 (EX2027)	22	EVQLVESGGGLVQAGGSLRLSCAASGF TFDDYAIGWFRQAPGKEREGVSCMDSS DGSTYYADSVKGRFTISSDNAKNMVY LQMNSLKVEDTAVYYCAILDCAWTT LGGEYDYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	22	EVQLVESGGGLVQAGGSLRLSCAASGF TFDDYAIGWFRQAPGKEREGVSCMDSS DGSTYYAGSVKGRFTISSDNAKNMVY LQMNSLKVEDTAVYYCAILDCAWTT LGGEYDYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	22	EVQLVESGGGLVQAGGSLRLSCAASGR TFSSHTIGWFRQAPGKDREFVAAIRWS SSNTYYADSVKGRFTISRDNKNTVYL QMNSLPEDTAVYYCAAGGSTVSWYY AHYDYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	22	EVQLVESGGGLVQAGGSLRLSCAASGR TFSSHTLGWFRQAPGKDREFVAAIRWIS SNTYYADSVKGRFTISRDNKNTVYLQ MNSLPEDTAVYYCAVGGSTVSWYYA HYDYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2010/037818 (EX2027)	22-23	EVQLVESGGGLVQPGGSLRLSCVGS GFSISAVGWYRQTPGKQREWVAVIFAS GSTDYAGSVKGRFTISRDNKNTVYLQ MNSLKPEDTAVYYCNAGVTTNPGVHR ASSYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	23	EVQLVESGGGLVQPGG SLRLSCVGS GFSISAVGWYRQTPGKQREWVAVIFAS GSTDYAGSVKGRFTISRDNKNTVYLQ MNSLKPEDTAVYYCNAGVTTNPGVHR ASRHWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	23	EVQLVESGGGLVQPGGSLRLSCVGS GFSISAVAWYRQTPGKQREWVGIFSS GSTDYADSVKGRFTISRDNKNTVYLQ MNSLKPEDTAVYYCNAGVTTNRGVHH ESNYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	23	EVQLVESGGGLVQPGGSLRLSCVGS GFSISAVGWYRQTPGKQREWVGIFSS GSTDYADSVKGRFTISRDNKNTVYLQ MNSLKPEDTAVYYCNAGVTTNRGVHR ESNYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	23	EXQLVESGGGLVQPGGSLRLSCVGS GFSISAVGWYRQTPGKQREWVADIFSS GSTDYADSVKGRFTISRDNKNTVYLQ MNSLKPEDTAVYYCNAGVTTNRGVHR ESSYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	23	EVQLVESGGGLVQAGGSLRLACAASG RTFSKNPMGWFRQAPGKGRDFVAGIS GSGFGKVYTGSVKGRFTISRDNKNA MYLDMISLKPEDTAVYYCAADTRNRD GTWIGVVDSDWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2010/037818 (EX2027)	23	EVQLVESGGGLVQPGGSLRLSCVASGF TLDYYAIGWFRQVAGKEREGVSCISS SSDGSTIYADSVKGRF'TISRDNVKN TVY LQMNSLKPEDTAVYYCATEVGNGFCS DFDPYEYDYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	23-24	EVQLVESGGGLVQAGGSLRLSCAASGR TFSSLDMA WFRQ APGKERDTV ASIN SS GGTTSYTDSVQGRFTISRDNAKNTVYL QMNSLKPEDTAVYYCAARVPSAVSAT PIYWGGGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	24	EVQLVESGGGLVQPGGSLRLSCAASGF AFSSYVMSWVRQAPGKGLEWVSGINT GGDDIRYADSVKGRFT IGRDNAKNTLYLQ MNSLKPEDTGVIYCGVGGVAVNAYDPRGQG TQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	24	EVQLVESGGGLVQAGGSLRLSCAASGF TFDD Y AIG WFRQ APGKEREG V ACIRN S DGSTHYVDSVKGRFTISSDSADNTVYL QMNSLKPEDTAVYYCAARVRLGCTSV LAAYDYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	24	EVQLVESGGGSVQPGGSLTSCAASGF AFSLYHMNWVRQAPGKGLEWVSRJSN DGTSTIYTD SVKGRFTISRNNAKNALYL QMNSLKPEDTAVYYCAKSTYDSRWRD HDYDYGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	24	EVQLVESGGGLVQAGGSLRLSCAASG GTFSSYAMGWFRQAPGKEREFVARVT WGANTYYAESVKGRFTISRDNAKNTV WLQMNSLKPEDTAAYYCAADRKYAG HINYTPLTSYDYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2010/037818 (EX2027)	24	EVQLVESGGGLVQAGDSLRLSCIASGR TLYSDPMGWFRQAPGNREFVASINWS GTGRVYDDSVKGRFTISRDNANTVYL QMNSLKPEDTAAYYCAARVGTEFQYW GQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	24	EVQLVESGGGLVQAGGSLRLSCAASGI TFSNARMGWFRQTPGKEREFVATISPS GSNTGYADSVKGRFSISRDNADTVYL QMNSLKAGDTAIYYCTCARDFYTDYT RSSEYDFWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	24	EVQLVESGGGLVQAGGSARLSCAASGI PGTLNDTAWFRQTPGEQREVVAIRRSR GNISYADSVKGRFTISRDNADQDSVYLQ MNLKLPEDTAIYYCAIAVFSRDFPPKR YEYWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
WO 2010/037818 (EX2027)	25	EVQLVESGGGLVQPGGSLRLSCAASF TLXDN AIG WFRQ APGKEREG VSCISS S DGSTYYTDSXKGRFTISRDNANTVYL QMNSLKPEDTAVYYCAAGVEDCTYYD GSYYISITADFGSWGQGTQVTVSS	Antibody	1-Oct-09	IL-15R	α	IL-15R Alpha Encoding Sequence(80% AA Identity)
US Patent No. 8,431,524 (EX2049)	3:20-21	Lys Val Thr Ala Met Thr Cys Phe Leu Leu	Peptide	30-Sep-09	IL-15R	α	
US Patent No. 8,431,524 (EX2049)	6:16-34	KVTAMKCFL	Peptide	30-Sep-09	IL-15R	α	
US Patent No. 8,431,524 (EX2049)	6:16-34	KVTAMKCFLA	Peptide	30-Sep-09	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 8,431,524 (EX2049)	6:16-34	KVTAMKCFAL	Peptide	30-Sep-09	IL-15R	α	
US Patent No. 8,431,524 (EX2049)	6:16-34	KVTAAMKCFLL	Peptide	30-Sep-09	IL-15R	α	
US Patent No. 8,431,524 (EX2049)	6:16-34	KVAAMKCFLL	Peptide	30-Sep-09	IL-15R	α	
US Patent No. 8,431,524 (EX2049)	6:16-34	KATAMKCFLL	Peptide	30-Sep-09	IL-15R	α	
US Patent No. 8,431,524 (EX2049)	6:16-34	KVTAMTCYLL	Peptide	30-Sep-09	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Leu Asp Glu Leu Gln Val Ile Ser Leu	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Leu Glu Glu Leu Gln Val Ile Ser Leu	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Leu Lys Glu Leu Gln Val Ile Ser Leu	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Leu Arg Glu Leu Gln Val Ile Ser Leu	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Leu Leu Glu Leu Gln Val Ile Asp Leu	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Leu Leu Glu Leu Gln Val Ile Glu Leu	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Leu Leu Glu Leu Gln Val Ile Lys Leu	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Leu Leu Glu Leu Gln Val Ile Arg Leu	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Leu Leu Glu Leu Gln Val Ile Ser Asp	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Leu Leu Glu Leu Gln Val Ile Ser Glu	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Leu Leu Glu Leu Gln Val Ile Ser Lys	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Leu Leu Glu Leu Gln Val Ile Ser Arg	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Glu Asp Leu Ile Ile	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Glu Glu Leu Ile Ile	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Glu Lys Leu Ile Ile	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Glu Arg Leu Ile Ile	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Glu Asn Leu Ile Asp	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Glu Asn Leu Ile Glu	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Glu Asn Leu Ile Lys	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Glu Asn Leu Ile Arg	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Asp Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Glu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Lys Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Asp Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Glu Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Thr Ser Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Lys Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Gln Ser Pro Ser Val Ile Asn Leu Val Asn Met His Cys Lys Arg Leu Ile Ile Val Ile Ile Asp Val Thr Glu Ser Leu Ala Ser Asp Ala Thr Ala Met Gly Asp Asn Asn Leu Lys Leu Tyr Lys Cys Lys Ile Thr Glu Phe Leu Glu Asp Ala Ser Ser Leu Ile His Ser Ser Ser Asp Leu Glu Asp Thr Asn Gly Leu Ile Val His Leu Gln Val Glu Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Gln Ser Met His Ile Asp Ala Thr Pro Ser Cys Lys Val Thr Ala Met Val Ile Ser Asp Glu Ser Gly Asp Leu Lys Lys Ile Glu Asp Leu Ile Leu Tyr Thr Glu Ser Asp Val His Lys Cys Phe Leu Leu Glu Leu Gln Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Glu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Lys Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Arg Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Lys Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Arg Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asp Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Glu Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Lys Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Arg Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Glu Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Gln Ser Met His Ile Asp Ala Thr Pro Ser Cys Lys Val Thr Ala Met Val Ile Ser Leu Glu Ser Gly Asp Leu Lys Lys Ile Glu Asp Leu Ile Leu Tyr Thr Glu Ser Asp Val His Lys Cys Phe Leu Leu Glu Leu Gln Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Lys Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Arg Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Asp Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Thr Ser Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Glu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Lys Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 7,858,081 (EX2103)	29-66	Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Arg Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser	Other (Mutein)	10-Feb-05	IL-15R	α	
US Patent No. 7,579,439 (EX2111)	4:45	m-IL-15-Fc(A149G, A156G)	Other (Fusion Protein)	30-Dec-03	IL-15R	α	
US Patent No. 5,795,966 (EX2105)	18	PEG-IL-15	Other (Modified Molecule)	22-Feb-95	IL-15R	α	
US Patent No. 5,795,966 (EX2105)	18	PEG-IL-15-D56C	Other (Modified Molecule)	22-Feb-95	IL-15R	α	
US Patent No. 10,202,433 (EX2028)	10:31	IL15-AN-Fc	Other (Fusion Protein)	27-Jun-14	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
Ruchatz H et al., <i>Soluble IL-15 receptor alpha-chain administration prevents murine collagen-induced arthritis: a role for IL-15 in development of antigen-induced immunopathology</i> , 160(11) J. IMMUNOL. 5654-60 (1998) (EX2017)	5655	sIL-15R α	Other (Soluble IL-15 Receptor)	31-Oct-97	IL-15R	α	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
Mortier E et al., <i>Soluble interleukin-15 receptor alpha (IL-15R alpha)-sushi as a selective and potent agonist of IL-15 action through IL-15R beta/gamma. Hyperagonist IL-15 x IL-15R alpha fusion proteins</i> , 281(3) J. Biol. Chem. 1612-29 (2006) (EX2113)	1616	sIL-15R α -Sushi	Other (Soluble IL-15 Receptor)	5-Aug-05	IL-15R	α	
WO 2015/044761 (EX2025)	6:38-39	(+)-2,9-diaminodecanedioic acid hydrochloride	Small Molecule	29-Sep-14	IL-15R	Primarily α , domain with concomitant blocking of IL-2R β & IL-2R γ	Preferred embodiment of disclosed formula

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent Pub. No. 2016/0235762 (EX2015)	3:29	(6R,7R)-7-[-(2-amino-2-phenylacetyl)amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid	Small Molecule	29-Sep-14	IL-15R	Primarily α , domain with additional inhibition of IL-2R β & IL-2R γ	Specific compound--also known as Cefazolin
WO 2017/046200 (EX2102)	27:28-29	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKR KAGTSSLTECVLNKATNVAHWTTPSLKCIRDPAL VHQRPAAPP	Peptide	15-Sep-16	IL-15R	fc	Specific sequence of peptide
WO 2017/046200 (EX2102)	28:1-2	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPS CKVTAMKCFLELQVISLESGDASIHDVTENLIILA NNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVH IVQMFINTS	Peptide	15-Sep-16	IL-15R	fc	Specific sequence of peptide
WO 2017/046200 (EX2102)	28:5-7	AHWTTPSLKCIRDPALVHQRPAAPPSGGSGGGGS GGGSGGGSGGNWVNVISDLKKIE DLIQSMHIDATLYTESDVHPSCKVTAMKCFLEL QVISLESGDASIHDVTENLIILANN SLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIV DMFINTS	Peptide	15-Sep-16	IL-15R	fc	Specific sequence of peptide
WO 2017/046200 (EX2102)	28:9-12	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKR KAGTSSLTECVLNKATNV AHWTTPSLKCIRDPALVHQRPAAPPSGGSGGGGS GGGSGGGSGGNWVNVISDLKKIE DLIQSMHIDATLYTESDVHPSCKVTAMKCFLEL QVISLESGDASIHDVTENLIILANN SLSSNGNVTESGCKECEEELEEKNIKEFLDSFVHIVD MFINTS	Peptide	15-Sep-16	IL-15R	fc	Specific sequence of peptide

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2000/002582 (EX2050)	1	Met Arg Ile Ser Lys Pro His Leu Arg Ser Ile Ser Ile Gln Cys Tyr Leu Cys Leu Leu Leu Lys Ser His Phe Leu Thr Glu Ala Gly Ile His Val Phe Ile Leu Gly Cys Phe Ser Ala Gly Leu Pro Lys Thr Glu Ala Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser His Glu Ser Gly Asp Thr Asp Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ile Leu Ser Ser Asn Gly Asn Ile	Other (Mutein)	9-Jul-99	IL-15	γ , β	Preferred embodiment of mutein
WO 2000/002582 (EX2050)	2-3	Met Arg Ile Ser Lys Pro His Leu Arg Ser Ile Ser Ile Gln Cys Tyr Leu Cys Leu Leu Leu Asn Ser His Phe Leu Thr Glu Ala Gly Ile His Val Phe Ile Leu Gly Cys Phe Ser Ala Gly Leu Pro Lys Thr Glu Ala Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser	Other (Mutein)	9-Jul-99	IL-15	γ , β	Preferred embodiment of mutein

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 6,001,973 (EX 2104)	24:40	FLAG-HMK-IL-15 Q156D	Other (Fusion Protein)	25-Apr-97	IL-15	α, β, γ	
WO 2012/061536 (EX2088)	41	CCAATGTGGCCAGGGAAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	CAGATGAACTCTTAGAAAT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GCAAACAGAGGAAGAATTT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TCTTAGAAATGAAGGCAGA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GTTTAAGGGTGATAGTCAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	CTAATGGAAGTGAAGAAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GGGTGAATGTAATAAGTGA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	AAACCACACTTGAGAAGTA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GAATCT GGATGCAAAGAAT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TGCAATAACTGGCATATAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GGCTTTGAGTAATGAGAAT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	CCACATTTGAGAAGTATTT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	CATAGCAAACAGAGGAAGA	Nucleotide	2-Nov-11	IL-15	Global Reduction	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2012/061536 (EX2088)	41	CCAAGTGGGTGAATGTAAT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TCAGATGAACTCTTAGAAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	CATATAATGTCCATCAGTA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	AGCCAGGACTCGATGGAGA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GCACAGAAATCAATGTTAG	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GATGGATGGCTGCTGGAAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	AGAAATCAATGTTAGCAGA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	CAACTG GG TGAATGTAATA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GCAATAACTGGCATATAAT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TAGGTAGAATGGTGTGCAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GAACTGTAAGAAAGATGAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	AGACCTTGGATCAGATGAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TGTTTAAGGGTGATAGTCA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TCTTGGTGGTGGTGGCAAT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GAGCAATGTTCCATCATGT	Nucleotide	2-Nov-11	IL-15	Global Reduction	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2012/061536 (EX2088)	41	ACAGAAGCCAACCTGGGTGA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GATGCAAGTATTCATGATA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	CTGCTTAGACATAACAAAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	AAGAAGATGATCAGACCTT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TGAACTTCTCTCAGACTTA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	CAGAGGAAGAATTTGTTAT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GTCACATGGAGCACAGAAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TCTTCTAATGGGAATGTAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	AGATGAACTCTTAGAAATG	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TAGAAATGAAGGCAGAAAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TTTAAGGGTGATAGTCAAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GTACCAATGCTGCAGGTCA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TCATTGACTTCCTTACTAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	AGCAAACAGAGGAAGAATT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GTGCAAGCTTGTCCAATCA	Nucleotide	2-Nov-11	IL-15	Global Reduction	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2012/061536 (EX2088)	41	AAGTGTGGCCCAAGACAAT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GTATTTCATCCAGTGCTA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GCCAACTGGGTGAATGTAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GGTGAATGTAATAAGTGAT	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GCTGCCTAGACATAACAAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	GCCAGGACTCGATGGAGAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
WO 2012/061536 (EX2088)	41	TTAGAAATGAAGGCAGAAA	Nucleotide	2-Nov-11	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	TTCTCATTACTCAAAGCC	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	TCTCATTACTCAAAGCCACGGTAAATCCTT	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	TCTCAAATGTGGTTTCGAAATTCTCATTAC	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	AGAAGTAAACACAAGTAGCAC	Nucleotide	7-Jul-99	IL-15	Global Reduction	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	CCAGTTGGCTTCTGTTT TAGGAAGCCC	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	CTTTGCAACTGGGGTGAACATCACT	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	ATCCCATTAGAAGACAAACTGTT	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	TCCAGTTCCTCACATTCTTTGCAT	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	CATTACTCAAAGCCACGGTAAATCCTT	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	TACTCAAAGCCACGGTAAATCCTT	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	TCAAAGCCACGGTAAATCCTT'	Nucleotide	7-Jul-99	IL-15	Global Reduction	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	CATTACTCAAAGCCACGGTAAATC	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	CATTACTCAAAGCCACGGTAA	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	CATTACTCAAAGCCACGG	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2003/0013668 (EX2087)	Sheet 2	CTAATGTCAGAGCCGCGG	Nucleotide	7-Jul-99	IL-15	Global Reduction	
US Patent Pub. No. 2002/0082230 (EX2029)	9	atatgtacaa tttcaataat	Nucleotide	4-May-01	IL-15	Global Reduction	
US Patent Pub. No. 2002/0082230 (EX2029)	9	aagagccaca tggccatata	Nucleotide	4-May-01	IL-15	Global Reduction	
US Patent Pub. No. 2002/0082230 (EX2029)	9	cattgatttc tgtgctccat	Nucleotide	4-May-01	IL-15	Global Reduction	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent Pub. No. 9 2002/0082230 (EX2029)		tcatactcaa agccacggta	Nucleotide	4-May-01	IL-15	Global Reduction	
US Patent Pub. No. 9 2002/0082230 (EX2029)		aaatacttct caaatgtggt	Nucleotide	4-May-01	IL-15	Global Reduction	
US Patent Pub. No. 10 2002/0082230 (EX2029)		catcactttc cgtatataaa	Nucleotide	4-May-01	IL-15	Global Reduction	
US Patent Pub. No. 10 2002/0082230 (EX2029)		aaaactctgc aaaaattctt	Nucleotide	4-May-01	IL-15	Global Reduction	
US Patent Pub. No. 10 2002/0082230 (EX2029)		agtgaataa cttgtaactc	Nucleotide	4-May-01	IL-15	Global Reduction	
US Patent Pub. No. 10 2002/0082230 (EX2029)		tcagattttc tactgtatca	Nucleotide	4-May-01	IL-15	Global Reduction	
US Patent Pub. No. 10 2002/0082230 (EX2029)		gagttcatct gatccaaggt	Nucleotide	4-May-01	IL-15	Global Reduction	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent Pub. No. 10 2002/0082230 (EX2029)		aagtaagtct gagagaagtt	Nucleotide	4-May-01	IL-15	Global Reduction	
US Patent Pub. No. 10 2002/0082230 (EX2029)		tcaacatttt acattattcc	Nucleotide	4-May-01	IL-15	Global Reduction	
US Patent No. 18 6,087,172 (EX2112)		TTAGAAAATC UGAUGAGTCC GTGAGGACGA AACTGTTTAG AA	Nucleotide	31-Oct-97	IL-15	Global Reduction	
US Patent No. 19 6,087,172 (EX2112)		UUCUAAACAG UCAUUUUCUA A	Nucleotide	31-Oct-97	IL-15	Global Reduction	
US Patent No. 19 6,087,172 (EX2112)		CAAAATGAAC UGAUGAGTCC GTGAGGACGA AACATGAATG CC	Nucleotide	31-Oct-97	IL-15	Global Reduction	
US Patent No. 19 6,087,172 (EX2112)		GGCAUUCAUG UCUUCAUUUU G	Nucleotide	31-Oct-97	IL-15	Global Reduction	
US Patent No. 20 6,087,172 (EX2112)		GTATCTCCGC UGAUGAGTCC GTGAGGACGA AACTCATGTG AA	Nucleotide	31-Oct-97	IL-15	Global Reduction	
US Patent No. 20 6,087,172 (EX2112)		UUCACAUGAG UCCGGAGATA C	Nucleotide	31-Oct-97	IL-15	Global Reduction	
US Patent No. 20 6,087,172 (EX2112)		CCATTAGAAC UGAUGAGTCC GTGAGGACGA AACAAGATGT T	Nucleotide	31-Oct-97	IL-15	Global Reduction	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 6,087,172 (EX2112)	21	AACAUCUUGU CUUCUAAUGG	Nucleotide	31-Oct-97	IL-15	Global Reduction	
US Patent No. 6,087,172 (EX2112)	21	GAACATTTGC UGAUGAGTCC GTGAGGACGA AACAATATGT AC	Nucleotide	31-Oct-97	IL-15	Global Reduction	
US Patent No. 6,087,172 (EX2112)	21	GUACAUAUUG UCCAAAUGUU C	Nucleotide	31-Oct-97	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	gtacatgacagccaggat	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	catagcaagtacatgaca	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	actctaggcccatagcaa	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	atttaggtaagctactct	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	ataatggtatggaggaag	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	tttaatctttacaataat	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	atgcatcacctttaatct	Nucleotide	25-Nov-98	IL-15	Global Reduction	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 5,985,663 (EX2030)	40:1-60	ccatccacgatgcctct	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	agctggctatggcaaggg	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	gtattgaagaagagctgg	Small Molecule	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	tacttctcaaattgtggtt	Antibody	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	acacaagtagcactggat	Peptide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	ccagcttcagttagaaaa	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	agacatgaatgccagctt	Other (Fusion Protein)	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	ttagctgcatcccaaat	Other (Modified Molecule)	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	actgggtatattagctgc	Other (Mutein)	25-Nov-98	IL-15	Global Reduction	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
US Patent No. 5,985,663 (EX2030)	40:1-60	gtaggtgcttgggcca	Other (Soluble IL-15 Receptor)	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	ctgaactgagagtcagat	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	ccaataccatgaaggcat	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	gccctgcactgaaacagc	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	ctgttttaggaagccctg	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	gggtgaacatcactttcc	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	tcacattcttgcaccca	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	ttgttatgtctaagcagc	Nucleotide	25-Nov-98	IL-15	Global Reduction	
US Patent No. 5,985,663 (EX2030)	40:1-60	atattactcaatgacatt	Nucleotide	25-Nov-98	IL-15	Global Reduction	

Prior Art: IL-15/IL-15 Inhibitors

Publication	Pincite	Structure/Sequence	Inhibitor Type	Filing Date (Patent) Publication Date (NPL)	Binds IL-15 or IL-15R?	Subunit	Notes
WO 2010/037818 (EX2027)	21	EVQLVESGGGLVQAGESLRLSCAASGSI VSGGAMGWYRQAPGKQRELVAAVDR RASPVGDSVKGRFTCSGDSARNTVYL QMNSLKPEDTAVYYCTALLGGRLYWG QGTQVTVSS	Antibody	1-Oct-09	IL-15		IL-15 Antibody Encoding Sequence(80% AA identity)
WO 2010/037818 (EX2027)	21	EVQLVESGGGLVQAGGSLRLSCAASGS TVTNGAMGWYRQAPGKQRELVAAVD RRASPVYADSVKGRFTCSGDSARNTVY LQMDSLKYEDTAVYYCTALLGGRLYW GQGTQVTVSS	Antibody	1-Oct-09	IL-15		IL-15 Antibody Encoding Sequence(80% AA identity)
WO 2010/037818 (EX2027)	21-22	EVQLVESGGGLVQAGESLRLSCAASGGI VSGGAMGWYRQAPGKQRELVAAVDR RASP VY GD svkgrftcsgd sarntvylqm NSLKPEDTAVYYCTALLGGRLYWGQGTQVT VSS	Antibody	1-Oct-09	IL-15		IL-15 Antibody Encoding Sequence(80% AA identity)
WO 2010/037818 (EX2027)	22	EVQLVESGGGLVQAGESLRLSCAASGSI VSGGAMGWYRQAPGKQRELVAAVDR R ASP VYGD SVKGRFTC S GO S ARNTVYLQM NSLKPEDTAVYYCTALLGGRLYWGQGAQVT VSS	Antibody	1-Oct-09	IL-15		IL-15 Antibody Encoding Sequence(80% AA identity)