

Patent Owner Demonstratives

**Forte Biosciences, Inc.
v.
University of Massachusetts**

**PGR2023-00014
Patent 11,278,505**

March 20, 2024

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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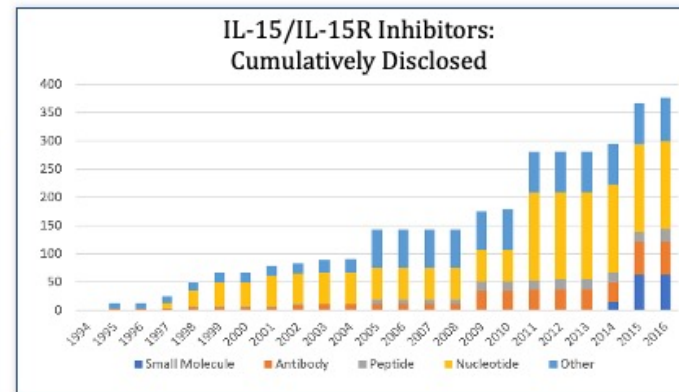
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Petitioner Has Not Established Unpatentability

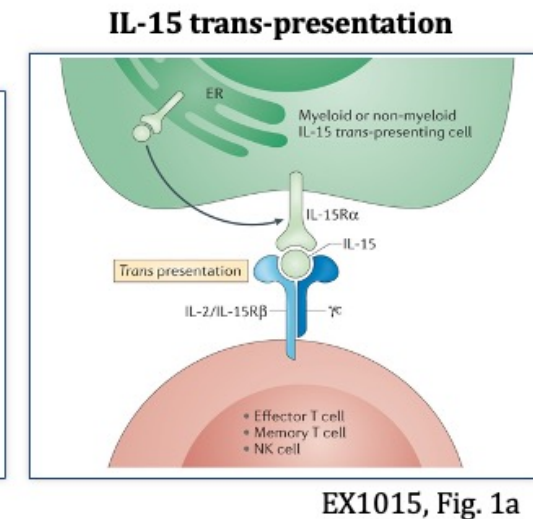
- Written Description and Enablement Grounds
 - Ignore the state of the art
 - Fail to apply legal standard for new use of a known class
 - Irreconcilable with own reliance on same data
- Obviousness Ground
 - Lacks a motivation to combine
 - Contradicted by teachings of the art

“it [was] common as of April 2017 to **expect that species that would antagonize IL-15 signaling would be useful in diseases—autoimmune diseases that had been identified as having an IL-15 mechanism.**”

EX2007, 74:19-75:10



EX2005, ¶70



EX1015, Fig. 1a

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State of the Art

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IL-15, Vitiligo, & Petitioner's Declarants

IL-15 inhibitors, targets, and class effect

- Well-known pathway and targets (E.g., POR, 5-8; Sur-Reply, 3-5; EX2005, ¶¶66-67; EX2002, 106)
- Primarily trans-presentation (E.g., POR 7-8; Sur-Reply, 3-5; EX2005, ¶¶66-67; EX1015; EX1016)
- Hundreds of known inhibitors (E.g., POR, 11-12; Sur-Reply, 4-5; EX2005, ¶¶68-69, 121-122, App'x A)
- Classic research paradigm (E.g., POR, 8-9; Sur-Reply, 3; EX2005, ¶¶52-63; EX2007, 65:21-67:20)
- Effective for multiple autoimmune diseases (E.g., POR, 12-13; Sur-Reply, 3-5; EX2005, ¶¶80-83; EX1011; EX1013; EX2014; EX2015; EX2019; EX2024; EX2025; EX2026; EX2118)
- Class effect expected and confirmed by Dr. Abbas (E.g., POR, 6, 13, 32, 71-72; Sur-Reply, 16-17; EX2007, 74:19-75:10)
- Harris mouse recapitulated human disease (E.g., POR, 15; Sur-Reply, 21-23)

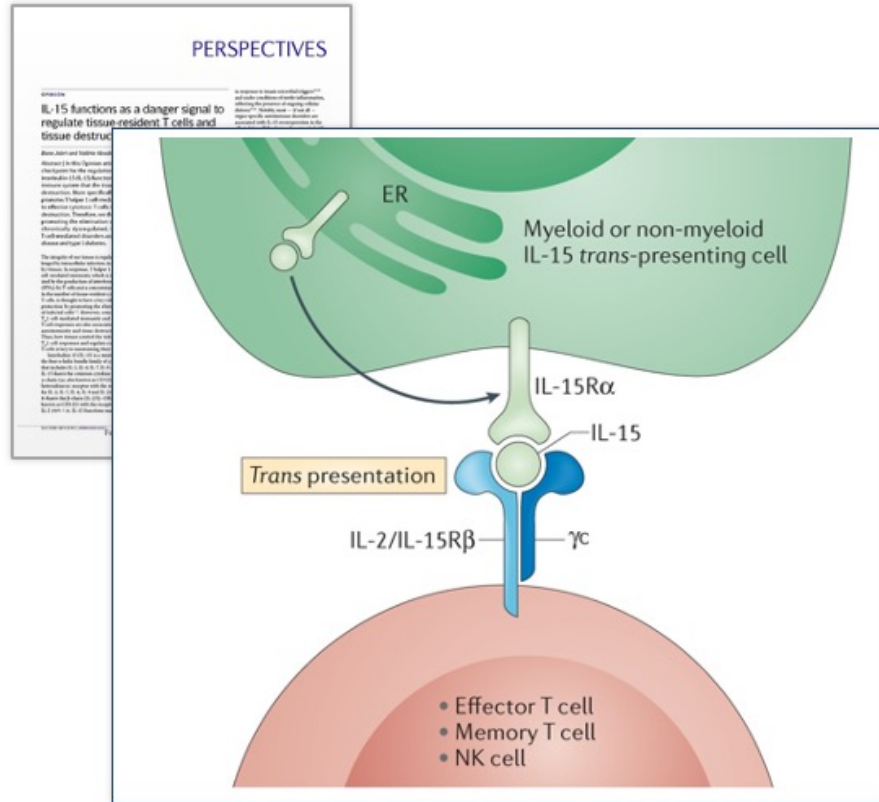
'505 patent disclosure

- 20 inhibitors from 9 classes (E.g., POR, 9-11; EX1001, 2:49-52, 7:33-8:37)
- Cited references are expressly incorporated (E.g., EX1001, 2:49-52; POR, 11-12, 21)

Declarants

- Dr. Abbas and Dr. Plott did not consider full scope of art (E.g., POR, 30-32; Sur-Reply, 7-10)
- Professor Damsky, M.D., Ph.D. considered the art as a whole (E.g., POR, 5 n.11; Sur-Reply, 23-26; Paper 37; EX2005; EX2006)

IL-15 Signaling Blocked By Inhibitors of IL-15 and Any Receptor Unit



EX1015, Fig. 1a

Q. And any of those would inhibit the transpresentation that's shown; correct?

A. Theoretically, yes.

EX2007, 71:3-5; generally id., 70:10-71:5

The ability of anti-CD122 monoclonal antibodies to inhibit cell proliferation mediated by trans-presented IL-15 was examined using TF-1β cells and scIL-15/IL-15Rα. In typical

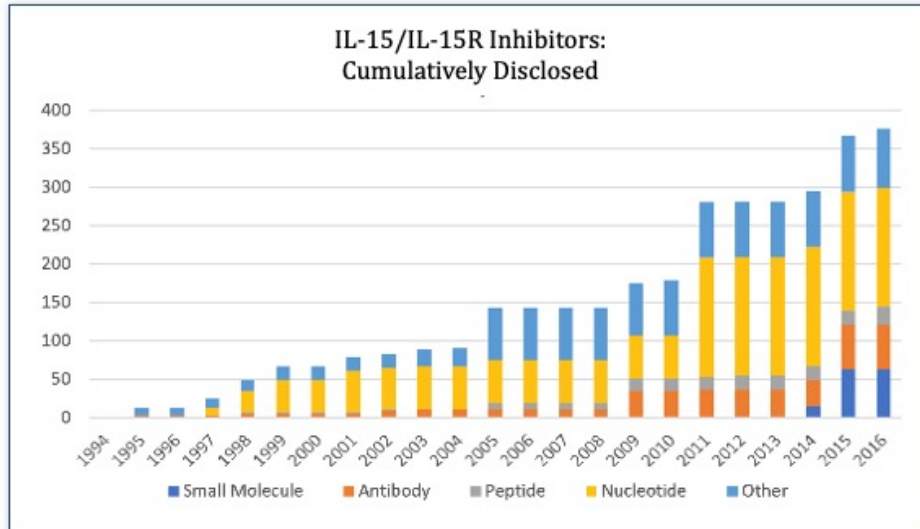
EX1011, 22:17-19

POR, 7-8, 43-45; Sur-Reply, 3-5; EX2005, ¶¶ 66-67

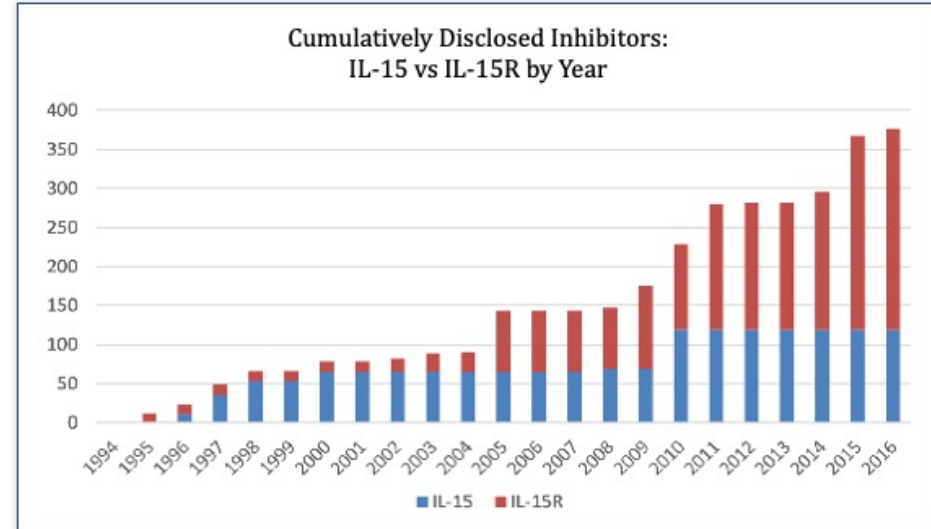
Known IL-15 and IL-15R Inhibitors



- EX1011 • EX2027 • EX2050 • EX2104 • EX2111
- EX2013 • EX2028 • EX2051 • EX2105 • EX2112
- EX2014 • EX2029 • EX2085 • EX2106 • EX2113
- EX2017 • EX2030 • EX2087 • EX2107 • EX2114
- EX2019 • EX2031 • EX2088 • EX2108
- EX2024 • EX2032 • EX2102 • EX2109
- EX2025 • EX2049 • EX2103 • EX2110



EX2005, ¶70



EX2005, ¶72

EX2005, ¶¶ 68-75, App'x A; POR, 5-14; Sur-Reply, 3-5

Expectation of Common Autoimmune Therapeutic Efficacy

2015 filing date



BACKGROUND OF THE INVENTION:

There remain considerable unmet medical needs for inflammatory and autoimmune diseases such as rheumatoid arthritis, psoriasis and intestinal inflammatory diseases. Cytokine targeting is now established as a feasible method for treating such chronic inflammatory diseases.

Cytokine 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, 3

2014 filing date



Significant involvement of IL-15 in the development of the pathogenesises of the aforementioned afflictions suggests that targeting this cytokine signaling pathway can reduce or eliminate the occurrence of IL-15-related disorders. This strategy has been proved lately by a number of biological assays. Reduction of IL-15-mediated biological responses, using the soluble receptor IL-15Ra (Liew F.Y., McInnes I.B., Ann. Rheum. Dis. 61 Supl. 2, ii100-2 (2002);

Significant involvement of IL-15 in the development of the pathogenesises of the aforementioned afflictions suggests that targeting this cytokine signaling pathway can reduce or eliminate the occurrence of IL-15-related disorders. This strategy has been proved lately by a number of biological assays.

always resulted in the alleviation of the disease symptoms

EX2025, 2-3

POR, 12-13; Sur-Reply, 3-5; EX2005, ¶¶ 52-65, 80-83; see also EX1011, 4:25-34; EX1012; EX1018, 2

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Expectation of Common Autoimmune Therapeutic Efficacy

- Dr. Abbas confirms expectations:

Q. Was it common -- to your knowledge, was it **common as of April 2017 to expect that species that would antagonize IL-15 signaling would be useful in diseases -- autoimmune diseases that had been identified as having an IL-15 mechanism?**

* * *

Dr. Abbas: **It's reasonable**, but it depends on how the mechanism was identified.

Q. Is that different today than in April 2017, about how people rely on proof of concepts to infer treatment activity for an antagonist?

* * *

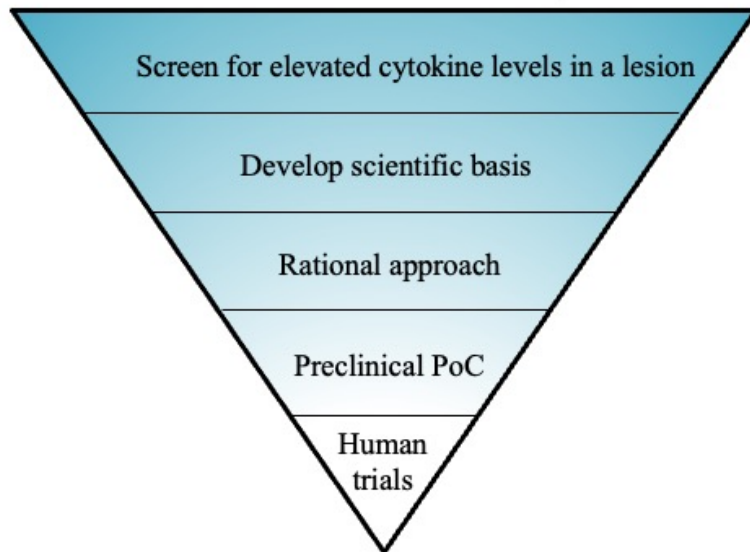
Dr. Abbas: **As far as I know, the principles have not changed.**

EX2007, 74:19-75:10

POR, 6, 13, 32, 71-72; Sur-Reply, 3-4, 16-17

Classic Research Paradigm: Dr. Abbas

Classic Research Paradigm



Q. And so the scientific basis would be finding that, for example, a **disease is associated with elevated IL-15?**

* * *

Dr. Abbas: That's part of it, or **blocking experiments in reliable animal models** would be another part of it. That's how these things are analyzed. So finding it **elevated in patients, in mouse models, then blocking it in mouse models**, those are all the pieces we consider.

Q. And then the next step of the rational design; how does that come in?

A. Well, the next step would be to block that cytokine pathway in an animal model, and that's your proof of concept -- your pre-clinical proof of concept. And then from there, you would consider going to clinical trials.

Q. So is that a fairly standard approach, that you have a **scientific basis** followed by **rational design** followed by **proof of concept** followed by **clinical trials?**

* * *

Dr. Abbas: It's -- in principle, that's the **standard approach, yeah.**

EX2007, 66:19-67:20

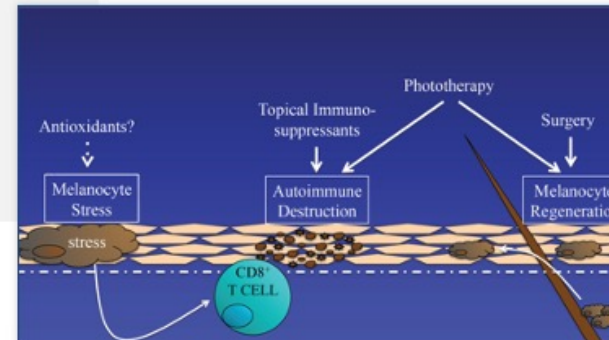
POR, 8-9; Sur-Reply, 3-4; EX2005, ¶106

Vitiligo

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Vitiligo

- Autoimmune disease of skin
- Results in patchy depigmentation of skin
- CD8+T Cells “are both necessary and sufficient for melanocyte destruction”



POR, 14; EX2060, Fig. 1; EX 2054, 5

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Vitiligo: Autoimmune disease with different initiation triggers

Vitiligo is a common, disfiguring autoimmune disease that negatively affects patients' self-esteem and quality of life (1, 2). Existing vitiligo treatments, which are used off-label, are general, non-targeted immunosuppressants that provide only modest efficacy. Developing safe and effective treatments requires a better understanding of disease pathogenesis to identify new therapeutic targets (3). Vitiligo is caused by a dynamic interplay between genetic and environmental risks that initiates an autoimmune attack on melanocytes in the skin.

EX2060, 1

This disease is indistinguishable from classical vitiligo by clinical examination or histology,²² and therefore chemical leukoderma does not appear to be distinct from vitiligo, but may be better classified as chemically induced vitiligo.²³

EX2053, 3

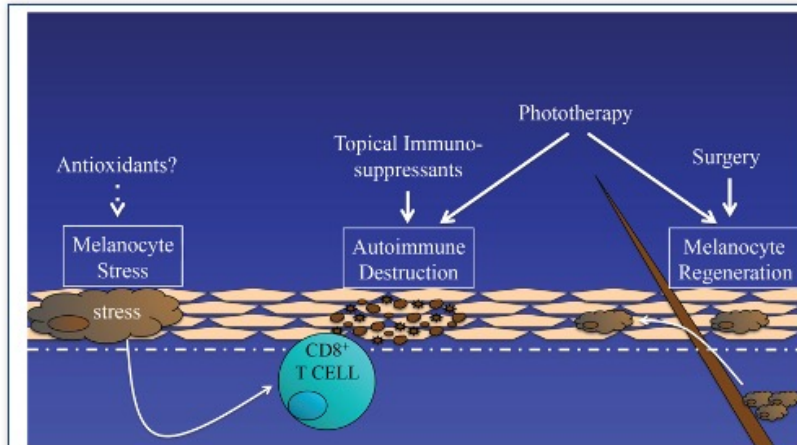


Fig. 1. Vitiligo pathogenesis begins with altered melanocytes that exhibit an elevated cellular stress response. This triggers autoimmunity, which targets melanocytes for destruction, resulting in focal depigmentation. Repigmentation requires the growth and migration of melanocytes, typically from hair follicles. Thus, there 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. Current treatments, including topical immunosuppressants, phototherapy, and surgical approaches, partially address these goals in overall non-targeted ways.

EX2060, Fig. 1

POR, 14-15; Sur-Reply, 5-7; see also, EX1002, ¶49; EX1004, ¶37; EX2060, 1-4; EX2118, 104:24-105:10

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Vitiligo: Autoimmune disease with different initiation triggers

● Petitioner's Reply

“The literature identified **multiple causes of vitiligo**, explained there was no singularly true mechanism behind the disease, and its pathogenesis was elusive. **EX1047, ¶47**; EX1057, Abstract, 153, 169.”

Reply, 16-17

● Dr. Plott did not opine on causes of vitiligo

Q. Are you offering any opinions on what causes vitiligo --

* * *

Q. -- in your declaration, **Exhibit 1047**?

* * *

A. No. I'm providing -- I'm providing responses in Paragraph 47 regarding what Dr. Damsky said. I've not offered opinion in this paragraph about the causes of vitiligo.

EX2118, 95:16-25

Sur-Reply, 6, 9-10; see also EX2118, 94:18-95:25, 96:2-8

Vitiligo: *Harris* Mouse Model Recapitulates Human Vitiligo

Recapitulates Hallmarks of Human Disease

1. Melanocyte-specific T cells drive skin depigmentation.
2. T cell recognition and reaction against common melanocyte-specific antigens that lead to melanocyte death and depletion in the epidermis.
3. T cells that exhibit a T resident memory phenotype and express CD122/IL-15R β .
4. IFN- γ is key driver in disease pathogenesis and levels of IFN- γ correlate with depigmentation.
5. Predominant site of depigmentation in the interfollicular epidermis.
6. Pigment retained within the hair follicles of vitiligo lesions.
7. Predilection for involvement of acral sites (ears, hands, feet), the face, and genitalia.
8. Disease progression from patchy areas of depigmentation to confluent areas of depigmentation, a sign of active vitiligo.
9. No visible clinical evidence of skin inflammation.

EX2005, ¶89

EX1006

POR, 15; EX2005, ¶¶84-89

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A Mouse Model of Vitiligo with Focused Epidermal Depigmentation Requires IFN- γ for Autoactive CD8 $^{+}$ T-Cell Accumulation in the Skin

John E. Harris,¹ Telle H. Harris,¹ Wolfgang Wessinger^{1,4}, E. John Wherry⁵, Christopher A. Hunter² and Laurence A. Turka³

Vitiligo is an autoimmune disease of the skin causing disfiguring patchy depigmentation of the epidermis and, less commonly, hair. Therapeutic options for vitiligo are limited, reflecting in part limited knowledge of disease pathogenesis. Existing models of vitiligo consist of hair depigmentation but lack prominent epidermal involvement, which is the hallmark of human disease. They are thus unable to provide a platform to fully investigate disease mechanisms and treatment. CD8 $^{+}$ T cells have been implicated in the pathogenesis of vitiligo, and expression of IFN- γ is increased in the lesional skin of patients; however, it is currently unknown what role IFN- γ has in disease. Here, we have developed 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. Like active lesions in human vitiligo, histology of depigmenting skin reveals a patchy mononuclear infiltrate and single-cell infiltration of the epidermis. Depigmentation is accompanied by accumulation of autoactive CD8 $^{+}$ T cells in the skin, quantifiable less than two weeks post-transfer, and local IFN- γ production. Neutralization of IFN- γ with antibody prevents CD8 $^{+}$ T-cell accumulation and depigmentation, suggesting a therapeutic potential for this approach.

Journal of Investigative Dermatology (2012) 122, 1006–1016. doi:10.1038/jid.2011.463; published online 2 February 2012

INTRODUCTION

Vitiligo is a skin disease that causes patchy depigmentation of the epidermis and often, at <5% of the population, without apparent cause or genetic component. Lesions occur on central face and genitalia, other locations to the hands and feet, and less commonly presents on the trunk and proximal extremities (Harris and Picardie, 2009). The disease is characterized by spread within lesional skin, and the successful treatment of vitiligo results in repigmentation that usually begins as small dark macules around the hair follicles, presumably because follicular melanocytes are protected by immune privilege (Jalili et al., 2005).

Previous studies have implicated autoactive CD8 $^{+}$ T cells in disease pathogenesis. For example, the frequency and intensity of melanocyte destruction in both the blood and skin of patients with vitiligo correlate with the severity of disease, and lesional CD8 $^{+}$ T cells induce melanocyte apoptosis in coinfected skin mice (Figg et al., 1996; van der Vliet et al., 2009), an observation that suggests a direct role for cytotoxic T lymphocytes in melanocyte destruction in human lesions. The role of inflammation in vitiligo pathogenesis is delivered although IFN- γ has been the most extensively studied. In human patients, IFN- γ is expressed in lesional skin and can be produced by autoactive CD8 $^{+}$ T cells *in vitro* (Bosch et al., 2009), but its role in depigmentation is not known.

Existing models of vitiligo have been established in wild-type C57BL/6 mice, which have black hair but little skin owing to the low melanocytes found in the epidermis. Consequently, the rigidity of these models obscures development of the hair follicle and the melanocytes, and because hair depigmentation predicts a poor response to treatment, they may represent more severe forms of vitiligo than seen in humans. To date, no reports of mouse models of vitiligo using adoptive transfer of melanocyte-specific CD8 $^{+}$ T cells into mice with increased epidermal

DISCUSSION

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Abbreviations: GFP, green fluorescent protein; IL-2, interleukin-2; and mouse melanocyte-specific CD8 $^{+}$ T cells, mCD8 $^{+}$ T cells.

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The '505 Patent

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Novel Method Using a Known Class of Inhibitor

Claims 1-5:

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

US01127850B2

(12) **United States Patent**
Richmond et al.

(19) **Patent No.:** US 11,278,505 B2
(41) **Date of Patent:** Mar. 22, 2022

(42) **DIAGNOSIS AND TREATMENT OF VITILIGO**

(71) **Applicant:** University of Massachusetts, Boston, MA (US)

(72) **Inventors:** **Jillian M. Richmond**, Deyville, CT (US); **John E. Harris**, Sterling, MA (US); **James Patrick Strummer**, Worcester, MA (US)

(73) **Assignee:** University of Massachusetts, Boston, MA (US)

(*) **Notice:** Subject to any disclaimer, the terms of this patent are intended to encompass all claims of the patent (U.S. 11439) by 72 days.

(91) **App. No.:** 14/008,116

(92) **PCT Filed:** Apr. 24, 2018

(93) **PCT No.:** PCT/US2018/021085

(94) **Pub. No.:** 2019/0146119

(95) **PCT Pub. Date:** May 30, 2019

(96) **PCT Pub. Date:** May 30, 2019

(97) **Priority Publication:** Apr. 20, 2019

(98) **US 2019/0087759 A1**, Apr. 4, 2019

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(51) **Int. Cl.:** A61M 31/00 (2018.01)
A61M 31/00 (2018.01)
A61M 31/00 (2018.01)

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EX1001, Claims 1-5

Describes Representative IL-15/IL-15R Inhibitors

9 classes of inhibitors and 20 compounds disclosed

	Class of Therapeutic Molecule	Compound(s)	Disclosure
1	Small molecule inhibitors of the IL-15 receptor alpha chain	Benzoic acid derivatives Amine derivatives	WO 2014/191822 (EX2013) WO 2014/191823 (EX2014)
2	Small molecule inhibitors of IL-15 induced cellular responses	Cefazolin Y-320	US 2016/0235762 (EX2015) Ushio, 2008 (EX2016)
3	Soluble IL-15 receptor alpha chains	sIL-15R α	Ruchatz, 1998 (EX2017)
4	IL-15/Fc-gamma 2a fusion proteins	Mutant IL-15/Fc γ 2a fusion protein	Kim, 1998 (EX2018)
5	Peptide inhibitors of the IL-15 receptor alpha chain	IL-15 peptide inhibitors	U.S. 7,736,638 (EX2019)
6	Anti-IL-15 antibodies	Human IL-15 mAb	WO 03/017935 (EX2020)
7	Anti-IL15 receptor antibodies, including those that bind to the IL-2/IL-15 receptor beta, gamma, and alpha subunits	CD122 (IL-15R β) antibodies IL-15R α antibodies IL-15 γ antibodies	U.S. 9,028,830 (EX1011) Hechinger, 2015 (EX1030) Epron, 2012 (EX2021)
8	Small molecule inhibitors of CD122	Ro26-4550 SP4206 ABT-737 Nutlin-2 Compound 3	Wilson & Arkin, 2010 (EX2022) Laio, 2013 (EX2023)
9	Inhibitory nucleic acids targeting IL-15 or IL-15R	siRNA shRNA LNA molecules PNA molecules	Routine methods

EX1001, 2:49-52, 7:34-8:37; POR, 9-11, 20-21

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Expressly Incorporates 300+ References

[illegible]

POR, 11-12, 21; EX2005, ¶71, n.2

Known: Classic Research Paradigm

Xing (EX1007)	Classic Research Paradigm	The '505 Patent
Characterized transcriptional profile of AA lesional skin	Screen for elevated cytokine levels in a lesion	Characterized transcriptional profile of vitiligo lesional skin
IL-15R and IFN response genes identified in AA lesional skin	Develop scientific basis	IL-15R expression identified in vitiligo lesional skin
Mechanistic studies confirm a role for IL-15 and IFN response genes in AA	Rational approach	Mechanistic studies confirm a role for resident and recirculating memory T cells in vitiligo
JAK and IL-15R inhibitor tested in an AA mouse model	Preclinical PoC	IL-15R inhibitor tested in reliable vitiligo mouse model
Efficacy of JAK inhibitors for the treatment of AA in humans advanced to human studies	Human trials	Villarix IND studies underway and human clinical development begins in 2023

EX2005, ¶¶57, 106; EX2007, 65:21-67:20; POR, 8-9; Sur-Reply, 3-4

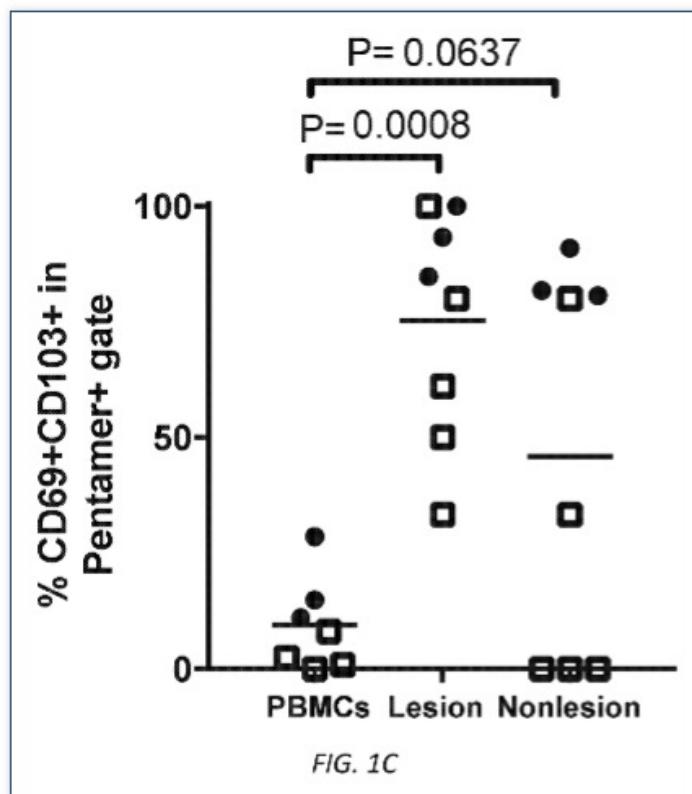
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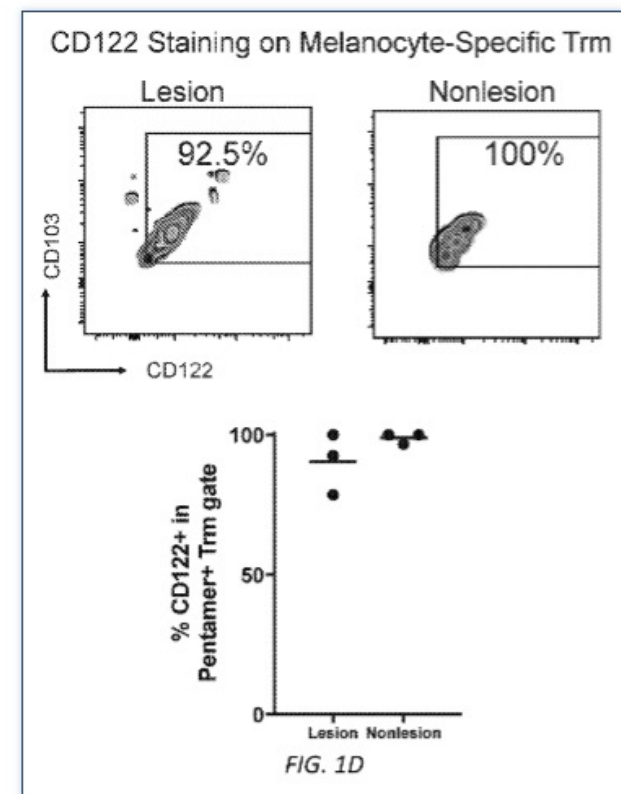
Patent Examples: IL-15R expression in vitiligo lesional skin

Example 1:

- Establishes human vitiligo patients express an antigen-specific Tm phenotype and express IL-15R.



EX1001, Fig. 1C



EX1001, Fig. 1D

EX1001, 30:53-31:12, Figs. 1A-1E; POR, 21-22

Patent Examples: Melanocyte-specific T cells

Example 2:

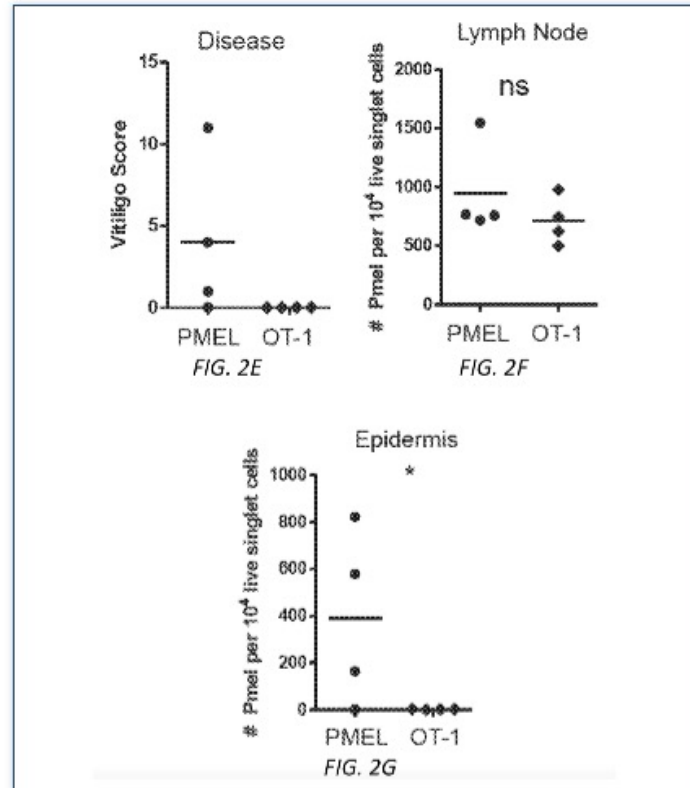
- only melanocyte-specific T cells establish Trm in epidermis where autoantigen is expressed compared to control cells (EX1001, 3:22-31, 31:14-43, Figs. 2A-2G).

Example 3:

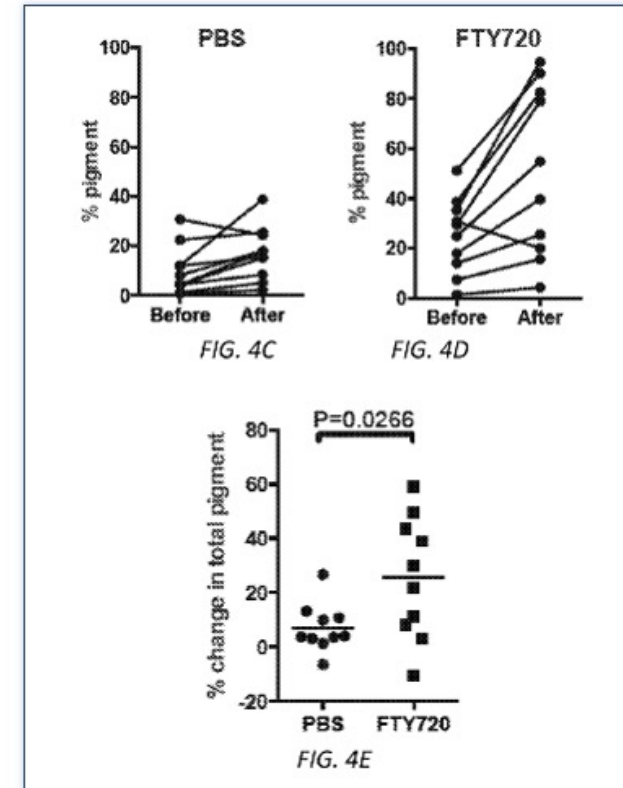
- "TRM are long-lived and maintain effector function for long periods." (EX1001, 3:32-45, 31:45-32:35, Figs. 3A-3D).

Example 4:

- "recirculating memory T cells contribute to sustained melanocyte killing during the maintenance of vitiligo. (EX1001, 3:46-56, 32:37-67, Figs 4A-4G).



EX1001, Figs. 2E-2G



EX1001, Fig. 4C-4D

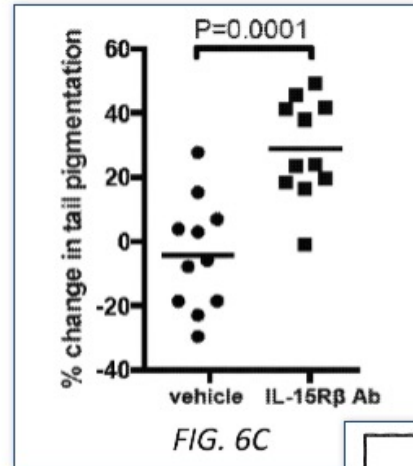
POR, 22-24

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

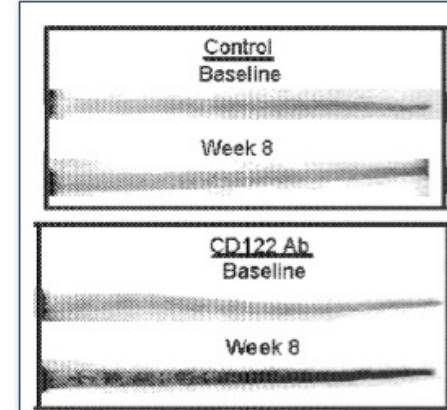
Patent Examples: In vivo efficacy

Example 5:

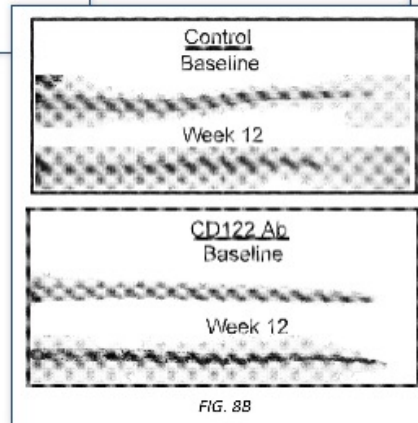
- *in vivo* efficacy in Harris mouse model (EX1001, 33:1-34:45, Figs. 5, 6A-6I, Fig. 7A-C, Figs. 8A-8E).
- “Existing treatments for vitiligo are not durable, as the disease returns at the site of treatment after discontinuation.” (EX1001, 33:5-6).



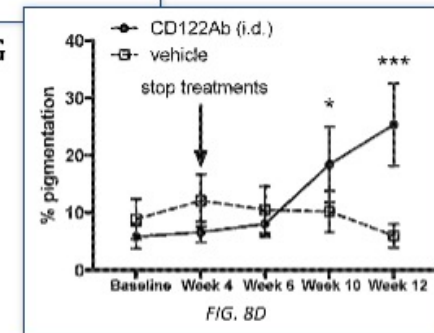
EX1001, Fig. 6C



EX1001, Fig. 6G



EX1001, Fig. 8B



EX1001, Fig. 8D

POR, 24-27

Forte's Reliance on '505 Patent Data and the Classic Research Paradigm

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Forte's Statements regarding its FB-102

Forte "Pipeline"



Asset	Indication	Preclinical	Phase 1
FB102	Graft vs Host Disease		
	Vitiligo		

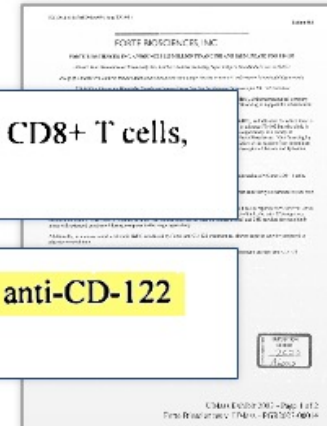
CD122 is subunit of IL-2/IL-15 receptors which are key regulators of NK cells and T cell subsets

Significant amount of proof-of-concept preclinical data supports activity of CD-122 blockade, including in GvHD and vitiligo



EX2045

Forte Press Release



Forte's wholly owned antibody, FB-102, targets CD-122, a subunit of the IL-2 and IL-15 receptor and mediates NK and CD8+ T cells, which have been implicated in a variety of autoimmune and immune related diseases.

Published preclinical PoC data also support the therapeutic potential of anti-CD122 in multiple autoimmune diseases anti-CD-122 including in vitiligo, celiac disease, alopecia areata, Type 1 diabetes and solid organ transplant.

EX2003, 1

POR, 33-35, 85-86; Sur-Reply, 10

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Forte's FB-102



Forte's Interrogatory Response to: "identify and describe the particular models referred to in the press release"

Richmond et al., reported in 2018 that the Fc-diminished chimeric rat/mouse CD122 antibody ChMBC7 depleted CD8+ PMEL in the dermis of the Harris transgenic mice and, by substantially eliminating the only remaining immune cells in the mice, reversed the vitiligo lesions induced by the transplanted CD8+ PMELs. 10 Sci. Transl. Med. 1- 20.

EX2009, 8-9 (citing EX2046); see also Paper 17, 3-5



Professor Damsky

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...

EX2005, 109

POR, 33-35; Sur-Reply, 10

Person of Ordinary Skill in the Art

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

POSA

- A person of ordinary skill in the art (POSA) of the '505 patent in April 2017 or April 2018 would have had an advanced degree (e.g., Ph.D., M.D., M.S., or equivalent), in a field related to medicine, immunology, molecular biology, cell biology, microbiology, pathology, biochemistry, peptide chemistry, or a related field, and at least 3-5 years of experience in treating autoimmune diseases or researching cytokine signaling pathways relevant to treating autoimmune diseases. This individual would have worked in consultation with a team including, e.g., a medical doctor who diagnoses and treated vitiligo, and a pharmaceutical scientist familiar with formulating drugs for administration. Moreover, skilled artisans also would have practical knowledge of immunology and *have been familiar with prior art pertaining to treatment of autoimmune diseases, including the patents and publications discussed herein.*
- A POSA having experience “researching cytokine signaling pathways” would have been *familiar with well-known inhibitors of IL-15 and IR-15R, as described in the '505 patent and recognized in the art as of April 2017.*

Pet., 18; POR, 26-27; Sur-Reply, 7

Dr. Abbas Did Not Consider or Investigate the State of the Art

POSA would have been familiar with
(1) *“prior art pertaining to treatment of autoimmune diseases, including the patents and publications discussed herein.*
(2) *“well-known inhibitors of IL-15 and IR-15R, as described in the '505 patent and recognized in the art as of April 2017”*

- ✗ Did not consider majority of 300+ references incorporated to patent
EX2007, 6:2-17; POR, 31; Sur-Reply, 7, 10
- ✗ Did not consider number and type of known inhibitors
EX2007, 71:11-24, 81:21-82:12, 83:14-84:12, 85:4-13; POR, 31

Q. As of April 2017, are you aware of how many species there were that were known to antagonize IL-15 signaling?

* * *

THE WITNESS: No.

Q. A ballpark?

A. Of course, I – I’m just trying to think. Not really – I know about CD122 blockers, but I am not sure if alpha chain blockers or cytokine blockers had been developed by then. I don’t know.

Q. You hadn’t looked into that in the context of your report in this case; correct?

A. No, I had not.

EX2007, 71:11-24; POR, 31; Sur-Reply, 10

Dr. Plott Did Not Consider or Investigate the State of the Art

POSA would have been familiar with
(1) *“prior art pertaining to treatment of autoimmune diseases, including the patents and publications discussed herein.*
(2) *“well-known inhibitors of IL-15 and IR-15R, as described in the '505 patent and recognized in the art as of April 2017”*

-  Did not consider majority of 300+ references incorporated to '505 patent
EX2008, 5:18-22; EX2118, 55:24-56:10, 186:11-20
-  Has little to no experience with IL-15 signaling inhibitors
EX2008, 16:14-17, 17:14-16
-  Has limited knowledge beyond this case for therapeutic uses for IL-15 inhibitors
EX2008, 19:23-20:8
-  Would have to consult others for this subject matter
EX2118, 8:24-9:4, 9:13-21, 11:1-3, 10:23-11:17, 12:6-14, 14:4-15:12, 15:21-16:3, 18:8-14, 22:3-14.
-  No specialized experience with vitiligo
EX2118, 22:24-23:10, 26:2-4, 26:20-25, 28:21-29:1

POR, 32; Sur-Reply, 7-10, 23-24

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Professor Damsky, M.D., Ph.D.



- Assistant Professor of Dermatology & Pathology (Clinician-Scholar Track), Yale University School of Medicine
- Board Certified Dermatologist & Dermatopathologist
- Ph.D., Cell and Molecular Biology (2011)
- M.D. (2013)
- Dermatology Resident (2014-2017)
- Dermatopathology Fellow (2018-2020)
- Research Fellow, Immunobiology (2017-2023)

POR, 5 n.11; Sur-Reply, 23-26, EX2005, ¶¶1-18, EX2006, 1-2

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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Professor Damsky, M.D., Ph.D.



- During Ph.D. research (pre-2011):
 - “intensively studied intracellular signaling pathways” and the effects of alerting signaling to those pathways, such as cytokines
- Between 2011 and 2017, research group was:
 - “active in researching cytokines in dermatology and beyond dermatology in a number of different settings using translational approaches, invasive approaches in clinical trials”

EX2005, ¶6

EX1046, 267:22-268:16

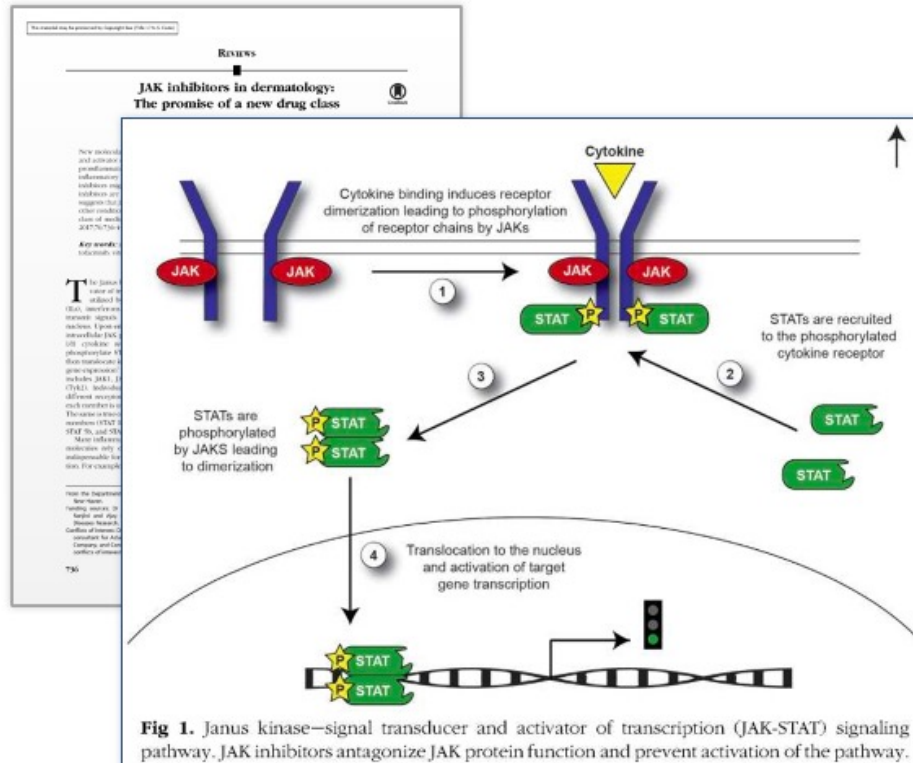
POR, 5 n.11; Sur-Reply, 23-26, EX2005, ¶¶1-18, EX2006, 1-2; Paper 37, 7

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Professor Damsky, M.D., Ph.D.

Damsky *et al* (EX1021)



Recognitions:

- Young Investigator Award; LEO Foundation Award
- Numerous clinical trial grants and funding
- >120 peer-reviewed publications, many related to cytokine inhibitors in treating inflammatory skin conditions
 - “JAK Inhibitors in Dermatology: the Promise of a New Drug Class” (EX1021)

POR, 5 n.11; Sur-Reply, 23-26, EX2005, ¶¶1-18, EX2006, 2-18; Paper 37

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Petitioner Has Not Established Lack Of Written Description or Nonenablement

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Facts Relevant to § 112

IL-15 inhibitors, targets, and class effect

- Well-known pathway and targets (E.g., POR, 5-8; Sur-Reply, 3-5; EX2005, ¶¶66-67; EX2002, 106)
- Primarily trans-presentation (E.g., POR 7-8; Sur-Reply, 3-5; EX2005, ¶¶66-67; EX1015; EX1016)
- Hundreds of known inhibitors (E.g., POR, 11-12; Sur-Reply, 4-5; EX2005, ¶¶68-69, 121-122, App'x A)
- Classic research paradigm (E.g., POR, 8-9; Sur-Reply, 3; EX2005, ¶¶52-63; EX2007, 65:21-67:20)
- Effective for multiple autoimmune diseases (E.g., POR, 12-13; Sur-Reply, 3-5; EX2005, ¶¶80-83; EX1011; EX1013; EX2014; EX2015; EX2019; EX2024; EX2025; EX2026; EX2118)
- Class effect expected and confirmed by Dr. Abbas (POR, 6, 13, 32, 71-72; Sur-Reply, 16-17; EX2007, 74:19-75:10)
- Harris mouse recapitulated human disease (E.g., POR, 15; Sur-Reply, 21-23)

'505 patent disclosure

- 20 inhibitors from 9 classes (E.g., POR, 9-11; EX1001, 2:49-52, 7:33-8:37)
- Cited references are expressly incorporated (E.g., EX1001, 2:49-52; POR, 11-12, 21)

Declarants

- Dr. Abbas and Dr. Plott did not consider full scope of art (E.g., POR, 30-32; Sur-Reply, 7-10)
- Professor Damsky, M.D., Ph.D. considered the art as a whole (E.g., POR, 5 n.11; Sur-Reply, 23-26; Paper 37; EX2005; EX2006)

Legal Standard

- *UroPep* analysis is applicable (E.g., POR, 38-43, 52-57, 60-73; Sur-Reply, 12-15)

Written Description For a Novel Use of a Known Class



“[W]hen a genus is well understood in the art and not itself the invention but is instead a component of the claim, background knowledge may provide the necessary support for the claim.”

Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co., 276 F. Supp. 3d 629, 648 (E.D. Tex. 2017), *aff’d* 739 F. App’x 643 (Fed. Cir. 2018) (“*UroPep*”)

“We find this case akin to *UroPep* in which the Court stated that the essence of the invention in *UroPep* was not the identification of compounds that would perform a particular function. Instead, the Court found that the invention is a method of treating a disease BPH (benign prostatic hyperplasia) using inhibitors of PDE V (phosphodiesterase) ...

By the same token, the challenged claims of the ’836 patent present us with the same issue here as addressed in *UroPep* of a method of treatment using two genera of compounds that perform a particular function. Patent Owner has pointed us to evidence of examples of these genera that Petitioner failed to address because of its incorrect focus on the two genera as if they were novel compositions that Patent Owner was claiming as the invention.

Merck Sharp & Dohme Corp. v. Genentech, Inc., PGR2021-00036, Paper 10, 19-20 (PTAB July 24, 2021)

POR 38-39, 44, ; Sur-Reply, 12-15

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Claimed Method of Treating Vitiligo Analogous to *UroPep*

UroPep

- “[T]he invention was to use a group of compounds well known in the art ... in a novel method of treating...”
- “[W]hen a genus is well understood in the art and not itself the invention but is instead a component of the claim, background knowledge may provide the necessary support for the claim.”
- “Given the evidence of the knowledge of a person of skill [at critical date] regarding [genus] inhibitors,... a reasonable jury could have found that the specification disclosed a sufficient number of representative species of selective... inhibitors.”

UroPep, 276 F. Supp 3d at 646, 648,

The '505 Patent

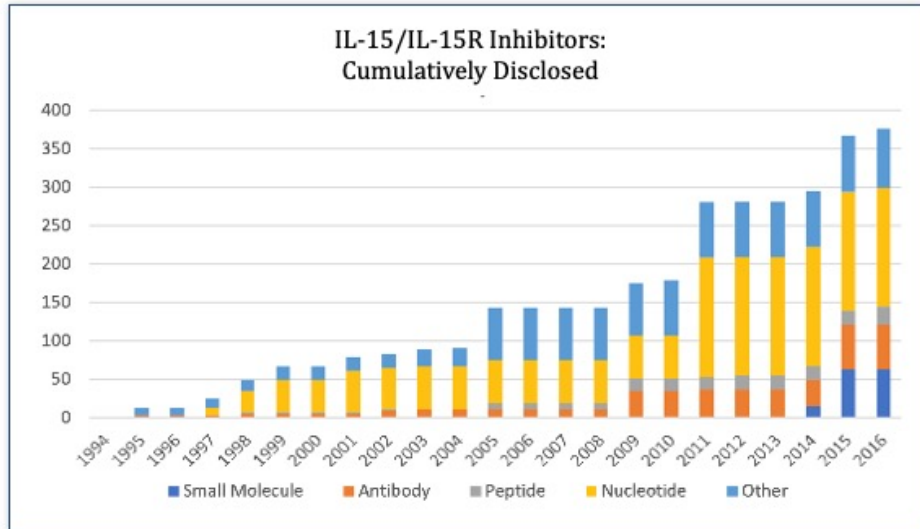
- Claims a **new** use of a known class of inhibitors, **not** novel compounds
- Hundreds of IL-15/IR-15 inhibitors and known for treating autoimmune diseases
 - EX2005, ¶¶68-69, 121-122, App’x A
 - EX2005, ¶¶80-83; EX1011; EX1013; EX2014; EX2015; EX2019; EX2024; EX2025; EX2026; EX2118
- Specification discloses 20 exemplary inhibitors from 9 different classes
 - EX1001, 2:49-52, 7:33-8:37

Sur-Reply, 12-15; *see also* POR, 38-39, 44, 51-57, 60-73

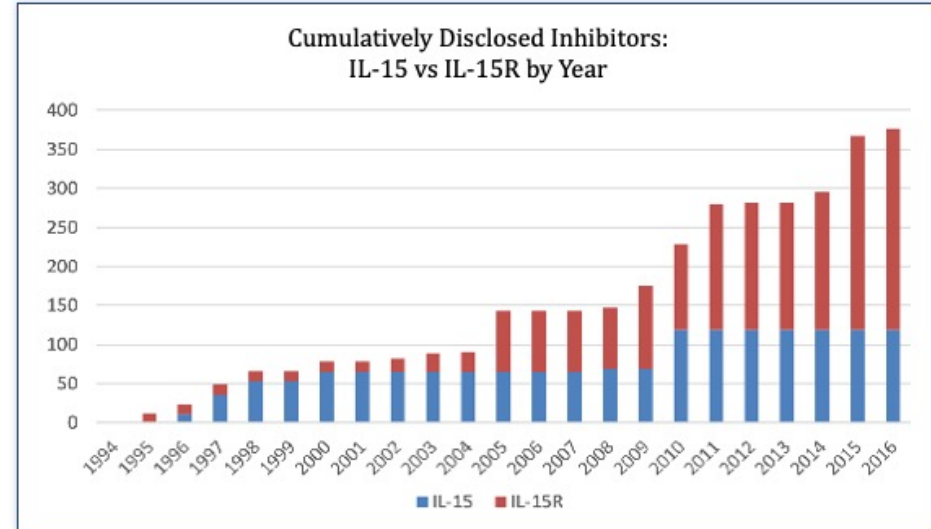
Known IL-15 and IL-15R Inhibitors



- EX1011 • EX2027 • EX2050 • EX2104 • EX2111
- EX2013 • EX2028 • EX2051 • EX2105 • EX2112
- EX2014 • EX2029 • EX2085 • EX2106 • EX2113
- EX2017 • EX2030 • EX2087 • EX2107 • EX2114
- EX2019 • EX2031 • EX2088 • EX2108
- EX2024 • EX2032 • EX2102 • EX2109
- EX2025 • EX2049 • EX2103 • EX2110



EX2005, ¶70



EX2005, ¶72

EX2005, ¶¶ 68-75, App'x A; POR, 5-14; Sur-Reply, 3-5

Expectation of Common Autoimmune Therapeutic Efficacy

2015 filing date



BACKGROUND OF THE INVENTION:

There remain considerable unmet medical needs for inflammatory and autoimmune diseases such as rheumatoid arthritis, psoriasis and intestinal inflammatory diseases. Cytokine targeting is now established as a feasible method for treating such chronic inflammatory diseases.

Cytokine 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, 3

2014 filing date



Significant involvement of IL-15 in the development of the pathogenesises of the aforementioned afflictions suggests that targeting this cytokine signaling pathway can reduce or eliminate the occurrence of IL-15-related disorders. This strategy has been proved lately by a number of biological assays. Reduction of IL-15-mediated biological responses, using the soluble receptor IL-15Ra (Liew F.Y., McInnes I.B., Ann. Rheum. Dis. 61 Supl. 2, ii100-2 (2002);

Significant involvement of IL-15 in the development of the pathogenesises of the aforementioned afflictions suggests that targeting this cytokine signaling pathway can reduce or eliminate the occurrence of IL-15-related disorders. This strategy has been proved lately by a number of biological assays.

always resulted in the alleviation of the disease symptoms

EX2025, 2-3

POR, 12-13; Sur-Reply, 3-5; EX2005, ¶¶ 52-65, 80-83; see also EX1011, 4:25-34; EX1012; EX1018, 2

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

39

Amgen Inc. v. Sanofi, 598 U.S. 594 (2023)



***“[I]t may suffice to give an example (or a few examples) if the specification also discloses **some general quality running through the class** that gives it a **peculiar fitness for the particular purpose**. In some cases, disclosing that **general quality may reliably enable** a person skilled in the art to make and use all of what is claimed, not merely a subset.*”**

Amgen Inc. v. Sanofi, 598 U.S. 594, 611-612 (2023)

POR, 51-55; Sur-Reply, 12-15

Amgen: “general quality running through the class”



Amgen v. Sanofi

“[I]t may suffice to give an example (or a few examples) if the specification also discloses **some general quality running through the class** that gives it a **peculiar fitness for the particular purpose**. In some cases, disclosing that **general quality may reliably enable** a person skilled in the art to make and use all of what is claimed, not merely a subset.

Amgen Inc. v. Sanofi, 598 U.S. 594, 611-612 (2023)

The '505 Patent

- Example 5: in vivo working example durably reversed vitiligo
 - EX1001, 33:1-34:45
- IL-15/IR-15 inhibitors commonly inhibit pathway known to treating IL-15 mediated autoimmune diseases
 - EX2005, ¶¶80-83; EX1011; EX1013; EX2014; EX2015; EX2019; EX2024; EX2025; EX2026; EX2118
- Exemplary compounds and classes disclosed, all references incorporated
 - EX1001, 2:49-52, 7:33-8:37

Sur-Reply, 13-14

Expectation of Common Autoimmune Therapeutic Efficacy

- Dr. Abbas confirms expectations:

Q. Was it common -- to your knowledge, was it **common as of April 2017 to expect that species that would antagonize IL-15 signaling would be useful in diseases -- autoimmune diseases that had been identified as having an IL-15 mechanism?**

* * *

Dr. Abbas: **It's reasonable**, but it depends on how the mechanism was identified.

Q. Is that different today than in April 2017, about how people rely on proof of concepts to infer treatment activity for an antagonist?

* * *

Dr. Abbas: **As far as I know, the principles have not changed.**

EX2007, 74:19-75:10

POR, 6, 13, 32, 71-72; Sur-Reply, 3-4, 16-17

Expectation of Common Autoimmune Therapeutic Efficacy

2015 filing date



BACKGROUND OF THE INVENTION:

There remain considerable unmet medical needs for inflammatory and autoimmune diseases such as rheumatoid arthritis, psoriasis and intestinal inflammatory diseases. Cytokine targeting is now established as a feasible method for treating such chronic inflammatory diseases.

Cytokine 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, 3

2014 filing date



Significant involvement of IL-15 in the development of the pathogenesises of the aforementioned afflictions suggests that targeting this cytokine signaling pathway can reduce or eliminate the occurrence of IL-15-related disorders. This strategy has been proved lately by a number of biological assays. Reduction of IL-15-mediated biological responses, using the soluble receptor IL-15Ra (Liew F.Y., McInnes I.B., Ann. Rheum. Dis. 61 Supl. 2, ii100-2 (2002);

Significant involvement of IL-15 in the development of the pathogenesises of the aforementioned afflictions suggests that targeting this cytokine signaling pathway can reduce or eliminate the occurrence of IL-15-related disorders. This strategy has been proved lately by a number of biological assays.

always resulted in the alleviation of the disease symptoms

EX2025, 2-3

POR, 12-13; Sur-Reply, 3-5; EX2005, ¶¶ 52-65, 80-83; see also EX1011, 4:25-34; EX1012; EX1018, 2

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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Petitioner's Written Description Cases Are Inapt



- ***Novel compounds and their use***

- ***Ariad***: undeveloped class of compounds with no working examples; failed to “sufficiently disclos[e] molecules capable of” practicing the claimed method (POR, 40)
- ***Juno***: new class of antibodies where “very few [claimed embodiments] were known” and specification provided no way “to distinguish” (POR 41-42)
- ***Idenix***: undeveloped nucleosides genus, where specification “provide[d] no method of distinguishing effective from ineffective compounds” “no[r] explain[ed] what ma[de] [examples] effective, or why” (POR, 41-42)
- ***AbbVie***: undeveloped genus of “fully human IL-12 antibody” with a particular binding activity (POR, 41)

- **Method for “selectively inhibiting”**

- ***Rochester***: failed to “disclose ***any*** compounds that can be used in its claimed methods” and *no evidence “that such a compound was known”* (POR, 41-42)

POR, 38-42

Petitioner's Enablement Cases Are Inapt



- **Amgen:**
 - novel genus of antibodies with specific binding properties
- **Enzo:**
 - genus of novel polynucleotide structures having particular functionality where “the specification fails to teach [a POSA] whether the many structural embodiments of the broad claims would exhibit that required functionality.”
- **Idenix:**
 - undeveloped nucleosides genus, where specification “provide[d] no method of distinguishing effective from ineffective compounds” “no[r] explain[ed] what ma[de] [examples] effective, or why”
- **Wyeth:**
 - undeveloped chemical genus, defined by unpredictable combination of structural and functional properties, where only one species was disclosed in specification and potentially four others known in the art.

POR, 51-57

Narrower Dependent Claims Are Described and Enabled

- Reply fails to address Patent Owner's cited support for claims 2-5. *See* POR 50-51, 73.

Narrower Dependent Claims	Exemplary Support in Specification	Exemplary Support in the Art
2. The method of claim 1, wherein the inhibitor is a small molecule inhibitor , an antibody , a peptide inhibitor , or an inhibitory nucleic acid targeting IL-15 or the IL-15 receptor.	EX1001, 7:33-8:37, 9:3-21	EX2024 (small molecule inhibitor) EX2032 (peptides inhibitor) EX2031 (antibodies) EX2030 (inhibitory nucleic acids)
3. The method of claim 1, wherein the inhibitor is administered to the lesion. 4. The method of claim 3, wherein the inhibitor is administered to the epidermis within the lesion. 5. The method of claim 3, wherein the inhibitor is administered to the epidermis within the lesion by subcutaneous or intradermal administration, or a microneedle array.	EX1001, 2:9-11, 20:30-54	Petitioner's declarant agrees methods of administration were "routine and common" (EX1004, ¶29) EX2005, ¶140

POR, 50-51, 73; Sur-reply, 11

Petitioner's Arguments Are Contradicted by the Evidence

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"the science or technology at issue, inhibiting IL-15 signaling to treat autoimmune diseases such as vitiligo, was nascent, not mature." Pet., 41	"Cytokine targeting is now established as a feasible method... in [RA], psoriasis and Crohn's diseases." EX2024, 3 "Significant involvement of IL-15 in the development of the pathogenesis of the aforementioned afflictions suggests that targeting this cytokine signaling pathway can reduce or eliminate the occurrence of IL-15 related disorders." EX2025, 2 IL-15/IL-15R Inhibitors: Cumulatively Disclosed Cumulatively Disclosed Inhibitors: IL-15 vs IL-15R by Year See also EX2013, 6; EX2014, 2; EX2015, 8-9; EX2024, 4, 17; EX2024, 17; EX2028, 1, 9; EX2118, 177:22-178:5, 179:22-180:11, 181:10-21, 182:21-183:6 EX2005, ¶¶ 70, 72

POR, 5-14; Sur-Reply, 3-5, 15-17

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"This petition is supported by the Declaration of Dr. Abul Abbas" Pet., 5	• Did not consider majority of references cited in specification EX2007, 6:2-17 • Unaware of and did not investigate the number and type of IL-15 signaling antagonists Q. As of April 2017, are you aware of how many species there were that were known to antagonize IL-15 signaling? ... [Dr. Abbas]. No. ... Q. You hadn't looked into that in the context of your report in this case; correct? [Dr. Abbas]: No, I had not. EX2007, 71:11-24, <i>see also</i> EX2007, 81:21-82:12, 83:14-84:12, 85:4-13 • Unaware of most common features between mouse model and human disease EX2007, 38:10-38:23, 43:16-19

POR, 30-31; Sur-Reply, 9-10

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"The petition also is supported by the Declaration of Dr. R. Todd Plott" Pet., 5	- Little to no experience with IL-15 signaling inhibitors EX2008, 16:14-17, 17:14-16, 19:23-20:8 - Perspective limited to a "medical practitioner" EX1004, ¶32 - Would need to consult experts including in cytokine signaling EX2118, 8:24-9:4, 9:13-21, 11:1-3, 10:23-11:17, 12:6-14, 14:4-15:12, 15:21-16:3, 18:8-14, 22:3-14 - Outdated experience with vitiligo treatment Q. Has treatment of vitiligo changed between 1990 and 2017? [Dr. Plott]. Not very much. ... Q. Have you had any publications on vitiligo since 1990? [Dr. Plott]. No, I have not. Q. Have you conducted any research on vitiligo since the 1980s? [Dr. Plott]. No, I have not. EX2118, 26:2-4, 16:20-25

POR, 30, 32; Sur-Reply, 7-10, 23-26

Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
IL-15 inhibitors "had no demonstrated efficacy in vivo"	• Anti-IL15 "antibody has shown efficacy in a Phase I/II clinical trial involving patients with rheumatoid arthritis". EX1016, 6 • "Antibody-mediated blockade of IL-15 reverses the autoimmune intestinal damage in transgenic mice that overexpress IL-15 in enterocytes." EX2012 • Dr. Plott: • "[t]he use of specific CD122 antibodies in a CD8+-dependent mouse model of autoimmune skin lesions to treat autoimmune skin lesions by depleting CD8+ T cells was known in the art (e.g., EX1007)" EX1004, ¶34 • "Well, I think that persons of the skill would -- would understand that" "an antibody specific for IL-15 had shown efficacy in a Phase I/II clinical trial for 18 rheumatoid arthritis" EX2118, 130:15-24

Reply, 21

POR, 58; Sur-Reply, 20-21

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"no expectation of class-wide efficacy" Reply, 8 (citing Plott Reply Declaration, EX1047, ¶10, 50)	- Dr. Abbas agreed: "it [was] common as of April 2017 [and today] to expect that species that would antagonize IL-15 signaling would be useful in diseases—autoimmune diseases that had been identified as having an IL-15 mechanism." EX2007, 74:19-75:10 "Cytokine targeting is now established as a feasible method... in [RA], psoriasis and Crohn's diseases." EX2024, 3 "Significant involvement of IL-15 in the development of the pathogenesis of the aforementioned afflications suggests that targeting this cytokine signaling pathway can reduce or eliminate the occurrence of IL-15 related disorders." EX2025, 2-3 See also EX2013, 6; EX2014, 2; EX2015, 8-9; EX2024, 4, 17; EX2024, 17; EX2028, 1, 9; EX2118, 177:22-178:5, 179:22-180:11, 181:10-21, 182:21-183:6

POR, 5-14; Sur-Reply, 3-5, 15-17

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"effects of using implicated molecules was complicated and unpredictable" Reply 8; <i>generally</i>, Reply, 3-8	- IL-15/IL-15R inhibitors - share a common trait—therapeutic activity from blocking IL-15 signal—regardless of specific mechanism Prof. Damsky: EX2005, ¶¶79, 115-118, 122, 124, 127-128 "[T]o the extent that something inhibited IL-15, I would expect that it is an IL-pathway inhibitor." Dr. Abbas: EX1046, 161:14-162:4 "reasonable" to expect that species that would antagonize IL-15 signaling would be useful in IL-15 mediated EX2007, 74:19-75:10

POR, 5-14; Sur-Reply, 3-5, 15-17

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

53

Petitioner's Arguments Are Contradicted by the Evidence

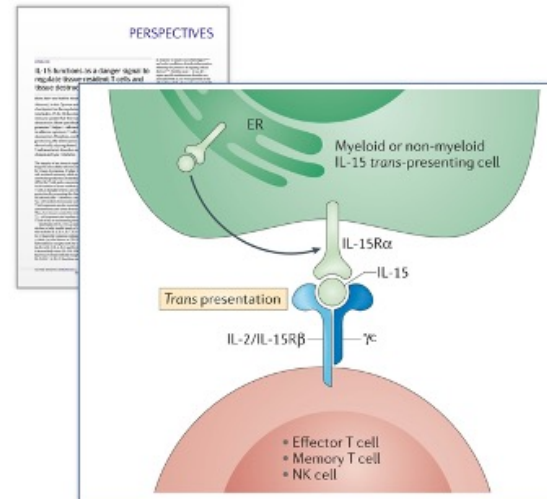
Petitioner's Arguments

"The claims also encompass inhibition of any one of the various types of IL-15 signaling and inhibition of any of the various versions of the receptor, *which implicate different results.*"

Reply, 4

Contrary Evidence

Signaling Blocked By Inhibitors of IL-15 and Any Receptor Unit



EX1015, Fig. 1a

Q. And any of those would inhibit the transpresentation that's shown; correct?

A. Theoretically, yes.

EX2007, 71:3-5; generally id., 70:10-71:5;

The ability of anti-CD122 monoclonal antibodies to inhibit cell proliferation mediated by trans-presented IL-15 was examined using TF-1 β cells and scIL-15/IL-15Rα. In typical

EX1011, 22:17-19

POR, 7-8; Sur-Reply, 3-5; EX2005, ¶¶ 66-67;

POR, 5-14; Sur-Reply, 3-5, 15-17

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

54

Petitioner's Arguments Are Contradicted by the Evidence

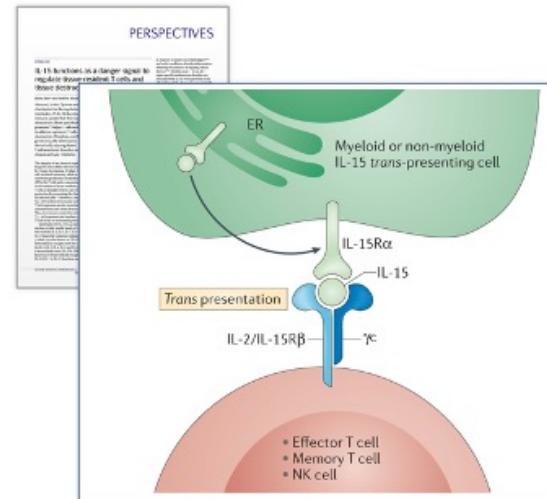
Petitioner's Arguments

"The specification is not enabling because it fails to demonstrate which targets are necessary or sufficient to achieve the desired effect, let alone the structural requirements for achieving that effect."

Reply, 4

Contrary Evidence

Signaling Blocked By Inhibitors of IL-15 and Any Receptor Unit



EX1015, Fig. 1a

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EX1011, 22:17-19

POR, 7-8; Sur-Reply, 3-5; EX2005, ¶¶ 66-67;

POR, 7-8, 43-45, 66-68; Sur-Reply, 3-5, 18-19

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

55

Petitioner's Arguments Are Contradicted by the Evidence

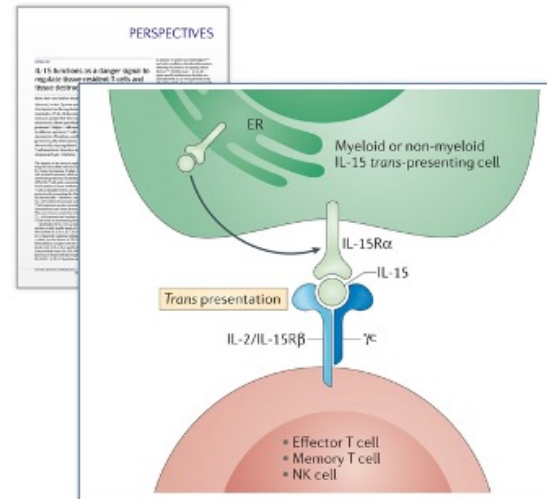
Petitioner's Arguments

"The '505 patent never demonstrated that ChMBC7 inhibition is representative of all CD122 inhibition."

Pet., 3

Contrary Evidence

Signaling Blocked By Inhibitors of IL-15 and Any Receptor Unit



EX1015, Fig. 1a

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EX1011, 22:17-19

POR, 7-8; Sur-Reply, 3-5; EX2005, ¶¶ 66-67;

POR, 7-8, 43-45, 66-68; Sur-Reply, 3-5, 18-19

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

56

Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments

"The '505 patent never demonstrated that ChMBC7 inhibition is representative of all CD122 inhibition."

Pet., 3

Contrary Evidence

Forte's FB-102



**Forte's Interrogatory
Response to: "identify and
describe the particular
models referred to in the
press release"**

Richmond et al., reported in 2018 that the Fc-diminished chimeric rat/mouse CD122 antibody ChMBC7 depleted CD8+ PMEL in the dermis of the Harris transgenic mice and, by substantially eliminating the only remaining immune cells in the mice, reversed the vitiligo lesions induced by the transplanted CD8+ PMELs. 10 Sci. Transl. Med. 1- 20.

EX2009, 8-9 (citing EX2046); see also Paper 17, 3-5



Professor Damsky

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...

EX2005, 109

POR, 33-35; Sur-Reply, 10

POR, 7-8, 43-45, 66-68; Sur-Reply, 3-5, 18-19

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

57

Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"The patent does not describe the sequence or structure" of ChMBC7. Pet., 27	• "[T]he specification need not include a working example of every possible embodiment to enable the full scope of the claims" <i>Bayer Healthcare LLC v. Baxalta Inc.</i>, 989 F.3d 964, 981-82 (Fed. Cir. 2021) • Prof. Damsky: Q. In your opinion, would a person of ordinary skill in the art have needed to understand the structure of CHMB7 or its epitope to understand the disclosure of the '505 patent? ... [Prof.Damsky] No. EX1046, 271:23-272:2 • Dr. Plott would not recognize structures of antibodies or need to know their binding epitopes. EX2118, 30:5-14; 31:11-17, 31:24-32:10, 32:20-35:12 • Forte relied on same data. EX2009, 8-9 (citing EX2046); <i>see also</i> Paper 17, 3-4; EX2005, ¶109

POR, 66-68; Sur-Reply, 18-19

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

58

Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"Some implicated molecules may inhibit only IL-15 signaling whereas other may inhibit both IL-15 and IL-2 signaling or just IL-2 signaling." Reply, 9, 14	• Claimed method to IL-15 inhibition. <i>E.g.</i>, EX1001, 6:5-9, 33:10-12, 30:53-31:12, Fig. 6D • IL-15/IL-15R inhibitors were recognized as a class based on their common property of blocking the IL-15 signaling pathway, regardless of specific blocking mechanism. EX2005, ¶¶79, 115-118, 122, 124, 127-128

POR, 60; Sur-Reply, 3

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

59

Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"trial and error" Reply, 9, 14	- IL-15 assays were routine - Prof. Damsky: A POSA would "have been able to conclusively determine whether a compound is an inhibitor of IL-15 or the IL-15 receptor..." EX1046, 270:2-19 - EX2013, 14-19; EX2014, 11-15; EX2015, 9-10; EX2024, 14-15; EX2118, 160:1-5, 178:7-183:17 - Known techniques for rationally designing and identifying pathway inhibitors "Routine methods can be used to design an inhibitory nucleic acid that binds to the target sequence" (EX1001, 9:3-5) - EX2013, 4, 25-26 (<i>in silico</i> methods identifying IL-15 inhibitors); EX2014, 5-6, 20-21 (same); EX2015, 8, 5 (same)

Sur-Reply, 4-5, 24-25

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

60

Petitioner's Arguments Are Contradicted by the Evidence

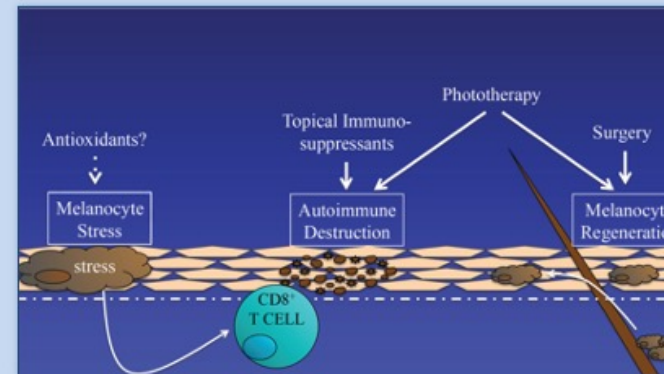
Petitioner's Arguments

"whether and how a given molecule would treat [vitiligo] thus depended significantly on its cause(s)"

Reply, 17

Contrary Evidence

- "Vitiligo is caused by a dynamic interplay between genetic and environmental risks that initiates an autoimmune attack of melanocytes in the skin."



EX2060, 1 & Fig. 1

- Chemically induced vitiligo "is indistinguishable from classical vitiligo."

EX2053, 3

Sur-Reply, 5-7, 21-23

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

61

Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"The Harris Mice Are Not Representative of Vitiligo" Reply, 15-17	• <i>Harris</i> mouse model • Recapitulates hallmarks of human diseases • Primary vitiligo model EX2005, ¶¶84-89 • Relied upon by Forte as basis for expected efficacy of FB-102 in human vitiligo EX2009, 8-9 (citing EX2046); see also Paper 17, 3-4; EX2005, ¶109 Recapitulates Hallmarks of Human Disease 1. Melanocyte-specific T cells drive skin depigmentation. 2. T cell recognition and reaction against common melanocyte-specific antigens that lead to melanocyte death and depletion in the epidermis. 3. T cells that exhibit a T resident memory phenotype and express CD122/IL-15Rβ. 4. IFN-γ is key driver in disease pathogenesis and levels of IFN-γ correlate with depigmentation. 5. Predominant site of depigmentation in the interfollicular epidermis. 6. Pigment retained within the hair follicles of vitiligo lesions. 7. Predilection for involvement of acral sites (ears, hands, feet), the face, and genitalia. 8. Disease progression from patchy areas of depigmentation to confluent areas of depigmentation, a sign of active vitiligo. 9. No visible clinical evidence of skin inflammation.  Forte's Interrogatory Response to: "identify and describe the particular models referred to in the press release" Richmond et al., reported in 2018 that the Fc-diminished chimeric rat/mouse CD122 antibody ChMBC7 depleted CD8+ PMEL in the dermis of the Harris transgenic mice and, by substantially eliminating the only remaining immune cells in the mice, reversed the vitiligo lesions induced by the transplanted CD8+ PMELs. 10 Sci. Transl. Med. 1- 20. EX2009, 8-9 (citing EX2046); see also Paper 17, 3-5

POR, 15; Sur-Reply, 21-23

Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"This great breadth is exacerbated by the absence of any limitation for the extent of inhibition." Reply, 4	• Dr. Plott: Q. "It's routine that if you have a lower affinity drug compared to a higher affinity drug, you just use more of the lower affinity drug to get equal effect, right?..." [Dr. Plott]. Yes. That would be a strategy for overcoming the inefficiency." EX2118, 113:1-9 • Petitioner: • "Indeed, even the '505 patent admits that the dosing 'can be determined by standard pharmaceutical procedures' and that the 'skilled artisan' will appreciate the factors that may influence the dosage. EX1001, 23:20-25, 23:29-34." Pet., 68

POR, 5-14; Sur-Reply, 3-5, 15-17

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

63

Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"Differential" effects Reply, 5-6	- Petitioner challenges only ~15 out of <i>over 300</i> inhibitors Sur-Reply, 17 - Dr. Plott confirms these outliers are <i>unexpected</i>: "the lead IL-15 antibody blocked some forms of IL-15 signaling <i>but unexpectedly</i> enhanced others" "<i>unexpectedly</i> increased the production of proinflammatory cytokines", "<i>unexpectedly</i> potentiated IL-15" EX1047, ¶25, ¶26, ¶29 "Even if some of the claimed [inhibitors] were inoperative, the claims are not necessarily invalid." <i>Atlas Powder Co. v. E.I. du Pont De Nemours & Co.</i>, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984)

Sur-Reply, 17-18

Petitioner's Arguments Are Contradicted by the Evidence

Petitioner's Arguments	Contrary Evidence
"The claims also encompass downstream inhibition" Reply, 9-11	• Patent distinguishes IL-15/IL-15R inhibitors from downstream JAK inhibitors • disclosing IL-15/IL-15R with specific header EX1001, 7:34-8:5 • disclosing JAK EX1001, 8:6-22 • Prof. Damsky: Q. Let me ask a new question. Do you agree that administering a therapeutically effective amount of tofacitinib to a subject in need of treatment satisfies Claim 1? ... [Prof. Damsky]: No. I think that people would think that tofacitinib or any JAK inhibitor was acting through interferon gamma in vitiligo." EX1046, 159:20-160:3 <i>see also</i> EX2118 (Plott Reply Dep. Tr.) 77:9-78:8

Sur-Reply, 19-20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

65

Petitioner Has Not Established Obviousness

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Vitiligo and Alopecia Areata: “Apples and Oranges”

Property	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

EX2005, ¶51; POR, 15-18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Vitiligo and Alopecia Areata: “Apples and Oranges”

Property	Vitiligo	Alopecia Areata (AA)
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

EX2005, ¶51; POR, 15-18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

68

Xing's Teachings: Specific to AA

- Focus on AA only
- C3H/HeJ mouse model
 - CD8+NKG2D+ T cells: not specific to PMEL
 - No evidence this model would develop vitiligo
- Results:
 - IL-15 antibody not able to reverse established AA
 - Prevented accumulation, not depletion, of cells



LETTERS

Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition

Luzhou Xing^{1,2}, Zhenpeng Dai^{1,2}, Ali Jabbari^{1,2}, Jane E Cerise^{1,3}, Claire A Higgins², Weiwan Gong²

tion studies in humans². Systemically administered blocking antibodies to either IL-2 (Fig. 2d–f) or IL-15Rβ (Fig. 2g–i) prevented AA in grafted mice, blocked the accumulation of CD8⁺NKG2D⁺ T cells in the skin and abrogated MHC upregulation. However, IL-21 blockade failed to prevent the development of AA in grafted C3H/HeJ mice (Supplementary Fig. 7). Notably, none of these blocking antibodies given alone was able to reverse established AA (data not shown).

...terted phenotypically by hair loss and, histologically, by infiltrating T cells surrounding the hair follicle bulb (reviewed in ref. 1). Previous studies have shown that transfer of naïve T cells (that are IL-15 dependent) can cause the disease in human xenograft models³, as well as in CHHMF mice⁴, a mouse strain that develops spontaneous AA.

...and NKG2D (Fig. 1e and Supplementary Fig. 1b). These CD8⁺ T cells expressed high levels of IFN-γ and exhibited NKG2D-dependent cytotoxicity against ex vivo-expanded epigenetic dermal melanocyte target cells (Fig. 1c). Gene expression analysis of the CD8⁺NKG2D⁺ T cells isolated from alopecia CHHMF lymph node cells using

¹Department of Pathology, Columbia University, New York, New York, USA. ²Department of Dermatology, Columbia University, New York, New York, USA. ³Department of Psychiatry, Columbia University, New York, New York, USA. ⁴Department of Dermatology, Columbia University, New York, New York, USA. ⁵Department of Genetics and Development, Columbia University, New York, New York, USA. ⁶Department of Medicine, Columbia University, New York, New York, USA. These authors contributed equally to this work. *These authors jointly directed this work. Correspondence should be addressed to: A.M.C. (e-mail: amc10@cumc.columbia.edu).

Received 22 December 2013; accepted 10 June 2014; published online 17 August 2014; doi:10.1038/nm.3045

EX1007, 4

NATURE MEDICINE | www.nature.com/naturemedicine

Forte Biosciences, Inc. Exhibit - 1007

Forte Biosciences, Inc. v. University of Massachusetts - PGR2023-00014

POR, 73-81

No Motivation to Combine or Reasonable Expectation of Success

Institution Decision, 33-34

- “Rather, we find Petitioner’s reasons to combine the references constitute impermissible hindsight reconstruction where the inventor’s own disclosure, rather than the prior art, supplies the rationale to combine the references.”
- “Although Petitioner articulates a reason why a person of ordinary skill in the art would combine Harris and Xing, this purported reasoning does not appear to comport with the disclosure of Xing itself.”
- “Xing postulates that IFN- γ produced by CD8 T cells leads to the collapse of immune privilege in hair follicles and induces additional production of IL-15 creating a feed-forward loop that promotes type I cellular autoimmunity. See Ex. 1007, 6. Petitioner’s rationale does not account for the increased IL-15 production or the cellular autoimmunity and how that would affect an ordinarily skilled artisan’s decision to use TM- β 1 to reduce the autoreactive CD8+ Trm cells in the skin.”
- “Rather, Petitioner’s challenge appears to be based on a mosaic of prior art disclosures cobbled together using the teachings of the ’505 patent, which is the very definition of impermissible hindsight analysis.”

**Petitioner
does not
respond**

ID (Paper 10), 33-34; POR, 73-38, 73-81; Sur-Reply, 26-27

Unexpected Results: Durable Repigmentation

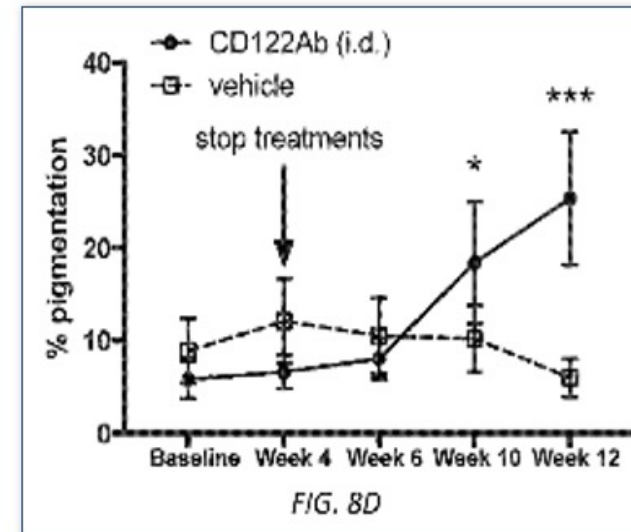
- Examiner considered and relied upon this evidence (EX1010, 15)
- Petitioner provides only attorney argument in response
 - No requirement that unexpected results must themselves be claimed

Example 5. IL-15R β is Required for the Function and Maintenance of Trm in the Skin, and IL-15R β Blockade Serves as a Durable Treatment

Existing treatments for vitiligo are not durable, as the disease returns at the site of treatment after discontinuation.

significant repigmentation compared to control mice without depletion of PMEL T cells (FIG. 8). This suggests that targeting IL-15 in the skin in vitiligo, unlike existing therapies, could provide a durable treatment option for patients, with longstanding effects after a limited treatment course.

EX1001, Example 5



POR, 82-84; Sur-Reply, 27-28 EX1001, Fig. 8D; EX1010, 15

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

71

Unexpected Results: Durable Repigmentation

Prior Treatments Did Not Provide Durable Reversal

tion studies in humans². Systemically administered blocking antibodies to either IL-2 (Fig. 2d-f) or IL-15R β (Fig. 2g-i) prevented AA in grafted mice, blocked the accumulation of CD8⁺NKG2D⁺ T cells in the skin and abrogated MHC upregulation. However, IL-21 blockade failed to prevent the development of AA in grafted C3H/HeJ mice (Supplementary Fig. 7). Notably, none of these blocking antibodies given alone was able to reverse established AA (data not shown).

EX1007, 4

Most 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," notes Julien Seneschal, a dermatologist at the University of Bordeaux in France.

EX2056, 10

Abstract

Vitiligo is a common acquired depigmenting disorder characterized by the development of white macules and patches due to the loss of melanocytes. Patients with vitiligo can be stigmatized by society, making the disease a source of psychological stress that can considerably affect quality of life. The goal of vitiligo treatment is to obtain skin repigmentation in the majority of cases, and less commonly to depigment the remaining normal skin. There is 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. Recently, JAK

EX2055, 1

POR, 82-84; Sur-reply, 27-28; EX2005, ¶34

Long-Felt Need, Commercial Value, and Copying

LARGE UNMET NEED IN VITILIGO AND ALOPECIA AREATA (COMBINED \$6 BILLION MARKET BY 2026)

Vitiligo

Vitiligo is an autoimmune disease of the skin mediated primarily by NK and CD8+ T cells that kill melanocytes and create white spots. In the US there are approximately 2 m people with vitiligo.

The global vitiligo treatment market size was valued at \$1.2 billion in 2018 and is projected to reach \$1.9 billion by 2026, exhibiting a CAGR of 5.8% (Fortune Business Insights)

Alopecia Areata (AA)

AA is an autoimmune disease in which immune cells attack and damage hair follicles and is mediated primarily by CD8+ T cells and NK cells

The global alopecia treatment market was valued at \$2.7 billion in 2018, and is projected to reach \$3.9 billion by 2026, registering a CAGR of 4.6% from 2019 to 2026 (Allied Mkt Research)



While JAK inhibitors have demonstrated efficacy in the treatment of vitiligo and alopecia areata, the lack of a class including black box warnings highlights the significant unmet need for new therapies.

LARGE UNMET NEED IN VITILIGO AND ALOPECIA AREATA (COMBINED \$6 BILLION MARKET BY 2026)

Vitiligo is an autoimmune disease of the skin mediated primarily by NK and CD8+ T cells that kill melanocytes and create white spots. In the US there are approximately 2 m people with vitiligo.

- Forte's statements to investors confirm unmet need and commercial significance

POR, 84-87; Sur-reply, 27-28; EX2004, 33

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Long-Felt Need, Commercial Value, and Copying

https://www.fortebios.com/pipeline/default.aspx September 27, 2023 at 1:27 PM EDT

FORTE BIOSCIENCES, INC.

HOME ABOUT US PIPELINE INVESTOR RELATIONS CONTACT US



Pipeline

Asset	Indication	Preclinical	Phase 1	Phase 2	Phase 3
FB102	Graft vs Host Disease	Progressing	Completed	Completed	Completed
	Vitiligo	Progressing	Completed	Completed	Completed
	Alopecia Areata	Progressing	Completed	Completed	Completed

FB-102

- CD122 is subunit of IL-2/IL-15 receptors which are key regulators of NK cells and T cell subsets
- FB-102 (Forte's anti-CD122 antibody) is designed to mediate NK and CD 8+ T cells specifically
- Significant amount of proof-of-concept preclinical data supports activity of CD-122 blockade, including in GvHD and vitiligo

FORTE BIOSCIENCES, INC.

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- Significant amount of proof-of-concept preclinical data supports activity of CD-122 blockade, including in GvHD and vitiligo

POR, 84-87; Sur-reply, 27-28; EX2045

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

74

Long-Felt Need, Commercial Value, and Copying

- **Dr. Plott:**

48. From the perspective of a clinician, inhibiting cytokine signaling to treat autoimmune diseases such as vitiligo, was nascent, at its very beginnings of experimentation in 2017 and 2018. It was not a mature or well-developed field of treatment. Additionally, as I explained above, the mouse model used for modeling

Dr. Plott (EX1004, ¶48)

- **Harris 2015:**

There are currently no FDA-approved treatments for vitiligo, and standard off-label treatments are limited in efficacy. Recently, significant repigmentation was

EX2001, 2

- **Forte Press Release:**

FB-102 R&D Updates

Forte's wholly owned antibody, FB-102, targets CD-122, a subunit of the IL-2 and IL-15 receptor and mediates NK and CD8+ T cells, which have been implicated in a variety of autoimmune and immune related diseases.

EX2003, 1

POR, 84-87; Sur-reply, 27-28

Petitioner's Motion to Exclude Should Be Denied

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

Petitioner's Objections Are Untimely



"The objection must identify the grounds for the objection *with sufficient particularity to allow correction in the form of supplemental evidence.*"

37 C.F.R. § 42.64(b)(1)

"The lack of an effective objection is sufficient basis to deny Petitioner's Motion."

B/E Aerospace, Inc. v. MAG Aerospace Indus., LLC, IPR2014-01511, Paper 104, 6-8 (PTAB Mar. 18, 2016)

- Forte's objections did not allege that Dr. Damsky was not a person of ordinary skill at the time of invention or that he was not an independent expert

See Paper 21, 3-4

Paper 37, 5-6

Professor Damsky, M.D., Ph.D.



Education:

- Assistant Professor of Dermatology & Pathology (Clinician-Scholar Track), Yale University School of Medicine
- Board Certified Dermatologist & Dermatopathologist
- Ph.D., Cell and Molecular Biology (2011)
- M.D. (2013)
- Dermatology Resident (2014-2017)

Recognitions:

- Young Investigator Award; LEO Foundation Award
- Numerous clinical trial grants and funding
- >120 peer-reviewed publications, many related to cytokine inhibitors in treating inflammatory skin conditions
 - “JAK Inhibitors in Dermatology: the Promise of a New Drug Class” (EX1021)

POR, 5 n.11; Sur-Reply, 23-26, EX2005, ¶¶1-18, EX2006; Paper 37

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Professor Damsky was a POSA as of April 2017

Petitioner's Arguments	Contrary Evidence"
Professor Damsky "lacked the requisite 3-5 years of experience in treating autoimmune diseases or researching relevant cytokine signaling pathways relevant to treating autoimmune diseases," as of April 2017. Paper 34, 3	• During Ph.D. research (pre-2011): • "intensively studied intracellular signaling pathways" and the effects of alerting signaling to those pathways, such as cytokines EX2005, ¶6 • Between 2011 and 2017, research group was: • "active in researching cytokines in dermatology and beyond dermatology in a number of different settings using translational approaches, invasive approaches in clinical trials" EX1046, 267:22-268:16 • Began treating vitiligo patients in medical school (pre-2013) EX2006, 1; EX1046, 116:16-117:9

Paper 37, 1-3, 6-10

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Professor Damsky's Qualifications

Q. Subsequent to your Ph.D. – **between obtaining your Ph.D. in 2011 and April 2017**, can you explain what experience you had, if any, treating autoimmune diseases or researching cytokine pathways relevant to treating autoimmune diseases?

A. ... [Dr. Damsky] In terms of research related to cytokine, similarly our group was active in researching cytokines in dermatology and beyond dermatology in a number of different settings using translational approaches, invasive approaches in clinical trials.”

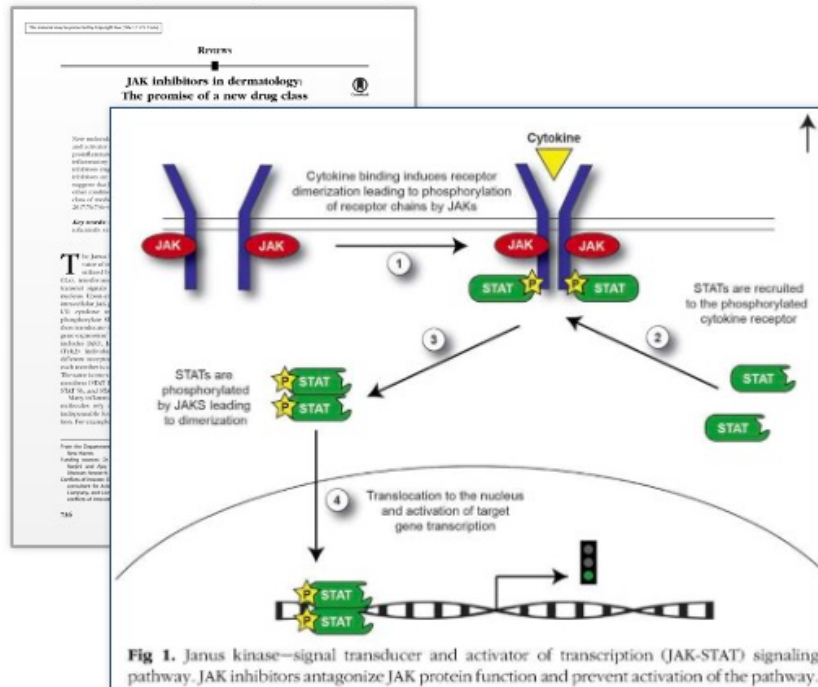
EX1046, 267:22-268:16

Paper 37, 7

Professor Damsky, M.D., Ph.D.

- Petitioner itself relied on Professor Damsky

Damsky *et al* (EX1021)



Filed on behalf of: Forte Biosciences, Inc.
By: Michael T. Rosato (mrosato@wgr.com)
Jad A. Mills (jmills@wgr.com)
Michael J. Hostetler (mhostetler@wgr.com)
Sonja R. Gerard (sgerard@wgr.com)

UNITED STATES PATENT AND TRADEMARK OFFICE

Cytotoxic CD8⁺ T cells were said to play a key role in the destruction of melanocytes in vitiligo and hair loss in AA. EX1008, 787; EX1020, Abstract (“Vitiligo patients have increased numbers of autoreactive, melanocyte-specific CD8⁺ T cells in the skin and blood, which are directly responsible for melanocyte destruction.”); EX1021, 737 (“The pathogenesis of [alopecia areata] involves hair follicle attack by autoreactive CD8⁺ T cells.”); EX1002, ¶50; EX1004, ¶39.

Pet., 9

Paper 37, 8-9

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Professor Damsky Is an Independent Expert

CONFLICT OF INTEREST

WD has research funding from Pfizer, the manufacturer of tofacitinib; however, this was not used to support this work, which was initiated before the research funding. WD is also a consultant for Eli Lilly. BK is an investigator for Concert Phar-

treatment of vitiligo. JEH is scientific founder of Villarix Therapeutics, Inc, which is focused on developing treatments for vitiligo. JMR and JEH are inventors on patent application #15/851,651, "Anti-human CXCR3 antibodies for the Treatment of Vitiligo," which covers targeting CXCR3 for the treatment of vitiligo.

EX1037, 3

Conflicts of interest

Dr Daneshjou is on the advisory board for VisualDx. Dr Richmond is an inventor on use patents for targeting CXCR3 (0#15/851,651) and IL15 (# 62489191) for the treatment of vitiligo. Dr Damsky is a consultant for Eli Lilly and TWi Biotechnology, has research funding from Pfizer, and receives licensing fees from EMD/Millipore/Sigma in unrelated works. Drs Ederaine, Kimball, Enwereji, Ftouni, and Junejo have no conflicts of interest to declare.

EX1039, 118

Agency: Incyte
I.D.# pending
Title: "Topical ruxolitinib in granuloma annulare: an opportunity for pathogenesis directed therapy"
Role: PI
Percent effort: 1%
Amount: \$200,000
Project period: 10/2023 – 12/2024

EX2006, 3

Paper 37, 10-13

Professor Damsky Is an Independent Expert

Q. Have you ever discussed this case or anything having to do with this case with John Harris?

A. No.

Q. Have you ever discussed this case or anything having to do with this case with Jillian Richmond?

A. No.

EX1046, 38:4-11

Q. In preparing your declaration, did you speak with any individual regarding the subject matter of this case other than the attorneys?

A. I don't think so, no.

Q. In preparing your declaration for this case, you did not speak with John Harris regarding the subject matter in this case. Is that correct?

A. That is correct.

EX1046, 131:20-132:2

Paper 37, 10-11

Professor Damsky Is an Independent Expert

Q. So with that correction, on March 22nd, 2021 in this tweet, you are congratulating Dr. Jill Richmond, the inventor of the '505 patent, on achieving—becoming a tenure track of assistant professor at the University of Massachusetts?

A. **That appears to be the case, but I want to contextualize that every time I go on Twitter or X, it is very common for me to congratulate someone on an achievement.**

EX1046, 69:18-70:1

Paper 37, 11