

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORTE BIOSCIENCES, INC.,
Petitioner,

v.

UNIVERSITY OF MASSACHUSETTS,
Patent Owner.

Case No. PGR2023-00014
Patent No. 11,278,505

PATENT OWNER'S RESPONSE

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TABLE OF ABBREVIATIONS

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
RA	Rheumatoid arthritis

Trm	Tissue resident memory T cells
UMass or Patent Owner	University of Massachusetts
USPTO or Office	U.S. Patent and Trademark Office

I. INTRODUCTION

The '505 patent claims the novel use of a known class of cytokine inhibitors based on the discovery—contrary to the direction of research at the time—that vitiligo could be treated by inhibiting the well-known IL-15 signaling pathway. The '505 patent's inventors' discovery tracks the classic medical science paradigm of identifying elevated cytokines associated with a disease followed by a preclinical animal study demonstrating disease treatment by blocking that cytokine signaling. POSAs routinely relied on such mechanistic proofs of concept (“PoC”) and expected common therapeutic activity from inhibitors in the same class, including newly developed inhibitors. This includes IL-15 specifically, where the art—and even Petitioner—understood that disease treatment effects were a common property of IL-15 signaling inhibitors based on their common mechanism of inhibiting IL-15 signaling.

Petitioner's written description and enablement challenges misunderstand and mischaracterize the art as “nascent.” By the '505 patent's priority date, “[c]ytokine targeting [was]... established as a feasible method for treating” numerous multiple diseases,¹ the IL-15 signaling pathway had been known for decades and was well-

¹ EX2024, 1.

characterized,² blockade of IL-15 signaling was known for treating numerous diseases,³ and hundreds of IL-15 signaling inhibitors were known with some already commercialized and in clinical use.⁴ On this foundation, the discovery and demonstration in the '505 patent that inhibiting IL-15 signaling treats vitiligo provided written description and enabling support for using this well-known class of inhibitors for the treatment of vitiligo.

Petitioner's contrary assertions rely on declarants who failed to consider disclosures in the '505 patent specification—including more than 300 expressly incorporated references—and who were admittedly unaware of and further failed to investigate the state of the art.⁵ For example, Petitioner's declarants failed to consider the hundreds of IL-15/IL-15R inhibitors known in the art, including from among each of the specifically claimed classes and others.⁶ Unlike *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023) ("*Amgen*"), and other inapt analogies relied upon by Petitioner, here the genus of inhibitors used in the claimed method "is well

² *E.g.*, EX1015; EX2002; *infra* §II.A.

³ *E.g.*, EX2010; EX1022; EX2011; EX2005, ¶¶80-83; *infra* §II.A.4.

⁴ *E.g.*, EX2005, ¶¶68-75; App'x A; *infra* §II.A.3

⁵ *E.g.*, *infra* §§III.B, IV.B.

⁶ *E.g.*, *infra* §§II.A.3, IV.B.

understood in the art and not itself the invention but is instead a component of the claim, [such that] 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) (“*UroPep*”), *aff’d*, 739 F. App’x 643 (Fed. Cir. 2018).

Petitioner’s obviousness challenge is likewise inapt. Their proposed obviousness combination attempts to force-fit results of an alopecia areata (“AA”) animal model that prevents accumulation of NKG2D⁺ CD8⁺ T cells associated with hair follicles (*Xing*, EX1007) into a distinct vitiligo model based on an excess of PMEL CD8⁺ T cells in the epidermis (*Harris*, EX1006). Beyond the absence of any motivation in the art, Petitioner fails to consider that the two diseases were understood to be like “apples and oranges” with AA being uniquely driven by a “feed-forward” IFN- γ loop that leads to the collapse of hair follicle immune privilege.⁷ Nor could the efficacious treatment of vitiligo via IL-15 inhibition have been reasonably expected prior to the inventors’ discovery. As the Board recognized, “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.” ID (Paper 10), 33. Petitioner’s obviousness ground further fails for not addressing the unexpected results of durable disease

⁷ EX1008, 1; EX1007, 6; EX2007, 20:10-19.

treatment disclosed in the '505 patent and considered during prosecution or other objective indicia of which Petitioner was aware. Its sole conclusory assertion that “[t]he '505 patent’s results thus were not unexpected in view of the prior art” (Pet., 77-78) fails to even mention—much less dispute—this evidence.

Finally, all of Petitioner’s grounds are undercut by its nonlitigation actions. Contrary to its written description and enablement grounds, Petitioner’s response to additional discovery (Paper 17) ordered by the Board shows that, based on data republished from the '505 patent, it understood that “[p]ublished preclinical [PoC] data also support the therapeutic potential of anti-CD122 in multiple autoimmune diseases anti-CD-122 [sic] including in vitiligo.⁸ Contrary to its alleged obviousness ground, Petitioner has relied on and promoted its own copy of the claimed method, developing an anti-CD-122 antibody “FB-102” for vitiligo.⁹ And, inconsistent with all grounds, Petitioner represented to shareholders that the “[m]echanism of FB-102 also shows activity in vitiligo” with potential for the “LARGE UNMET NEED IN VITILIGO,” the market for which it “valued at[]\$1.2 billion in 2018.”¹⁰

⁸ EX2003, 1; EX2004; EX2009; EX1026, 4-5.

⁹ EX2045.

¹⁰ EX2004, 8, 26, 33.

II. SCIENTIFIC BACKGROUND

A. IL-15 and Its Relevance to Human Disease

Interleukin-15 (“IL-15”) is a textbook cytokine known to be involved in the survival and proliferation of CD8⁺ T and natural killer (NK) cells. EX2002, 106; Pet., 11 (“Prior to the earliest claimed filing date of the ’505 patent, POSAs appreciated that IL-2 and IL-15 are involved in the ‘life and death’ of CD8⁺ T cells.” (citing EX1015, 782 n.69, 771; EX1016, Abstract; EX1002, ¶54)); EX2005, ¶¶64-65.

As Patent Owner’s expert, Dr. William Damsky,¹¹ explains, there have been extensive studies examining the molecular and cellular biology of this cytokine and its potential clinical utility as a therapeutic target including in rheumatoid arthritis (“RA”), multiple sclerosis, ulcerative colitis, celiac syndrome, and psoriasis since it was first cloned in 1994. EX2005, ¶64; EX2010, 1, 10-13; EX1022, 1. By 2004, the “emerging understanding of the IL-15/IL-15R system” had provided the “scientific basis for the development of rational approaches for the IL-15-targeted treatment of

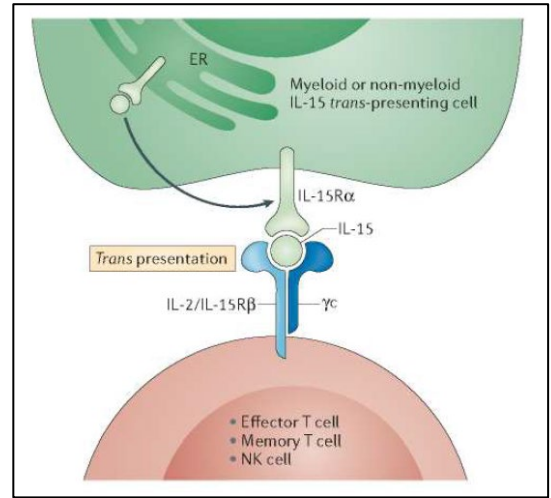
¹¹ Dr. Damsky, author of Petitioner’s cited EX1021, is an Assistant Professor of Dermatology and Pathology at Yale School of Medicine and has authored more than 120 publications including on use of cytokine inhibitors to treat inflammatory skin diseases such as vitiligo. EX2005, ¶¶1-28; EX2006.

autoimmune diseases.” EX1022, 3. Additionally, by 2008, preclinical data “overwhelmingly suggest[ed]” an important role of IL-15 in cancer therapy. EX2011, 4; EX2005, ¶¶64-65.

By April 2017, the efficacy of blocking IL-15 signaling for treating multiple autoimmune conditions was well established. EX1011, 4:25-34 (disclosing several autoimmune diseases for treatment with anti-CD122 antibodies); EX2007, 74:19-75:10; EX2005, ¶65. 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 was in Phase I/II clinical trials. EX1016, 6; *see also* EX1018, Abstract. It had also been demonstrated that blockade of IL-15 signaling reversed autoimmune intestinal damage related to celiac disease. EX2012; EX2009, 6-7. Despite decades of IL-15 research, however, there was no established connection between blocking IL-15/IL-15R and the treatment of vitiligo. EX2005, ¶65.

1. IL-15 Signaling Biology

IL-15 is a heterotrimeric signaling pathway involving a common cytokine receptor γ -chain (CD132), a unique β -chain receptor (CD122, also shared with IL-2), and a third receptor subunit- α (CD215). EX1015, 1; EX1016, 1-2; EX1018, 10 (“The α -chain is crucial for binding of IL-15, whereas the β - and γ - chains are essential for signaling processes.”); EX2005,



EX1015, Figure 1a

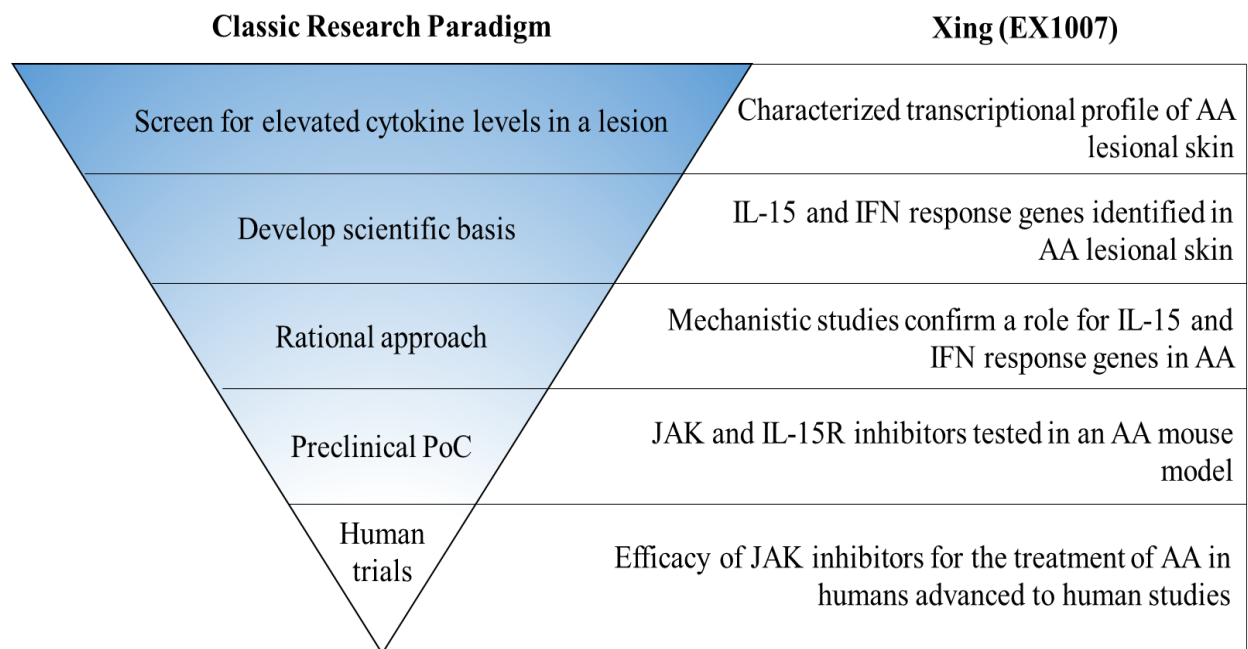
¶¶66-67. Despite sharing some receptor components with other cytokines, signaling through IL-15 was recognized as having distinct functions. *Id.*

For instance, unlike IL-2, IL-15 functions mainly by *trans*-presentation, i.e., IL-15R α presents IL-15 to other cells expressing IL-15R β and γ c. EX1011, 2:46-48; EX1016, 3-4, Fig. 2; EX1015, 1, 2, (Fig. 1); Pet., 11-12 (*trans*-presentation common for IL-15, not IL-2); EX2007, 69:9-70:9. This means that IL-15 signaling depends on IL-15 plus all three receptor subunits, and blockade of any (IL-15, IL-15R α , IL-15R β , γ c) inhibits signaling. EX2005, ¶67; EX2007, 70:10-71:5; EX1011, 22:17-38 (anti-CD122 antibodies suppressed cell growth “mediated by the trans-presentation of IL-15”); EX1002, ¶77 (“[A] CD122 antibody might effectively inhibit IL-15 *trans*-presentation to cells expressing the $\beta\gamma$ complex but without substantially

inhibiting cells (e.g., activated mature T lymphocytes and Treg cells) that highly express the high affinity IL-2 receptor CD25/CD122/CD132.”).

2. Classic Research Paradigm for Autoimmune Disease Treatments

A common research paradigm for evaluating cytokine blockade for treating autoimmune diseases was to first determine whether a particular disease was associated with elevated gene expression levels, such as cytokines (e.g., IL-15). EX2005, ¶¶52-63; EX2007, 65:21-67:20; EX1022, 3; EX1006; EX2071; EX1022; EX1030; EX2012; EX2024; EX2025; EX2031; EX2032; EX2042; EX2072; EX2073, 5; EX2074, 5; EX2075; EX2076. This provided a “scientific basis” for a therapeutic target and for a PoC study based on blocking the relevant pathway in an animal model. EX2007, 65:21-67:20. This classic research paradigm was applied to IL-15 specifically as early as 2004. EX1022, 3. And by April 2017, it had been used extensively for autoimmune diseases, including for AA as taught by *Xing* (EX1007) and as illustrated in the figure below.



However, as noted herein, the mechanism of inhibiting IL-15 signaling to treat vitiligo was not known and could not have been reasonably expected prior to its discovery by the '505 patent inventors. EX2005, ¶112.

3. Inhibitors of IL-15 Signaling

a. Exemplary Inhibitors Disclosed in the '505 Patent

The '505 patent described and specifically incorporated by reference 20 exemplary compounds across nine classes of inhibitors of IL-15/IL-15R:

	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)

	Class of Therapeutic Molecule	Compound(s)	Disclosure
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)

	Class of Therapeutic Molecule	Compound(s)	Disclosure
9	Inhibitory nucleic acids targeting IL-15 or IL-15R	siRNA shRNA LNA molecules PNA molecules	Routine methods ¹²

EX1001, 2:49-52, 7:33-8:37.

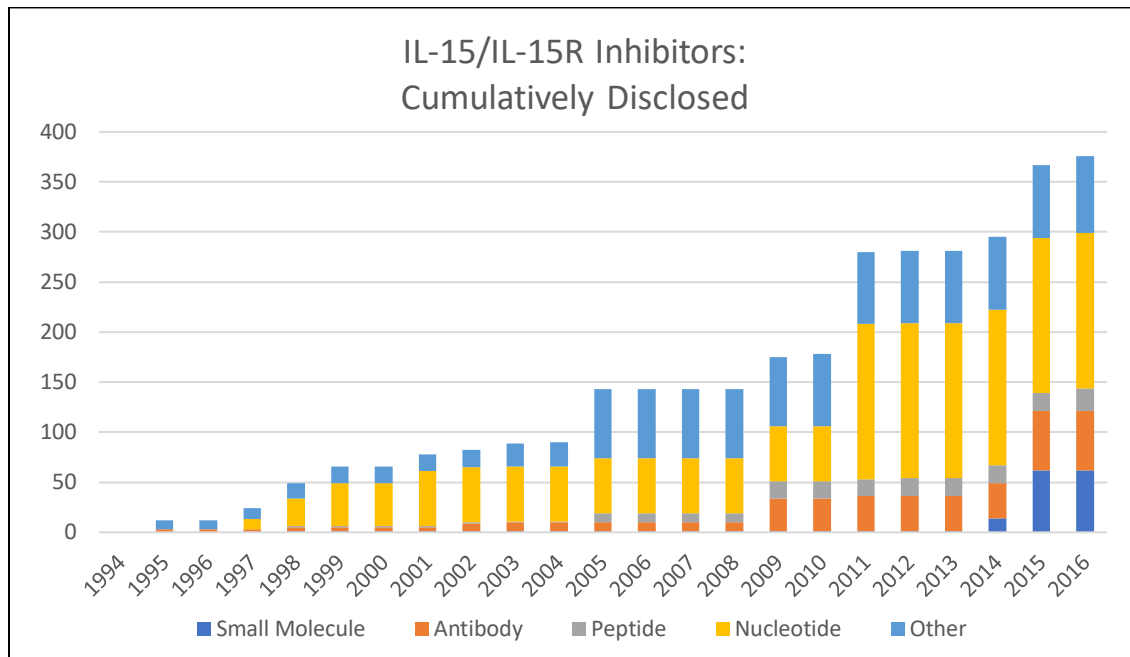
b. Inhibitors Disclosed in the Prior Art

In addition to the exemplary inhibitors in the '505 patent specification, as conservatively illustrated below, *hundreds* of other IL-15/IL15R inhibitors were known in the art as of April 2017. EX2005, ¶¶68-79, 121-122, App'x A; EX1011, 1-4; EX2013, 10:3-9; EX2014, 11; EX2015, 3:29; EX2017, 5655; EX2019, 4:16-17; EX2024, 4:8-31-6:14, 16:24-26:02; EX2025, 6:38-39; EX2027, 22-24; EX2028, 10:31; EX2029, 9-10; EX2030, 40:1-60; EX2031, 2:46; EX2032, 25; EX2049, 3:20-21, 6:16-34; EX2050, 1-3; EX2051, 46:24-44; EX2085, 31:55-32:65; EX2087; EX2088, 41-42; EX2102, 27:28-29, 28:1-12; EX2103, 29-66; EX2104, 24:40; EX2105, 16:46, 18; EX2106, 16; EX2107, 25; EX2108, 15-17; EX2109, 16:28;

¹² Petitioner does not dispute that the '505 patent discloses that “[r]outine methods can be used to design an inhibitory nucleic acid that binds to the target sequence” (EX1001, 9:3-5) and provides examples of various types of inhibitory nucleic acids (EX1001, 13:18-20:13).

EX2110, 46:24; EX2111, 4:45; EX2112, 18-21; EX2113, 1616; EX2114, 5819.

Techniques for rationally designing and making inhibitors were also employed for developing new compounds with improved binding to components of the IL-15 signaling pathway. *E.g.*, EX2015, [0027]; EX2005, ¶¶77; EX2018; EX2079; EX2080



4. Therapeutic Applications Based on Known Mechanism

By 2017, it was recognized that inhibiting IL-15 signaling would have beneficial therapeutic effects based on PoC models for multiple sclerosis, RA, lupus, diabetes, allergies, asthma, and GvHD. EX1011, 4:25-34; EX2005, ¶¶80-83; EX2019; EX2024; EX2025; EX2026; EX2027; EX2028; EX2029. Its “pivotal role” and therapeutic potential “in other inflammatory diseases, like psoriasis,” had been recognized since 2003. EX1018, 2. IL-15 signaling inhibition had even progressed to Phase I clinical trials for leukemia. EX1012.

Inhibitors of a given cytokine signaling pathway, such as IL-15, were understood to share common therapeutic effects resulting from their signaling inhibition mechanism. EX2005, ¶¶52-63, 80-83, 130. Petitioner’s declarant Dr. Abbas similarly admits that “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. For example, WO2015/181394 disclosed a genus and more than 50 species of small molecule IL-15R antagonists taught to be useful for the treatment of autoimmune diseases, relying on “[c]ytokine targeting [being] 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, 1; *see also* EX2026; EX2025, 1-2 (“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.... This strategy... always resulted in the alleviation of the disease symptoms.”). EX2027, 5-6; EX2019, 2:1-6; EX2028, 1:18-29; EX2029, [0009]; EX2005, ¶82.

While not prior art but still reflective of the POSA’s perspective as of April 2017, Petitioner relied on established PoC studies for extrapolating therapeutic

efficacy of its own anti-CD122 antibody to other autoimmune diseases including vitiligo. *Infra* §IV.C.

B. Vitiligo

Vitiligo is an autoimmune disease of the skin in which CD8⁺ T cells “are both necessary and sufficient for melanocyte destruction,” resulting in patchy depigmentation of skin. EX1008, 2; EX2005, ¶¶29-30; EX2052. It affects about 1% of the population worldwide (EX1001, 1:36-38), yet as of 2017, there were no FDA-approved treatments for vitiligo (EX1020, 1). EX2005, ¶¶33-35; EX2054, 2; EX2055, 1; EX2056, 1; EX2057, Abstract; EX2058, 1; EX2059, 1; EX2060, 14. Conventional treatments included topical steroids, calcineurin inhibitors, and narrow-band ultraviolet B light therapy. EX1008, 1; EX2005, ¶51. Despite treatment, vitiligo lesions frequently returned. EX1001, 1:32-36.

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

By 2017, preclinical work by Harris (an inventor of the '505 patent) and others, together with the treatment success seen in the clinic, had focused the vitiligo community on targeting the interferon (IFN)- γ response, including with JAK inhibitors. EX2005, ¶¶31-32; EX1006, 6; *see also* EX1033, 2; EX1032, 2; EX1021, 5; EX2053, 9; *cf.* EX2007, 51:25-52:4. Notably, Petitioner’s Dr. Abbas was unaware of this when rendering his opinion of this case. EX2007, 52:6-10.

2. The *Harris* Vitiligo Mouse Model Recapitulates Human Disease

In *Harris* (EX1006), the '505 patent's inventors describe the *Harris* vitiligo mouse model relied upon in working Example 5 of the '505 patent. Using adoptive transfer of melanocyte specific CD8⁺ T cells into mice (also known as PMEL CD8⁺ T cells), *Harris* explains that "PMEL CD8⁺ T cells gradually accumulated in the ear skin of mice over the course of disease," "epidermal depigmentation appeared 4-5 weeks after transfer" of the inducing virus, and that "[s]imilar to the common forms of human vitiligo, depigmentation in these mice affects the epidermis but spares the hair." EX1006, 2; EX2005, ¶¶84-89.

By 2017, the *Harris* mouse model was relied upon as the primary vitiligo model. EX2036, 3-4; EX2033, 2; EX2007, 52:6-10; EX2005, ¶¶86, 168. Indeed, models like *Harris* were routinely used to support the human therapeutic use of cytokine inhibitors. *E.g.*, EX2005, ¶178; EX1030, 2, 4 (Fig. 1); EX2009, 11 (relying on BALB/c mice); EX2090, 1. Petitioner likewise relies on the *Harris* mouse model—and indeed the '505 patent's own data—to develop its own IL-15R inhibitor to treat vitiligo in human subjects. *Infra* §IV.C; EX2005, ¶86

3. Differences Between Vitiligo and AA

By 2017, it was understood that vitiligo and AA have fundamental biological differences, including, but not limited to, cell types targeted, effect of the immune response, clinical appearance, and treatment. EX2005, ¶¶36-51; EX1008, 1, 3 (Table

1) (listing additional differences between vitiligo and AA); *id.*, 4 (“Immune privilege of the hair follicle is thought to be protective against alopecia areata... and may prove to be responsible for protecting hair from depigmentation in vitiligo.”); EX1019, 5 (“notable differences” exist between the two diseases); *id.* (“[I]t is not clear whether the immune response in alopecia areata is against a specific cell type, and the disease autoantigens are currently unknown.”); EX2065, 1, 3. Indeed, they were described in the art as like “apples and oranges.” EX1008, 1.

In vitiligo, the immune response targets melanocytes, which reside in the upper layer of the skin and are destroyed by PMEL-specific CD8⁺ T cells that recognize a melanocyte-specific differentiation antigen, resulting in permanent depletion in the epidermis. EX2005, ¶¶37-38; EX1008, 2; EX1019, 5; EX2038, 4; EX2061, 2; EX2063, 3; EX2064, 3. In AA, the targeted cells are groups of follicular epithelial cells called keratinocytes that exist in the deepest portion of the hair follicle termed the “bulb.” EX2005, ¶39; EX1019, 5; EX1008, 3 (Fig. 2). A specific subset of CD8⁺ T cells with features of natural killer cells (CD8⁺NKG2D⁺ T cells) infiltrate the epithelial layers of the hair follicle, which overexpress the NKG2D ligand. EX2005, ¶¶42-44; EX1007, 1; EX2012, 1; EX1031, 8 (“The key role of NKG2D⁺ cells (incl. NK and CD8⁺ T cells) is increasingly recognized not only in AA pathobiology, but also in type I diabetes mellitus, multiple sclerosis, rheumatoid arthritis, and Crohn’s disease. (citations omitted)”).

Unlike vitiligo, AA does not result in permanent destruction of these cells. Keratinocytes are preserved, but the disease includes a shift in cycling and collapse resulting in hair loss. EX1019, 5; EX2005, ¶40. These cellular differences—permanent cell depletion in the epidermis (vitiligo) versus altered cycling dynamics with preserved cellular hair growth components (AA)—are significant; EX2005, ¶¶38-44; EX2039, 2-3.

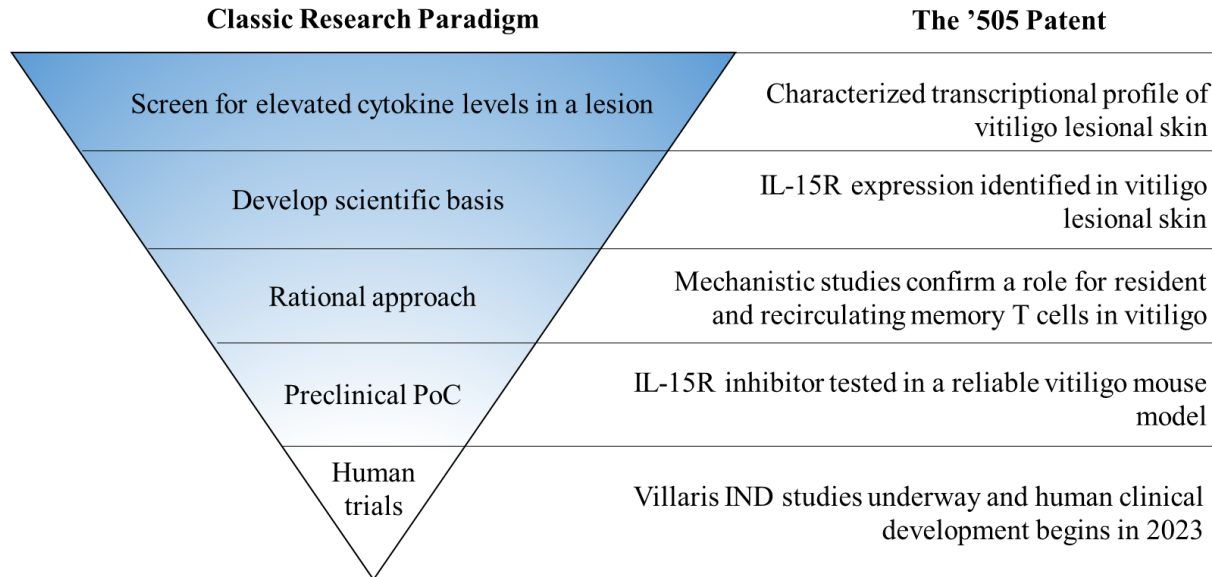
First, cellular differences and location of inflammation within the skin led to different treatment approaches. EX1008, 1; EX2005, ¶¶47-51; EX2001; EX2066; EX2067; EX2068; EX2069; EX2070. Second, this led to the clinical expectation that treatment of one disease was not predictive of treatment for the other disease. For example, *Xing* observed that “CD8⁺NKG2D⁺ T cells promote AA pathogenesis” and postulated that “IFN- γ produced by CD8 T cells leads to the collapse of immune privilege in the hair follicle, inducing further production of IL-15 and a feed-forward loop that promotes type I cellular autoimmunity.” EX1007, 6 (citations omitted). No comparable effect had been recognized for vitiligo. EX2007, 20:10-19; EX2005, ¶¶90-93. While *Xing* demonstrated that treatment with a JAK inhibitor “could reverse established disease” (EX1007, 6), an antibody to IL-15R β was *not* “able to reverse established AA” (EX1007, 4), further undermining the motivation to pursue inhibition of IL-15 for treating vitiligo. EX2005, ¶¶199-201.

These clinical and cellular differences necessitated the development of distinct mouse models for vitiligo (EX1006) and AA (EX1031; EX1034; EX1007), used separately for each condition. *Compare* EX1006, 1 (describing a mouse model using melanocyte-specific CD8⁺ T cells, which recapitulates human vitiligo by inducing epidermal depigmentation while sparing the hair), *with* EX1034, 1, 2 (Fig. 1) and EX1031, 1 (both describing a mouse model with peripheral blood mononuclear cells (PBMCs) enriched for NKG2D⁺ and CD56⁺ that results in “all the characteristic clinical and histological features of human AA”); EX2005, ¶¶86-89.

III. THE '505 PATENT

Following the classical research approach applied in *Xing* and others, the '505 patent's inventors “sought to define autoreactive [tissue resident memory T cells] Trm using vitiligo as a model autoimmune disease....” EX1001, 5:33-36. In the process, they discovered that “targeting IL-15 preferentially affects autoreactive T cells while leaving most endogenous T cell populations intact,” thereby “resulting in a long-lasting, durable response to treatment” for vitiligo.¹³ EX1001, 6:22-29; EX2005, ¶106.

¹³ Clinical development is expected for Auremolimab, an anti-CD122 antibody developed by Villarís and acquired by Incyte, as a treatment of vitiligo. EX2101.



A. The Challenged Claims

The '505 patent has five claims, all directed to methods of treating vitiligo in a subject by administering an effective amount of an inhibitor of IL-15 or the IL-15 receptor. EX2005, ¶¶95. Independent claim 1 of the '505 patent recites:

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

EX1001, 44:13-17; EX2005, ¶¶96. The challenged dependent claims additionally 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); and

- the inhibitor is administered to the lesion (claim 3), the epidermis within the lesion (claim 4), and by subcutaneous or intradermal administration, or a microneedle array (claim 5).

EX1001, 44:18-27; EX2005, ¶97.

B. The Specification

The specification describes that “inventors sought to define autoreactive Trm” using lesional skin biopsies and a mouse model of vitiligo developed by Harris et al., 2012, that “target[s] mouse melanocytes” and “mirrors human disease.” EX1001, 5:33-45. It includes extensive support for targeting IL-15 signaling “as a strategy to clear autoreactive memory cells from the tissue, resulting in a long-lasting, durable response to treatment.” EX1001, 6:16-24; EX2005, ¶¶98-106.

The specification also describes that “IL-15 is much more potent at generating CD8⁺ Trm pools than residual IL-2 signaling in skin tissue” and “IL-15 is required for the generation of CD8⁺ Trm in viral models in mice,” supporting “that IL-15 signaling is required for maintenance of these [Trm] cells.” EX1001, 6:3:21.

It further describes multiple inhibitors of IL-15 and the IL-15 receptor, including nine classes of inhibitors and 20 specific compounds, that were known in the art and exemplary for use in the claimed methods. EX1001, 7:34-8:37. The specification also describes techniques commonly used in the art, e.g., designing inhibitory nucleic acids that bind to the desired target sequence (EX1001, 9:3-5) and

determining standard pharmaceutical procedures (EX1001, 23:29-34). EX2005, ¶¶98-100.

The specification includes and expressly incorporates 300+ references describing biological mechanisms (*e.g.*, EX2037 (EX1001, 1:30), EX2038 (EX1001, 1:34), EX2039 (EX1001, 6:7-9, 33:13), EX2040 (EX1001, 5:21-24, 28:23-27)); known inhibitors of IL-15/IL-15R (*e.g.*, EX2013 (EX1001, 7:36-40), EX2015 (EX1001, 7:40-44), EX2017 (EX1001, 7:44-47), EX2018 (EX1001, 7:47-51), EX2022 (EX1001, 7:58-64), EX1030 (EX1001, 7:64-67), EX2021 (EX1001, 7:67-8:3)); and methods of administration (*e.g.*, EX2043 (EX1001, 21:47-51), EX2044 (EX1001, 22:37-38), among other disclosures. EX1001, 2:49-52.

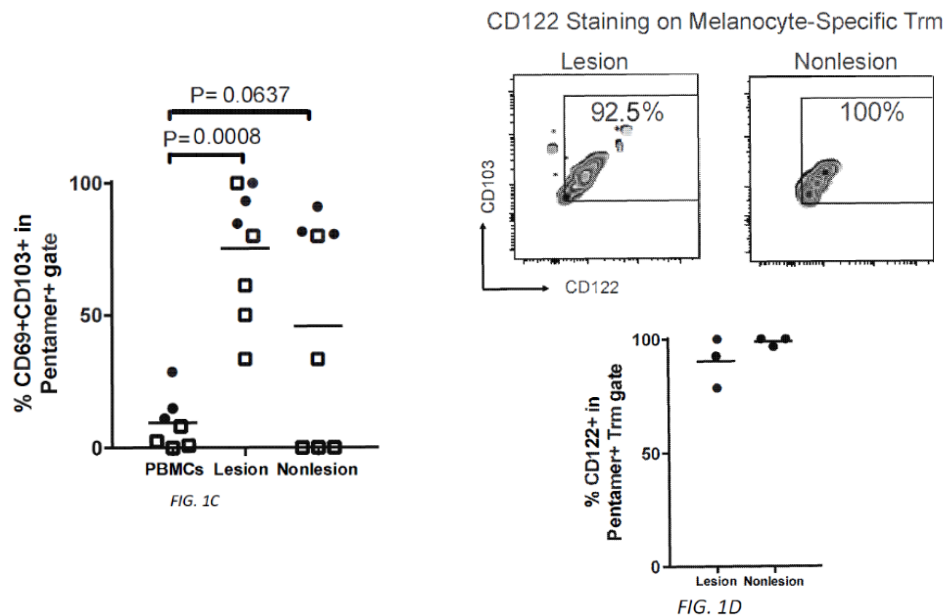
C. The Examples

Supported by six examples, extensive data, and 52 figures,¹⁴ the inventors surprisingly discovered that targeting the IL-15 pathway results in *effective and durable* treatment for vitiligo. EX1001, 30:53-37:17; EX2005, ¶¶101-106.

A POSA would understand Example 1 to establish that human vitiligo patients express an antigen-specific Trm phenotype and express IL-15R. EX1001, 30:53-31:12, Figs. 1A-1E. The reported experiment entailed taking biopsies from vitiligo

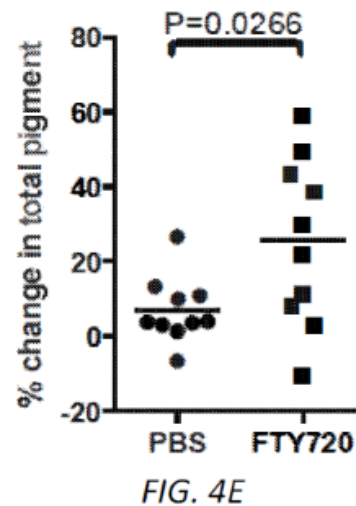
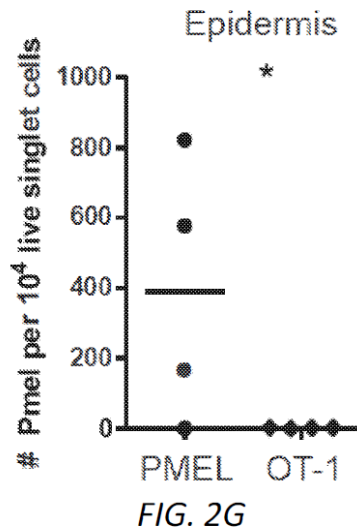
¹⁴ Total based on each individual figure from Figures 1A-1F, 2A-2G, 3A-D, 4A-4G, 5, 6A-6I, 7A-7C, 8A-8E, 9A-9F, 10A-10C, 11A-11C, and 12A-12B.

patients having both active and stable diseases, and identifying antigen-specific T cells in their blood and skin fluid. *Id.* The inventors reported an enrichment of antigen-specific Trm cells in lesional fluid that express IL-15R β /CD122 in patients with active (“lesional”) and stable (“nonlesional”) vitiligo as compared with peripheral blood mononuclear cells (PBMCs). EX1001, Figs. 1C, 1D (reproduced below showing the quantification of the frequency of melanocyte-specific cells with a Trm phenotype and flow cytometry staining of CD122 on melanocyte-specific Trm); EX2005, ¶101.



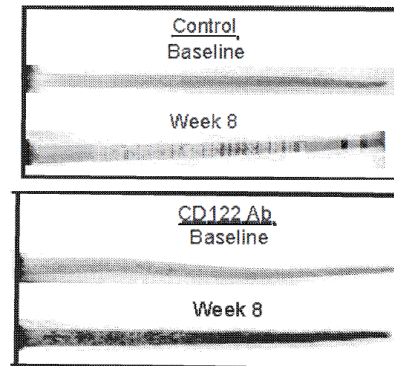
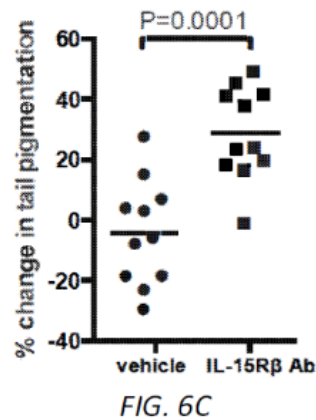
A POSA would understand Examples 2, 3, and 4 to establish the functional role of Trm in vitiligo using an established *in vivo* mouse model of vitiligo previously described by *Harris* (EX1006). EX1001, 5:40-47, 28:55-57, 31:14-32:67; EX1006. In particular, a POSA would understand Example 2 to demonstrate that

only melanocyte-specific T cells establish Trm in the epidermis where autoantigen is expressed compared to control cells. EX1001, 3:22-31, 31:14-43, Figs. 2A-2G (Figure 2G below showing that only T cells, called PMEL, establish long-lived epidermal cells compared to the foreign OVA antigen OT-1). A POSA would understand Example 3 to report 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. A POSA would understand Example 4 to further demonstrate that inhibiting the circulation 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 to sustained melanocyte killing during the maintenance of vitiligo....” EX1001, 3:46-56, 32:37-67, Figs. 4A-4G (Figure 4E below showing an increase in pigmentation with FTY720 compared to the PBS vehicle control). EX2005, ¶¶102-103.

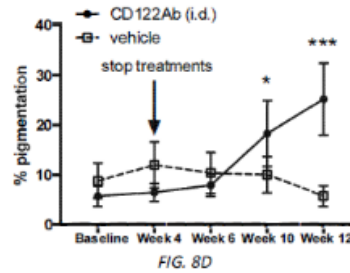
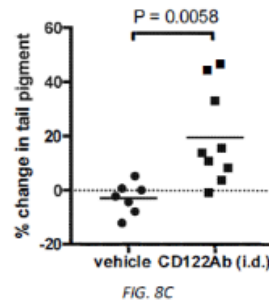
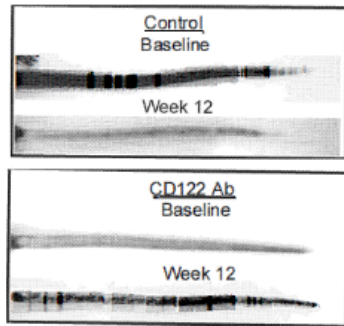
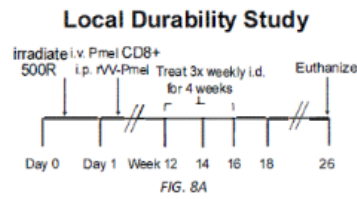


A POSA would understand Example 5 to describe and demonstrate *in vivo* efficacy in the *Harris* (EX1006) mouse model of vitiligo. EX1001, 33:1-34:45. It reports that blocking IL-15 signaling with the anti-mouse IL-15R β /CD122 antibody (ChMBC7) significantly repigments mice after 8 weeks of treatment compared to controls and further provides a durable vitiligo treatment effect. EX1001, 33:1-34:45, Figs. 5, 6A-6I (Figures 6C and 6G below showing sample photos and a statistically significant increase in pigmentation of IL-15R β Ab treated animals compared to control). As the '505 patent explains, “[e]xisting treatments for vitiligo are not durable, as the disease returns at the site of treatment after discontinuation.” EX1001, 33:5-6. When administering the CD122 antibody for 4 weeks and then stopping treatment, the inventors found that repigmentation was maintained even after treatment was stopped for 10 weeks. EX1001, 33:36-34:45, Figs. 7A-7C, 8A-8E

(Figures 8A, 8B,¹⁵ 8C, and 8D showing sample photos and the statistically significant increases in total and tail pigmentation in IL-15R β Ab treated animals compared to control); EX2005, ¶104.



¹⁵ In Figure 8B, the tail image for the control mouse at baseline appears darker apparently due to an imaging error of producing the figures in black and white. See EX1001, Figs. 8C, 8D (quantifying pigmentation of control (“vehicle”) and CD122 treated subjects).



Finally, a POSA would understand Example 6 to describe 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); EX2005, ¶105.

D. Level of Skill in the Art

Patent Owner does not contest Petitioner's proposed definition of a person of ordinary skill in the art (POSA) (Pet., 18), except the need for one modification: 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. EX2005, ¶94; *see* §II.A.3.

IV. THE PETITION, PETITIONER'S DECLARANTS, AND PETITIONER'S RELIANCE ON POC STUDIES

A. The Petition

Several fundamental problems undercut Petitioner's arguments and grounds.

First, Petitioner advances inconsistent positions between its §112 and §103 grounds, none accurately reflecting the state of the art at the relevant time. Its §112 grounds, for example, are premised on characterizing the art as "nascent." *E.g.*, Pet., 53. This ignores *decades of research* related to therapeutic applications of cytokine inhibition. *Supra* §II.A. Petitioner also contradicts itself by its characterization of the art for obviousness, including that the art taught inhibiting IL-15 or IL-15R to reduce T-cell activity for the treatment of autoimmune diseases (Pet., 1), and reliance on the "rational underpinnings and reasonable expectation of success" of using cytokine signaling inhibitors for autoimmune disease (Pet., 69).

Second, Petitioner's inconsistent grounds are all fatally undermined by two key facts. By 2017, the therapeutic applications of cytokine inhibition, including IL-15, were scientifically advanced, were in clinical use, and were the subject of textbook science. Once cytokine inhibition had been shown as therapeutically effective for a given disease with a single inhibitor, POSAs understood to use other inhibitors of the same pathway for the same therapeutic effect. *Supra* §II.A.4.

Further, notwithstanding a long-felt need for vitiligo treatments, no experiments demonstrated targeting IL-15 signaling as a treatment of vitiligo. Instead, vitiligo treatment was focused on IFN- γ inhibition. EX2007, 52:6-10; EX2005, ¶¶31-32; *Supra* §II.B. Based on these facts, the '505 patent specification provides a sufficient written description and enabling disclosure of a novel and nonobvious invention. *Infra* §§VII, VIII, IX.

Third, Petitioner's §112 grounds commonly mischaracterize the nature of the invention as being directed to IL-15 signaling *inhibitors* and IL-15 *pathways* themselves as opposed to their use in the claimed methods, in order to force inapt caselaw analogies. *E.g.*, Pet., 24-25. The '505 patent does not claim novelty in either, and in fact teaches, including via references incorporated therein, that both IL-15 signaling inhibitors and their various pathways were well-known in the art. Instead, like *UroPep*, "the invention was to use a group of compounds well known in the art... in a novel method of treating" vitiligo. 276 F. Supp. 3d at 648. That novel method is the proper focus for both written description and enablement. *Id.*; *see also United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1369-70 (Fed. Cir. 2023).

Fourth, Petitioner concedes that the '505 patent's specification provides a working example of the claimed subject matter, a key point for both written description and enablement (Pet., 2-3). Petitioner's contention that this working

example is nevertheless insufficient for written description and enablement is belied by the practice in the art and in its own development of therapeutic agents targeting cytokine pathways, all reflecting the understanding and expectation that therapeutic effects due to mechanisms of action elucidated with one cytokine pathway inhibitor would be expected with other inhibitors of the same pathway (Pet., 2-4). That human clinical testing will ultimately be required for each individual inhibitor to confirm safety and efficacy is certainly relevant for FDA approval but not for compliance with §112. *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995); *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994); *In re Anthony*, 414 F.2d 1383, 1395 (CCPA 1969); MPEP §2107.03.

Finally, as discussed further below, Petitioner relies on declarants who did not consider the entirety of the specification, including the 300+ references expressly incorporated therein; lacked knowledge of and failed to consider the state of the art; and made admissions contrary to their declaration testimony. *Infra* §§IV.B.1, IV.B.2. Worse still, Petitioner relies on its declarants for opinions they never offered. *Compare* Pet., 65 (“Harris describes a simplified mouse model for vitiligo lesions, in which the depigmentation lesions are induced by introducing CD8⁺ cytotoxic T cells and are straightforwardly reversed by depleting *those same* CD8⁺ cytotoxic T cells. EX1002, ¶¶95-97.”), *with* EX2007, 44:20-22 (Dr. Abbas admitting that ¶¶95-

97 of his declaration are not trying to convey that *Harris* and *Xing* have the same CD8⁺ T cells).

B. Petitioner's Declarants

Petitioner's declarants fail to provide competent testimony on patentability as they assert conclusory opinions without considering the entirety of the specification (with its incorporated references) or the underlying state of the art as a whole. *See, e.g., Gilead Scis., Inc. v. Regents of Univ. of Minn.*, IPR2017-01753, Paper 46 at 6 (PTAB Dec. 21, 2020) (“*Gilead*”); *CSL Behring LLC v. Bioverativ Therapeutics Inc.*, IPR2018-01313, Paper 10 at 16 (PTAB Jan. 9, 2019) (“*CSL*”); *Sanofi-Aventis U.S. LLC v. Immunex Corp.*, IPR2017-01129, Paper 19 at 14 (PTAB Oct. 4, 2017) (“*Sanofi-Aventis*”); *Alcon Rsch. Ltd. v. Barr Lab 'ys, Inc.*, 745 F.3d 1180, 1189 (Fed. Cir. 2014) (“*Alcon*”). Significant portions of their testimony are near-verbatim recitations of the Petition or simply lack evidentiary support. *See Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (PTAB Aug. 24, 2022) (precedential) (declarant's conclusory, copy-and-paste assertions are “entitled to little weight”); *see, e.g.*, EX1002, ¶79 (Pet., 37), EX1002, ¶¶38 (Pet., 15-16), 68 (Pet., 28), 69 (Pet., 29), 73 (Pet., 30-31), 74 (Pet., 32-33), 75 (Pet., 33), 76 (Pet., 34), 77 (Pet., 34-35), 85 (Pet., 40); EX1004, ¶¶39 (Pet., 9), 41 (Pet., 10-11).

1. Dr. Abbas

Dr. Abbas confirmed that he did not rely on or consider other information beyond that cited in EX1002. EX2007, 6:2-17. Dr. Abbas thus failed to consider the vast majority of the more than 300 references incorporated in the '505 patent specification as part of its written description and enabling support. *Supra* §III.B (identifying certain incorporated references not considered by Petitioner's declarants).

Dr. Abbas also was not aware of, did not investigate, and did not consider the number and type of IL-15 signaling antagonists as of April 2017. EX2007, 71:11-24, 81:21-82:12. For example, he had no knowledge of and did not investigate small interfering RNA or peptides to antagonize cytokine signaling. EX2007, 83:14-84:12, 85:4-13. Yet he offered opinions on all this subject matter. *E.g.*, EX1002, ¶68.

Similarly, Dr. Abbas testifies extensively about what a POSA would understand from the '505 patent's mouse model data regarding treatment of vitiligo in humans. However, he admitted to not being aware of any common features between the mouse model and human disease beyond (1) loss of pigmentation and (2) involvement of CD8⁺ T cells. EX2007, 38:10-38:23, 43:16-19; *supra* §II.B.2.

Admissions from Dr. Abbas undercut the reliability and credibility of his testimony. For example, his declaration states that “[t]he only way for a POSA to know if another CD122 antibody, a CD132 antibody, an IL-15 antibody, or an IL-

15 α antibody would treat vitiligo would be trial and error.” EX1002, ¶64. By contrast, he admitted on cross-examination that “[i]t’s reasonable” as of April 2017 (and today) to expect that species that would antagonize IL-15 signaling would be useful in treating autoimmune diseases identified as having an IL-15 mechanism. EX2007, 74:19-75:10.

2. Dr. Plott

Dr. Plott confirmed that he did not rely on or consider other information beyond that cited in his declaration. EX2008, 5:18-22. Dr. Plott thus also failed to consider the majority of the more than 300 references incorporated in the ’505 patent specification as part of its written description and enabling support. *Supra* §III.B. His declaration, including at least fifteen wholly unsupported paragraphs, is conclusory, and should be entitled to little or no weight. *See* EX1004, ¶¶35, 36, 42, 44, 48-53, 56-61.

Moreover, his “perspective as a medical practitioner” (*e.g.*, EX1004, ¶32) undermines his opinions on the patentability of the ’505 patent’s claims, as FDA approval and safety for administration to a human are not claimed requirements. EX2008, 24:22-29:6 (“As a physician, you would err on the side of safety.”); *see also United Therapeutics*, 74 F.4th at 1369 (“Questions of safety and efficacy in patent law have long fallen under the purview of the FDA.”).

C. Petitioner's Reliance on PoC Studies for Therapeutic Activity

Petitioner is developing its own CD122 antibody designated “FB-102” for treating GvHD, vitiligo, and AA. EX2045; EX2003, 1; EX2004, 26, 33; EX2005, ¶¶107-110. Petitioner has touted the “significant current value” of FB-102, asserting that “FB-102 is more advanced than Villarís”¹⁶ who was developing an IL-15R inhibitor for vitiligo and was acquired for up to \$1.4 billion. EX2004, 1, 27. In this regard, Petitioner represented that there was a “LARGE UNMET NEED IN VITILIGO” with a global treatment market size “valued at[]\$1.2 billion in 2018 and... projected to reach \$1.9 billion by 2026, exhibiting a CAGR of 5.8% (Fortune Business Insights).” EX2004, 33. Because Petitioner’s FB-102 inhibits “CD-122, a subunit of the... IL-15 receptor,” and “shows activity in vitiligo,” use of FB-102 to treat vitiligo in a selected subject is an embodiment of the ’505 patent. EX2003, 1.

While Petitioner reports testing FB-102 in a GvHD animal model, it infers activity of FB-102 in “multiple autoimmune diseases,” including vitiligo and others, based on “[p]ublished preclinical PoC data” using *other* anti-CD122 antibodies. EX2003, 1 (“Published preclinical PoC data also support the therapeutic potential of anti-CD122 in multiple autoimmune diseases anti-CD-122....”).

¹⁶ Villarís Therapeutics, Inc. is a real party-in-interest with Patent Owner.

According to Petitioner's response to additional discovery, the preclinical PoC data relied upon to support the therapeutic potential of FB-102 in vitiligo was Richmond 2018 (EX2046), which taught that the "CD122 antibody ChMBC7 depleted CD8+ PMEL in the dermis of the Harris transgenic mice and... reversed the vitiligo lesions induced by the transplanted CD8+ PMELs." EX2009, 8-10 (citing, EX2046); Paper 17, 2. Petitioner's response to additional discovery further shows its reliance on other PoC studies for touting the untested "therapeutic potential" of FB-102 in celiac disease and AA (EX1007), among others. EX2009, 8-10; EX2009, 6-10 (citing EX2012 for celiac disease and EX1007 for AA).

Notably, Richmond 2018 (EX2046) relied upon by Petitioner for the therapeutic potential of FB-102 in vitiligo is a republication of the '505 patent's *same mouse model data*. EX2005, ¶¶108-110. That is, Petitioner relied on the same preclinical data that it contends did not describe or enable anything beyond the use of the specific ChMBC7 antibody in the specific *Harris* mouse model.¹⁷ See, e.g.,

¹⁷ Petitioner's inconsistent positions are also undoubtedly reflected in its multiple unpublished patent applications identified in its SEC filings (EX2096, 16 ("We also own five pending US patent applications related to the FB-102 program")) and developmental documents related to FB-102 (EX2045). Petitioner would be

Pet., 25-34, 57-58; *see Allergan, Inc. v. Sandoz, Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015) (“[T]he enablement inquiry turns on whether the skilled artisan, *after reading the specification*, would be able to make and use the claimed invention without undue experimentation.”).

V. INSTITUTION DECISION

The Institution Decision (Paper 10, “ID”) found that Petitioner had shown that at least one claim was more likely than not unpatentable for lack of written description (ID, 14) and lack of enablement (ID, 20) but not for obviousness (ID, 27).

For written description, the ID analogized the present case to *University of Rochester v G.D. Searle & Co.*, 358 F.3d 916, 925-27 (Fed. Cir. 2004) (“*Rochester*”). ID, 18. However, unlike the ’505 patent, in *Rochester*, “it [was] undisputed that the [challenged] *patent does not disclose any compounds* that can be used in its claimed method... *[N]or has any evidence been shown that such a compound was known....*” 358 F.3d at 927-28 (distinguishing *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989, 997 (Fed. Cir. 2000) (holding that a “descri[ption of] the exact

obligated to produce relevant information inconsistent with its petition as a matter of routine discovery under Rule 42.51(b)(1)(iii) but has not. *See* EX2097.

chemical component of each combination that falls within the range claims of the... patent” is not necessary to comply with §112)).

The ID further found that there was not “evidence presented in the current record that such information [regarding why the FC-diminished antibody exemplified in the ’505 patent was representative] was generally known in [the] art.” ID, 19. The ID distinguished *Merck Sharp & Dohme Corp. v. Genentech, Inc.*, PGR2021-00036, Paper 10 at 20 (PTAB July 24, 2021), and *Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, No. 2:15-CV-1202-WCB, 2016 WL 6138124, at *15 (E.D. Tex. Oct. 21, 2016) (“*Erfindergemeinschaft*”), because “evidence that there were well-known classes of compounds known to perform the function recited in the claim methods... [is] not presented on the current record.” ID, 20. Patent Owner has now more fully addressed 20 different inhibitors expressly incorporated in the ’505 patent (*supra* §III.B), and the hundreds of additional inhibitors known in the art (*supra* §II.A.3), and why—consistent with the art and Petitioner’s own practice—the inhibitor used in the ’505 patent to elucidate the pathology of vitiligo is representative of other inhibitors blocking the same signaling for the treatment of vitiligo (*supra* §§II.A.4, IV.C).

As for enablement, the ID analogized to *Amgen*. ID, 24-27. The ID found, *inter alia*, that the

specification's listing of nine classes and 20 individual compounds that could be used as an inhibitor of IL-15 or the IL-15 receptor (with references where information about each inhibitor may be located) is unsatisfactory because ***these references do not appear to be incorporated by reference***, nor does these references fully explain how to make each inhibitor of IL-15 or the IL-15 receptor. *See* Ex. 1001, 7:34-8:4.

ID, 26. This was a misunderstanding as the '505 patent expressly incorporated by reference all cited publications cited therein, each of which explain how to make its respective inhibitor. *See* EX1001, 2:49-52 ("All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety."); EX1011, 20:54-21:52; EX2016, 1-2; EX2017, 1-2; EX1018, 1-2; *supra* §III.B. "In any event, formal incorporation by reference is not necessary if the material being incorporated is background art." *Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006, at *12 (Fed. Cir. Nov. 15, 2022) (citation omitted).

In finding no threshold showing of obviousness, the Board found Petitioner's challenge 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." ID, 33. Noting *Xing's* "feed-forward loop" related to hair follicle autoimmunity, the Board found Petitioner's rationale deficient because it did "not account for the increased IL-15 production or the cellular autoimmunity" and how

that would affect a POSA's decision to use an anti-CD122 antibody to reduce autoreactive CD8+ Trm cells in the skin for the treatment of vitiligo. *Id.* The Board also found insufficient evidence regarding Patent Owner's objective indicia of nonobviousness and invited the parties to develop the record. ID, 31.

VI. CLAIM CONSTRUCTION

Patent Owner agrees with Petitioner that solely for the purpose of this PGR, "the claims should be understood according to their plain meaning" and no express construction is necessary. Pet., 23.

In response to the Board's invitation to address whether "the claims encompass transient and/or sustained treatment given that the claims themselves do not recite durability of treatment" (ID, 31-32), Patent Owner submits that a durable treatment response is an unexpected result not addressed in the Petition but which is not required by the claims. *See Purdue Pharma L.P. v. Endo Pharms. Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006) (unexpected results achieved by a claimed invention are not claim limitations); *see also United Therapeutics*, 74 F.4th at 1369 (declining "to insert the FDA's responsibilities into claims by importing requirements where they do not recite such limitations").

VII. PETITIONER FAILS TO ESTABLISH THAT CLAIMS 1-5 LACK WRITTEN DESCRIPTION SUPPORT

The level of detail required for written description depends on "the existing knowledge in the particular field, the extent and content of the prior art, the maturity

of the science or technology, [and] the predictability of the aspect at issue.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (alteration in original) (citation omitted). Here, the claims are narrowly drawn to the use of an IL-15 or IL-15R inhibitor to treat vitiligo, not the discovery or claiming of new inhibitors themselves. Given that exemplary inhibitors are disclosed in the ’505 patent’s specification and were further well-known in the art, the question does not turn on “possession of the entire genus” of IL-15 or IL-15R inhibitors. “[T]he proper inquiry... is whether the disclosure in the specification shows that the inventors possessed the invention that administering an effective amount of a[n]... inhibitor would treat [the claimed disease]. Thus, given that at least some... inhibitors were known and were disclosed..., the written description issue does not turn on whether the patentees were in possession of the entire genus of... inhibitors.” *Erfindergemeinschaft*, 2016 WL 6138124, at *15. Petitioner focuses on the wrong inquiry and fails to show any written description deficiency for the claimed method of treating vitiligo. *See* EX2005, ¶¶111-140.

A. Written Description Standard

Written description requires that the specification “reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter.” *Ariad*, 598 F.3d at 1351. But, as the Federal Circuit recently clarified, this does not

require a written description of all unclaimed subspecies within a broader a disease or condition:

It would be incorrect to fractionate a disease or condition that a method of treatment claim is directed to, and to require a separate disclosure in the specification for each individual variant of the condition... in order to satisfy the enablement and written description provisions of 35 U.S.C. § 112, unless these variants are specified in the claims.

United Therapeutics, 74 F.4th at 1370-71.

Petitioner broadly argues that, “[l]ike prior cases..., the ’505 patent’s scant details are simply insufficient to justify the great breadth of the many, disparate methods encompassed by the claims.” Pet., 46. But Petitioner ignores that its cited cases all involve classes of novel or largely unknown compounds, *making the novel compounds themselves the invention*. See, e.g., *Ariad*, 598 F.3d at 1355 (addressing written description of an *undeveloped class of compounds* where the specification provided no working examples and failed to “sufficiently disclos[e] molecules capable of” practicing the claimed method); see also Pet., 39; *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1336, 1339 n.3 (Fed. Cir. 2021) (finding inadequate written description for claims to a new class of antibodies with “*any* scFv for binding *any* target” where “very few [claimed embodiments] were known” and specification provided no way “to distinguish scFvs that bind to selected targets from

those that do not” (emphases in original)), *cert. denied*, 143 S. Ct. 402 (2022); *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019) (invalidating claims to a broad genus of largely undeveloped nucleosides where specification “provide[d] no method of distinguishing effective from ineffective compounds” “no[r] explain[ed] what ma[de] [examples] effective, or why”), *cert. denied*, 141 S. Ct. 1234 (2021); *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301-02 (Fed. Cir. 2014) (inadequate written description for claims to undeveloped genus of “fully human IL-12 antibody” with a particular binding activity where “[patentee] used a trial and error approach” to identify disclosed embodiments without providing guidance as to which antibodies would and wouldn’t work).

Rochester, discussed in the Institution Decision (ID, 18), is similarly distinct. The *Rochester* claims were directed to methods “for selectively inhibiting” PGHS-2 activity in a human host, it was “undisputed” that the specification failed to “disclose **any** compounds that can be used in its claimed methods,” and there was even **no evidence “that such a compound was known.”** *Rochester*, 918, 926-27. Written description in *Rochester* this required disclosure of inhibitor compounds because “[t]he claimed method **depends upon finding a compound that selectively inhibits PGHS-2 activity.** Without such a compound, it is impossible to practice the claimed method of treatment.” *Id.* at 926 (cleaned up).

In stark contrast to *Rochester* and other cases Petitioner cites, claim 1 of the '505 patent is directed to treating vitiligo using a well-known class of compounds (IL-15/IL-15R inhibitors) in a novel method of treating vitiligo and *do not* “depend[] upon finding a compound that” inhibits IL-15 or IL-15R. *Id.* And unlike *Rochester*, claim 2 narrows scope to particular classes of inhibitors exemplified in the specification—much more than a “vague functional description.” *Id.* at 928. Moreover, the specification discloses 20 exemplary compounds that can be used to treat vitiligo with *hundreds more* known in the art. EX1001, 2:49-53, 7:33-8:37; EX2005, ¶¶114-125; EX2082, 1; EX2083, 1. There is also no evidence of any “ineffective compounds.” *Idenix*, 941 F.3d at 1164.

Thus, the '505 patent has done more than merely provide a functional description of only a single species. Written description here does not require discovering new inhibitors¹⁸ and “[p]recedent [requires] the patentee need only describe the invention as claimed.” *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1333 (Fed. Cir. 2003).

¹⁸ The specification, however, does provide specific and undisputed guidance on developing new inhibitors. *See, e.g.*, EX1001, 9:3-21.

B. Petitioner Fails to Establish that the Challenged Claim Lacks Written Description

Analogous to *United Therapeutics*, the question here is whether the specification shows possession of the claimed method of treating vitiligo as opposed to subspecies not recited in the claims. EX1001, claim 1. Petitioner, however, challenges written description from the wrong perspective. Petitioner argues about whether the specification describes unclaimed subject matter relating to (i) direct and indirect inhibitors; (ii) CD122 (β -chain) inhibition including both Fc-intact and Fc-diminished antibodies; or (iii) CD132 (γ -chain) inhibition, even though this subject matter is indeed described. *See United Therapeutics*, 74 F.4th at 1370-71; *cf.* Pet., 28-36. Petitioner’s underlying premise—“the science or technology at issue, inhibiting IL-15 signaling to treat autoimmune [disorders]... was nascent, not mature”¹⁹ (Pet., 41)—is also fundamentally flawed and infects all its arguments. EX2005, ¶¶147-159.

1. “Genus of Inhibition Pathways Claimed”

Decades of research taught inhibiting cytokine signaling pathways to treat autoimmune diseases, and hundreds of IL-15 signaling pathway inhibitors were

¹⁹ Petitioner’s admission that “inhibiting IL-15 signaling to treat... *vitiligo*[] was nascent” (Pet., 41) is accurate though understated, and cuts against its obviousness ground.

known and well-characterized. EX2005, ¶¶68-79, 121-122, App'x A; *supra* §II.A; *Cf.* Pet., 27-29. Building on this knowledge, the specification explains how the claimed treatment worked by depleting and inhibiting autoreactive Trm. EX1001, 1:59-66; EX2005, ¶¶98-106. It further describes in extensive detail a range of inhibitors, pathways, and techniques for the treatment of vitiligo by inhibiting IL-15 signaling. EX2005, ¶¶98-100; *e.g.*, EX1001, 1:66-2:17, 7:34-20:13. This disclosure includes no less than 300 references, all of which are expressly incorporated (EX1001, 2:49-52), and nearly all are ignored by Petitioner. EX2005, ¶71.

Contrary to Petitioner's argument (Pet., 27), the treatment of vitiligo demonstrated with the ChMBC7 antibody in the '505 patent would have been understood to be representative with respect to the claimed method. EX2005, ¶¶126-134; EX2084. In this regard, it was recognized that unlike other cytokines, IL-15 functions mainly through a *trans*-presentation such that antagonizing any one of IL-15, IL-15R α , IL-15R β , or γ c inhibits IL-15 signaling. *Supra* §II.A.1. This is reflected in the specification, including Example 1, which describes that "[k]eratinocytes express the CD215 chain of the IL-15 receptor [IL-15R α] to present IL-15 in trans to T cells, and keratinocytes in lesional skin express higher CD215 than in non-lesional skin (FIG. 1E)." EX1001, 31:6-9. Given the established *trans*-presentation of IL-15, a POSA would have recognized that the '505 patent's treatment of vitiligo with a CD122 inhibitor was representative with respect to treating vitiligo by

blocking IL-15 signaling, as all other “inhibition pathways” would likewise block IL-15 signaling. EX2005, ¶¶127-130.

Petitioner’s argument that “the specification fails to explain whether inhibiting [*cis*- or *trans*-presentation] is necessary or sufficient to achieve the intended result” (Pet., 26) ignores that *trans*-presentation was known to be the predominate IL-15 physiological pathway. *Supra* §II.A.1; EX2005, ¶¶66-67. Nor does Petitioner provide evidence that IL-15 *cis*-presentation has any physiological significance for vitiligo pathogenesis. Regardless, although the written description requirement does not “require a separate disclosure in the specification for each individual variant of the condition,” a POSA would have understood that IL-15 *cis*-presentation is also inhibited by the exemplary CD122 inhibitor. *United Therapeutics*, 74 F.4th at 1370-71; EX2005, ¶128.

2. “Genus of Chemicals Claimed”

Petitioner’s “chemicals” argument (Pet., 36-39) is inapt as no chemicals are claimed in the ’505 patent. While the ’505 patent provides exemplary “chemicals” across a range of classes (*supra* §II.A.3.), this is not required because the “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.” *UroPep*, 648; *supra* §II.A; EX2005, ¶¶118-125.

Petitioner's declarants' contrary opinions are entitled to no weight, as they failed to consider relevant subject matter incorporated in the specification or the state of the art for IL-15 signaling pathway inhibitors. *Supra* §§III.B, IV.B. Especially in view of this failure, Petitioner failed to show that the disclosure in the specification—including at least 20 species of exemplary inhibitors from nine different classes (*supra* §III.B), is insufficient written description of the “genus of chemicals claimed” or otherwise in view of the advanced state of the art. *See UroPep*, 646 (“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.”).

Contrary to Petitioner's assertions (Pet., 36-39) but like *Ajinomoto*, a POSA would have considered the '505 patent's demonstrated efficacy treating vitiligo with ChMBC7 as representative with respect to the effect of treating vitiligo with IL-15 and IL-15R inhibitors generally. *See Ajinomoto Co. v. ITC*, 932 F.3d 1342, 1359 (Fed. Cir. 2019) (finding sufficient written description based on disclosure of a representative number of “well-known” promoters in view of the background in the art); EX2005, ¶¶118-125. The genus of IL-15 signaling inhibitors, including CD122 inhibition by antibodies such as ChMBC7 (both Fc-diminished and Fc-intact), was

well-explored in the art and exemplified in the specification.²⁰ *Infra* §II.B.3; EX1001, 7:33-8:5; EX2005, ¶120. The specification teaches and the prior art further shows that therapeutic efficacy demonstrated with one IL-15 signaling inhibitor would be shared with another IL-15 signaling inhibitor. *Infra* §II.A.3-II.A.4; EX1001, 6:22-24 (“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.”), 34-35 (“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.”), 30:53-31:12; *supra* §II.A.4. The ’505 patent’s specification still further describes the pathophysiology underlying the invention. EX1001, 30:53-31:12. Petitioner’s copying of the claimed invention based on patent’s same ChMBC7 data likewise reflects that understanding that therapeutic efficacy demonstrated with one IL-15 signaling inhibitor would be understood to be common to others for vitiligo specifically. *Supra* §IV.C.

²⁰ In addition to the inhibitor categories recited in claim 2 (small molecule, antibody, peptide, and nucleic acid inhibitors), the other types were known as well. App’x A (inhibitor chart); EX2005, ¶121.

3. “Genus of Subjects Claimed”

Petitioner’s “Genus of Subjects Claimed” argument (Pet., 39-41)—essentially that cytokine blocking experiments in mice fail to provide written description support for claims encompassing human subjects—is inapt. Moreover, both the practice in the art as well by Petitioner itself rely on preclinical PoC models to support human treatment. EX2005, ¶¶107-110, 135-136; *supra* §§II.A.2.-II.A.4., IV.C. Any requirement for human testing is also contrary to long-standing precedent that—unlike what’s needed for FDA approval—reliance on animal models is more than sufficient for patentability. *United Therapeutics*, 74 F.4th at 1369; *In re Brana*, 51 F.3d at 1567; *Scott*, 34 F.3d at 1063; *In re Anthony*, 414 F.2d at 1395; MPEP §2107.03. It also would be inappropriate to fractionate or require a separate disclosure in the specification for subgenus of subjects; no specific sub-categories are claimed. *United Therapeutics*, 74 F.4th at 1370-71.

4. Additional Factors Confirm Written Description Support

Petitioner cites *Ariad* for additional factors of (1) the maturity of the technology; (2) the existing knowledge in the field; (3) “the predictability of the aspect at issue”; and (4) the extent and content of the prior art in determining written description sufficiency. Pet., 41 (quoting *Ariad*, 598 F.3d at 1351). Here, all weigh in favor of the ’505 patent having sufficient written description support.

Addressing the first factor, Petitioner narrowly describes “the science or technology at issue[]” as “inhibiting IL-15 signaling to treat autoimmune diseases such as vitiligo,” nearly synonymous with the claimed invention of inhibiting IL-15 signaling to treat vitiligo. *Id.* Petitioner ignores the advanced state of “the science and technology” related to cytokine inhibition to treat autoimmune diseases. *Supra* §II.A. As Petitioner’s declarant admits, use of other cytokine signal inhibitors—particularly JAK inhibitors—had already been demonstrated clinically based on preclinical studies. EX2007, 50:16-51:21; EX1007. Similarly, in asserting obviousness, Petitioner admits that “the extent and content of the prior art” was advanced. Pet., 43-44.

For the second and third factors, Petitioner again attacks from the wrong direction and without support. Petitioner relies on its declarants for the proposition that “POSAs knew that disparate means of IL-15 or IL-15R could provide very disparate results depending on which ligand or subunit was targeted, where it was targeted, and how it was targeted.” Pet., 42 (citing EX1002, ¶81). But considering *Ariad*’s specific direction to consider “the predictability of the *aspect at issue*,” 598 F.3d at 1351 (citation omitted), the alleged “disparate results” are entirely nonspecific to “the aspect at issue” with respect to the predictable effect—in view of the ’505 patent—of IL-15 signaling inhibitors on treating vitiligo. *Supra* §II.A.4; EX2005, ¶120.

Petitioner mischaracterized the record in arguing that “[Patent Owner] only obtained allowance of the claims over the prior art by arguing that the [prior art] failed to provide data to support its teachings”; thus, “[Patent Owner] cannot now argue that the state of the art was sufficiently predictable to extrapolate the entire genus of IL-15 and IL-15 receptor inhibition.” Pet., 43. However, in overcoming an obviousness rejection, Patent Owner aptly highlighted that the asserted reference provided nothing “showing the use of agonistic or antagonistic therapeutic agents for the treatment of any disorder.” EX1010, 38. In other words, the prior art did not show that IL-15 inhibition would treat vitiligo as established in the ’505 patent. But it was predictable that IL-15 or IL-15R inhibitors—hundreds of which were known—will inhibit IL-15 signaling. They unquestionably do. *Supra* §II.A.1 (CD122 inhibition representative of IL-15 inhibition). What was not known in the prior art, and what the ’505 patent first demonstrated in detail, was how inhibiting IL-15 signalling treats vitiligo. EX2005, ¶79.

5. Dependent Claims

a. Claim 2

In addition to the foregoing, Petitioner’s challenge to claim 2 fails because each specific category of inhibitors recited in claim 2 (small molecule inhibitor, antibody, peptide inhibitor, and inhibitory nucleic acid) are specifically exemplified in the patent and were well-known in the prior art. EX1001, 7:33-8:37, 9:3-21; *see*

also EX2024 (disclosing small molecule inhibitors); EX2032 (disclosing peptide inhibitors); EX2031 (disclosing antibodies); EX2030 (disclosing inhibitory nucleic acids). *Supra* §§III.B, II.A.3; EX2005, ¶¶137-139.

b. Claims 3-5

For at least the reasons set forth above, Petitioner fails to demonstrate the lack of adequate written description of claims 3-5. Further, the methods of administration required by those claims are supported by the specification, and a POSA would appreciate that each was common practice, as Petitioner's own declarants acknowledge. EX1001, 2:9-11, 20:30-54; EX1004, ¶29 ("Each of these modes of administration were routine and common in the field of vitiligo treatment at the time."); EX2005, ¶140.

VIII. PETITIONER FAILS TO ESTABLISH THAT CLAIMS 1-5 ARE NONENABLED

Petitioner's enablement ground (Pet., 48-63) relies on speculation and inapt analogies belied by admissions of its declarants who failed to consider the full intrinsic record or investigate the state of the art. *Supra* §IV.B. Unlike *Amgen*, *Enzo*, and *Wyeth*, where the novelty resided in new or undeveloped genera of compounds, the '505 patent claims are (like *UroPep*) directed to a *new use* of a well-known and well-developed class of inhibitors.

A. Enablement Standard

“To prove that a claim is invalid for lack of enablement, a challenger must show... that a [POSA] would not be able to practice the claimed invention without ‘undue experimentation.’” *Alcon*, 1188. In this regard, the “usual requirement [is] that the challenger identify specifics that are or may be within the claim but are not enabled.” *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1104 (Fed. Cir. 2020); *Alcon*, 1189-90. “Unsubstantiated statements indicating that experimentation would be ‘difficult’ and ‘complicated’ are not sufficient” to establish nonenablement. *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1339 (Fed. Cir. 2013); *Amgen*, 598 U.S. at 615 (“[E]nablement is not measured against the cumulative time and effort it takes to make every embodiment with a claim....”).

Where novelty is based on the *new use* of known elements, the analysis necessarily focuses on enablement of the *novel use* without regard to unclaimed structures or effects.²¹ In this regard, *Genentech, Inc. v. Novo Nordisk, A/S* distinguishes what is well-known in the art—which “a specification need not

²¹ Even where novelty is based on novel compounds, exhaustively describing every possible species is not required. *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 555 F. App’x 961, 967 (Fed. Cir. 2014).

disclose”—from the novel aspects of an invention since “[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.” 108 F.3d 1361, 1366 (Fed. Cir. 1997) (citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986)); *Pharmacyclics*, 2022 WL 16943006, at *11 (affirming that provisional application enabling even if *absence* of undue experimentation was not shown for “Intermediate 2” because it was not a “novel aspect[]” of the claim (citation omitted)).

Applying this principle, *UroPep* explained that it was “not the correct inquiry” as to whether

undue experimentation would be required for one artisan to synthesize all members of the genus of selective PDE5 inhibitors.... The '124 patent's disclosure specifies the mechanism by which PDE inhibitors work, how those inhibitors may be used to relax smooth muscle tissue, and how relaxation of prostatic smooth muscle tissue to treat BPH was known in the prior art. Given that evidence, a reasonable jury could have found that claim 1 was sufficiently enabled regarding the use of PDE5 inhibitors to treat BPH.

UroPep, 661-62 (citation omitted). In this regard, the patent was not based on

the “novel result” of inhibiting PDE5. Such compounds were already well known and the effect of inhibiting PDE5 already achieved; instead, the invention was to use a group of compounds

well known in the art, including tadalafil, in a novel method of treating BPH.

Id. at 648 (“[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.”).

By contrast, *Amgen* applied the principle that “the specification must enable the full scope of the invention *as defined by its claims*” to hold nonenabled claims to a novel and undeveloped genus of antibodies that (1) bind to specific amino acid residues on PCSK9, and (2) block PCSK9 from binding to LDL receptors. *Amgen*, 598 U.S. at 602, 610. Unlike the use of a well-known class as addressed in *UroPep*, the *Amgen* antibodies themselves were both specifically claimed and the basis of novelty, making their enablement dispositive.

Similar to *Amgen* but unlike *UroPep*, Petitioner relies on cases involving a novel or undeveloped chemical genus. For example, *Enzo* addressed claims to a 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.” *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1346 (Fed. Cir. 2019) (“*Enzo*”); *Enzo Life Scis., Inc. v. Gen-Probe Inc.*, No. 12-104-LPS, 2017 WL 2829625, at *7 (D. Del. June 28, 2017) (polynucleotides were a novel aspect of the invention); *see also*

Idenix, 941 F.3d at 1162-63 (claims were not enabled where their novel aspect was a genus of previously unidentified nucleosides and identifying those “candidate compounds... would require synthesis and each of which would require screening”).

Similarly, *Wyeth* addressed claims relying on an undeveloped chemical genus defined by the unpredictable combination of structural and functional properties where only one species (sirolimus) was disclosed in the specification and perhaps four others were known in the art. *Wyeth & Cordis Corp. v. Abbott Lab ’ys*, 720 F.3d 1380, 1382-83, 1385-86 (Fed. Cir. 2013) (“*Wyeth*”). More specifically, although directed to method of treatment, the claims were based on the use of “rapamycin” construed as “a compound containing a macrocyclic triene ring structure produced by *Streptomyces hygroscopicus*, having immunosuppressive and anti-restenotic effects.” *Id.* at 1383 (citation omitted). The inquiry was thus focused on enablement of the largely unknown genus claimed by both structure (“a compound containing a macrocyclic triene ring produced by *Streptomyces hygroscopicus*”) and function (“having immunosuppressive and anti-restenotic effects”).²² The *Wyeth* claims relying on the rapamycin genus were held nonenabled because “[t]he specification is silent about how to structurally modify [the sole disclosed species] sirolimus, let

²² *United Therapeutics* further emphasized that enablement is tied to the elements of the claim *as construed*. 74 F.4th at 1370.

alone in a way that would preserve the recited utility,” the field was “unpredictable and poorly understood,” and “until you test compounds, you really can’t tell whether they work or not[,] *i.e.*, have antirestenotic effects.” *Id.* at 1385-86 (cleaned up). The lesson of *Wyeth* is that,

[i]n cases involving claims that state certain structural requirements and also require performance of some function (*e.g.*, efficacy for a certain purpose), we have explained that undue experimentation can include undue experimentation in identifying, from among the many concretely identified compounds that meet the structural requirements, the compounds that satisfy the functional requirement.

McRO, 959 F.3d at 1100 n.2 (citing *Wyeth*, 1384, 1387).

Unlike *Amgen*, *Enzo*, *Idenix*, and *Wyeth*, the novel feature claimed by the ’505 patent is a new use for a well-known genus with 20 exemplified species from nine different classes disclosed in the specification. *Supra* §§II.A.3, III.B. These claims are supported by the inventors’ discovery that the well-developed class of IL-15/IL-15R inhibitors, already taught for the treatment of other autoimmune diseases, is effective for the treatment of vitiligo. *Supra* §III.B. These facts are unlike cases involving undefined, nascent, or undeveloped classes of compounds. Here, as in *UroPep*, POSAs would know and appreciate that there were hundreds of existing inhibitors that would work as intended in the claimed treatment method, including (1) the sequences or structures of the claimed inhibitors; (2) IL-15/IL-15R binding

sites; and (3) representative binding that confer IL-15/IL-15R inhibition. *Supra* §§II.A-B; ID, 26.

B. Objective Enablement of the Claimed Method

Before turning to Petitioner’s specific arguments, it is important to cohesively address the basis of novelty, what was already known in the art, and what the patent demonstrated. *See* EX2005, ¶¶141-182.

First, as in *UroPep*, “the invention was to use a group of compounds well known in the art... in a novel method of treating [vitiligo].” *UroPep*, 648. The claimed invention is not directed to inhibition of IL-15 signaling per se, which is not novel and had, in fact, been researched for decades and was already the subject of textbook science with known therapeutic effects. *Supra* §II.A. Nor is the claimed invention premised on the novelty of any inhibitor; instead, exemplary prior art species are disclosed in the specification and hundreds were known. *Supra* §II.A.3; EX2005, ¶¶163, 172-174, App’x A.

Second, contrary to Petitioner’s repeated mischaracterizations of the state of the art as “nascent,”²³ even by 2015 it was reported that “[c]ytokine targeting is *now established* as a feasible method for treating” certain diseases. EX2024, 1; *see also supra* §II.A.1. Indeed, relying on preclinical PoC models, inhibition of cytokine

²³ *E.g.*, Pet., 53.

signaling was taught as therapeutic for a range of autoimmune conditions, including AA (*Xing*), celiac disease (*Yokoyama*), and psoriasis (*van der Fits* 2009). EX1007, EX2012, EX2072; *Supra* §II.A.2; EX2005, ¶¶52, 144. This is further admitted by Petitioner’s declarant Dr. Plott, who opined that “[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) and also was obvious to a [POSA] at the relevant time.”²⁴ EX1004, ¶34.

Third, also based on PoC models, it was recognized that identified disease treatment effects of one cytokine inhibitor were a common property of other inhibitors of the same cytokine. *Supra* §II.A.4. This expectation that cytokine signaling inhibitors share common therapeutic utility based on their common mechanisms of inhibiting cytokine signaling is reflected in Petitioner’s own practice of attributing untested therapeutic activity to its anti-IL-15R antibody “FB-102.” *Supra* §IV.C.; EX2005, ¶¶107-110. Thus, a POSA would have understood from the ’505 patent that its demonstrated therapeutic mechanisms of action for treating vitiligo by inhibiting IL-15 signaling was representative of the therapeutic effects of

²⁴ To be clear, as discussed in Sections III, *supra*, and IX, *infra*, what was not known and could not have been reasonably expected was that inhibition of IL-15/IL-15R would treat vitiligo.

inhibiting IL-15 signaling generally. *Supra* §II.A.4.; EX2005, ¶¶80-83, 150; *UroPep*, 662 (“The... patent’s disclosure specifies the mechanism by which PDE inhibitors work, how those inhibitors may be used to relax smooth muscle tissue, and how relaxation of prostatic smooth muscle tissue to treat BPH was known in the prior art. Given that evidence, a reasonable jury could have found that claim 1 was sufficiently enabled regarding the use of PDE5 inhibitors to treat BPH.” (citation omitted)).

Fourth, hundreds of IL-15 signaling inhibitors were already known. *Supra* §II.A.3; EX2005, ¶¶150, 157 (App’x A). This information need not be repeated in the ’505 patent since “a patent need not teach, and preferably omits, what is well known in the art.” *Hybritech*, 802 F.2d at 1384. Indeed, Dr. Abbas admitted that commercial IL-15 signaling inhibitors were known. EX2007, 71:11-72:11. There is also no requirement that the patent disclose “how to make a claimed inhibitor” (ID, 26) when hundreds of inhibitors, including their structures and functions, were known in the prior art and where disclosure of 20 exemplary inhibitors were expressly incorporated by reference in the specification. *See Pfizer*, 555 F. App’x at 967.

Fifth, the *Harris* mouse model relied upon in the specification is sufficient to enable the scope of treating subjects, including human subjects not expressly recited in the claim. *Supra* §II.B.2; EX2005, ¶¶149-153. Indeed, as reflected in the art (*supra* §II.A.3.-II.A.4.) and Petitioner’s own research and development (*supra*

§IV.C.), it was routine to rely upon animal models for enablement, and human testing is not required. *In re Brana*, 51 F.3d at 1567; *Scott*, 34 F.3d at 1063; *In re Anthony*, 414 F.2d at 1395; MPEP §2107.03; *see also United Therapeutics*, 74 F.4th at 1370-71.

Finally, the specification demonstrates why the claimed method is directed to IL-15 and not IL-2. *Cf.* Pet., 2. Example 1 first establishes that human and mouse Trm are present in lesional skin and express components of the IL-15 receptor. EX1001, 30:53-31:12. Specifically, melanocyte-specific T cells express the CD122 subunit of IL-15 (IL-15R β), whereas keratinocytes express the CD215 subunit of IL-15R (IL-15R α), consistent with the ability of the keratinocytes to present IL-15 to T cells in trans. *Id.* The inventors then administered an anti-CD122 antibody (ChMBC7) and showed that it reversed established vitiligo in mice by depleting IL-15-dependent CD8⁺ Trm cells. EX1001, 6:5-9, 33:10-12, 33:1-35, Fig. 6D; *see also* EX2039 (incorporated in '505 patent by reference); EX2040 (incorporated in '505 patent by reference).

C. Petitioner's Argument Is Based on a Misguided Premise, Failed to Consider the Full Scope of the Specification, and Ignored the Advanced State of the Art

Petitioner's nonenablement arguments rest on declarants who failed to consider the entirety of the specification—in particular the more than 300 references expressly incorporated therein—and were neither familiar with nor had reasonably

investigated the state of the art. §IV.B.1.-IV.B.2. Consequently, their opinions are entitled to little, if any, weight. §IV.B.

Worse, Petitioner's arguments are contradicted by the record and the state of the art. For example, Petitioner relies on its declarants to assert that "treating autoimmune diseases such as vitiligo... using cytokine signaling inhibitors is a very complex invention, and the limited knowledge at the time of the invention about using cytokine signaling inhibition to treat[] vitiligo in the genus of subjects claimed supports a finding of no enablement." Pet., 51. However, there was extensive knowledge about using cytokine inhibitors for the treatment of autoimmune diseases. *Supra* §II.A. Petitioner's "complex[ity]" and "limited knowledge" argument are further contradicted by the admitted "rational underpinnings" and mechanistic understanding of using cytokine signaling inhibitors as alleged in its obviousness ground. *E.g.*, Pet., 69; *see also* EX1002, ¶¶98, 104; EX1004, ¶¶34, 60.

Petitioner's arguments are further misguided for focusing on enablement of subject matter other than what's claimed. Attempting to force an analogy with *Wyeth*, a core Petitioner contention is that "[t]he specification is not enabling because it fails to demonstrate which targets are necessary or sufficient to achieve the desired effect, let alone essential structural requirements for achieving that effect." Pet., 52. Unlike *Wyeth*, where the claims were *defined* in terms of specific chemical structure having unpredictable biological properties from among a largely unexplored genus, here the

claims are directed to the new use of a well-known class of compounds. Under these facts, requiring identifying “essential structural requirements” is misdirected. *See UroPep*, 653.

Enabling the claimed method of treating vitiligo lesions, the ’505 patent provides a detailed and comprehensive scientific analysis and working example demonstrating how and why inhibition of IL-15 signaling—by targeting IL-15 or IL-15R—is effective to treat vitiligo lesions. *Supra* §§III.B.-III.C. Enablement based on this disclosure is consistent with the art (§II.A.4.) and Petitioner’s reliance on the same information (§IV.C.). Moreover, while it is undisputed that a working example is provided, Petitioner’s argument about what the ’505 patent “fails to demonstrate” is further misdirected since “[n]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples.” *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993).

Equally misdirected is Petitioner’s argument that enablement “would require synthesizing and screening an incalculable number of compounds....” Pet., 52. Again, unlike *Wyeth*, “synthesizing and screening” is not required to practice the claimed method where inhibition of IL-15/IL was known and well-characterized for the treatment of other diseases (*supra* §§II.A.1.-II.A.3.) and hundreds of such inhibitors across a range of classes had been reported (*supra* §II.A.3.) *See UroPep*,

648 (“[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.”); *see also Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) (“[W]e hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences..., satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences.” (footnote omitted)). Indeed, with over 375 known IL-15/IL-15R inhibitors, they were more than “well understood in the art” as compared to the roughly 100 PDE-V inhibitors known in *UroPep*, 639.

Where practicing the claimed method is already enabled based on both disclosed inhibitors and hundreds more known in the art, Petitioner’s reliance on an “incalculable number of compounds” (Pet., 52) is equally baseless. The Supreme Court rejected as “untenable” an argument that claims involving ore compositions that “*var[y] infinitely*, each one presenting its special problem,” were invalid because “it is obviously impossible to specify in a patent the precise treatment which would be most successful and economical in each case.” *Minerals Separation v.*

Hyde, 242 U.S. 261, 270-71 (1916).²⁵ Here, as in *Minerals Separation*, the patent, “while leaving something to the skill of persons applying the invention, is clearly sufficiently definite to guide those skilled in the art to its successful application, as the evidence abundantly shows.” *Id.* at 271; *see also Amgen*, 598 U.S. at 611 (“All this is not to say a specification always must describe with particularity how to make and use every single embodiment within a claimed class. It may suffice to give an example if the specification also discloses ‘some general quality...running through’ the class that gives it ‘a peculiar fitness for a particular purpose.’”).

The question is thus whether the patent sufficiently guides a skilled artisan to the “successful application” of the claimed method. *Id.* As reflected in the following *Wands* analysis, the answer is necessarily “yes” when the claimed subject matter is properly considered.

1. *Wands* factors 1 (quantity of experimentation) and 7 (predictability)

The claimed invention is directed to the treatment of vitiligo with an IL-15 or IL-15R inhibitor based on the inventor’s discovery of the mechanism by which

²⁵ *Minerals Separation* was relied upon by the Supreme Court in *Amgen*, 598 U.S. at 611-12, as well as by the Federal Circuit in *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014); *Wands*, 858 F.2d at 737 n.19; and *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557 (Fed. Cir. 1983).

blocking IL-15 signaling depletes autoreactive Trm to effectively treat vitiligo. *See, e.g.,* EX1001, 1:59-65 (“[T]reatment with an IL-15R β blocking antibody effectively depleted autoreactive Trm, inhibited their function, and resulted in durable reversal of disease in mice.”); *see also* *UroPep*, 662 (“The... patent’s disclosure specifies the mechanism by which PDE inhibitors work, how those inhibitors may be used to relax smooth muscle tissue, and how relaxation of prostatic smooth muscle tissue to treat BPH was known in the prior art.”). No more than routine experimentation is required to practice the claimed method given the ’505 patent’s disclosure, the hundreds of IL-15 signaling inhibitors were known in the art, and given the predictability of inhibiting the well-studied IL-15 signaling pathway known from the treatment of other autoimmune diseases. *Supra* §§II.A.2., II.A.3.b., II.A.4.; EX2005, ¶¶161-163, 171-180; *see also* *infra* *Wands* factors 4-5.

Petitioner focuses on the alleged need to synthesize and screen new compounds through an “iterative, trial-and-error process” and argues that “very small changes to the structure of a compound (e.g., small molecule or antibody) can have very large and disparate effects on biological function.” Pet., 61-62. This unsupported platitude is irrelevant to the enablement of the present invention where, unlike the necessity to synthesize and screen in *Wyeth*, hundreds of IL-15/IL-15R inhibitors were known to inhibit this pathway. Alleged but unspecified “disparate effects on biological function” do not speak to what “would be necessary in order to

practice the claimed invention,” which is based on the inventor’s discovery that inhibition of IL-15/IL-15R treats vitiligo. *Alcon*, 1189 (emphasis in original). At most, the potential for unspecified disparate effects implicates balances of safety and efficacy, optimization, and FDA requirements—but not enablement. *Id.*; *United Therapeutics*, 74 F.4th at 1369.

Petitioner then repeats its assertion that, “[a]s Drs. Abbas and Plott testify, the mouse model for vitiligo is not representative of treating natural vitiligo....” Pet., 62-63. As discussed, their testimony is incompetent on this issue, both having admitted to lack of familiarity with and not having investigated the relationship between the *Harris* mouse model and human vitiligo. *Supra* §IV.B. The implicit demand for clinical testing in humans is also contrary to law. *In re Brana*, 51 F.3d at 1567; *Scott*, 34 F.3d at 1063; *In re Anthony*, 414 F.2d at 1395; MPEP §2107.03. As Dr. Damsky explains and as reflected in Petitioner’s public statements, animal models—including the same *Harris* mouse model used in the specification—are indeed relied upon for expected human therapeutic utility. EX2005, ¶¶86-89, 151-152, 168; *supra* §IV.C.

2. Wands factors 2 (direction and guidance) and 3 (working examples)

Repeating its prior points, Petitioner argues that “sparse guidance” and a “single sole working example” weigh towards nonenablement. Pet., 59-61. Petitioner’s rehashed argument fails for the same reasons as above, including for not

considering the entirety of the specification—including the incorporated references—or the state of the art. *Supra* §§III.B., IV.B.; EX2005, ¶¶164-170; EX1001, 2:49-52; *Gilead*, 6; *CSL*, 16; *Sanofi-Aventis*, 14; *Alcon*, 1189. Moreover, the admitted working example provides direction and guidance that necessarily weights *towards* enablement. *E.g.*, *Bayer Healthcare LLC v. Baxalta Inc.*, 989 F.3d 964, 981-82 (Fed. Cir. 2021) (relying on a single working example for “non-random cysteine PEGylation” and evidence “bridging the gap between the patent’s disclosures about cysteine PEGylation on the one hand and non-random PEGylation,” reiterating that “the specification need not include a working example of every possible embodiment to enable the full scope of the claims”).

Ignoring its burden, Petitioner argues that “[t]here is no evidence” that the ’505 patent’s working example is “representative of results in natural or spontaneous vitiligo lesions or of results in animal species different than mice (e.g., humans).” Pet., 59. Petitioner further argues that the specification does not disclose the structure of ChMBC7 and does not explain why ChMBC7 would be representative of other CD122 antibodies, other IL-15R antibodies, IL-15 antibodies, or inhibitors that “do not physically interact with any of IL-15 or its receptor subunits.” Pet., 59-61. Petitioner is doubly wrong.

The only basis for the first assertion is a head-in-the-sand approach that ignores detailed disclosure in the specification linking vitiligo in the *Harris* mouse

model with natural or spontaneous vitiligo lesions in humans based on common features. *Supra* §II.B.2. Indeed, as noted, Petitioner relies on declarants who were simply not familiar with these correlations. *Supra* §IV.B.

Contrary to both of Petitioner's contentions, it was routine to rely on PoC models to expect common therapeutic effects among inhibitors of a common mechanism. §II.A.4. The *Harris* mouse model was (and remains) the primary model of vitiligo and has been recognized as representative of human disease pathology (§II.B.2), and Petitioner itself relied on the '505 patent's disclosure to project efficacy of a different inhibitor (FB-102) in treating vitiligo (§IV.C). EX2005, ¶168.

**3. *Wands* factors 4 (the nature of the invention) and 5
 (the state of the prior art)**

The nature of the invention is the *new use* of a known class of cytokine inhibitors known to treat other autoimmune diseases. *See UroPep*, 648. The state of the art included decades of research on cytokine inhibition and has led to therapeutic treatment of multiple autoimmune diseases. *Supra* §II.A.2. IL-15 signaling inhibition, specifically, had been shown to be effective for psoriasis, RA, and diabetes. *Supra* §§II.A.1., II.A.4. Petitioner itself admits that "inhibiting IL-15-induced signaling by blocking binding of IL-15 to the $\beta\gamma$ receptor had been proposed as a treatment for autoimmune diseases... almost a decade before the critical date"

(Pet., 53-54),²⁶ thus contradicting its allegations that the state of the art was nascent. Based on this, *Wands* factors 4 and 5 both point towards enablement. EX2005, ¶¶147-159.

Petitioner misrepresents that “the complex nature of the invention and the nascent state of the art... favor a finding of no enablement.” Pet., 53-54; *supra* §§II.A., II.B. Beyond the novel use of IL-15 and IL-15R inhibitors that Petitioner alleges was predictable,²⁷ the claimed methods require only routine methods as Petitioner also repeatedly asserted.²⁸

4. *Wands* factor 6 (relative skill in the art)

According to Petitioner, “[t]he relative skill of those in the art (*Wands* factor 6) is neutral in this case.” Pet., 63. To the contrary, this factor must weigh strongly in favor of enablement, considering the advanced state of the art in terms of IL-15 biology, known IL-15 signaling inhibitors, and therapeutic application of cytokine

²⁶ Petitioner seeks to set up a false conflict with the prosecution history. Pet., 53-54. What was explained was that in contrast to the laundry-list disclosure of Pavlakis failing to provide a reasonable expectation of success, the application provided actual data showing the treatment of vitiligo. EX1010, 38-39.

²⁷ *E.g.*, Pet., 64-65; EX1002, ¶¶109-110; EX1004, ¶34.

²⁸ *E.g.*, Pet., 3-5; EX1002, ¶¶103; EX1004, ¶29.

inhibition, including IL-15 specifically. *Supra* §II.A.; EX2005, ¶¶94, 160. Petitioner’s POSA definition and obviousness allegations—which assume that a POSA can readily extrapolate from AA to vitiligo without any verification—all further assume a high level of skill. EX2005, ¶¶160, 188; *supra* §III.D.

5. *Wands* factor 8 (breadth of the claim)

Petitioner argues that the breadth of the claims in terms of inhibitory pathways, structure for each pathway, and “disparate genus of subjects implicated” weighs toward nonenablement. Pet., 54-58. In addition to the testimony of Petitioner’s declarants being incompetent for having failed to investigate the state of the art with respect to these considerations (*supra* §IV.B.), they offer no more than speculation as to potential differences between different embodiments and do “not show that any claimed embodiments would be inoperable.” *Alcon*, 1190; EX2005, ¶¶149-156.

Petitioner’s repeated speculation about whether the examples in the specification are “representative” of other inhibitors (Pet., 55-56, 59-60) or species (Pet., 57-59) in some unspecified general sense of “representative” is immaterial to enablement.²⁹ Disclosed examples and embodiments need not be “representative” of,

²⁹ “Representative” is a key point in the Petition, raised more than 50 times. *E.g.*, Pet., 3, 27, 29, 30, and 55. Not once does Petitioner provide supported evidence that

for example, unclaimed properties relating to the rate or degree of treatment or to safety. *See Lochner Techs., LLC v. Vizio, Inc.*, 567 F. App'x 931, 939 (Fed. Cir. 2014) (agreeing that “there is no precedent requiring a patentee to disclose or enable unclaimed elements”). The selection of an inhibitor, for instance, “may be relevant to *optimizing*..., but [Petitioner] proffered no evidence that any experimentation, let alone undue experimentation, with those variables would be necessary in order to *practice* the claimed invention.” *Alcon*, 745 F.3d at 1189 (emphases in original) (reversing district court’s nonenablement ruling for lacking foundation). And Petitioner “adduced no evidence [in its Petition] that changing any of the [conditions] would render [Patent Owner’s] claimed invention inoperable, nor was there any evidence that experimenting with those variables was required for an ordinarily skilled artisan to be capable of” practicing the claimed method. *Id.*; EX2005, ¶141.

In terms of being “representative” of *treating vitiligo*, there is no dispute that inhibiting IL-15 signaling via inhibition of IL-15 or IL15R will inhibit the IL-15 pathway, the mechanism taught in the ’505 patent to be effective to treat vitiligo. EX1001, 6:16-21; EX2007, 69:9-71:5; EX2005, ¶¶148-156. And as Dr. Abbas concedes, it was “reasonable” as of April 2017 (and today) to expect that species

other embodiments—whether other inhibitors or other subjects—would not be effective in treating vitiligo to at least some degree.

that would antagonize IL-15 signaling would be useful in autoimmune diseases identified as having an IL-15 mechanism. EX2007, 74:19-75:10. The '505 patent's PoC with ChMBC7 is thus "representative" and enabling of treating vitiligo with inhibitors of IL-15 or IL-15R as claimed.

The '505 patent's enablement of antagonizing IL-15 signaling—whether by antagonizing the cytokine or its receptor subunits—to treat vitiligo is consistent with the “emerging understanding” more than ten years earlier of “the scientific basis for the development of rational approaches for the IL-15-targeted treatment of autoimmune diseases....” EX1022, 3; EX2007, 65:10-67:20. As described therein, the therapeutic effect is based on the “disruption of IL-15 action” and can be achieved by “agents that inhibit IL-15 action”—whether by antagonism of IL-15 itself or any of its receptor subunits. EX1022, 2-3. That is, the key is inhibiting IL-15 signaling, not the precise manner in which the signaling is inhibited. This is also consistent with the recognized therapeutic effects for inhibiting the action of other cytokines and in other diseases. EX2005, ¶154; *supra* §II.A.

Similarly, it is immaterial whether the effects of cytokine blocking could differ to some degree between mice and humans. Pet., 58. As previously addressed, the *Harris* mouse model is scientifically and legally sufficient to enable the claimed method, including for humans, and indeed has been relied upon by Petitioner to

project billions in potential revenue for treating vitiligo with its untested FB-102 antibody. EX2005, ¶¶107-110.

D. Dependent Claims

1. Claim 2

For the same reasons as described above in §VIII.C.1.-VIII.C.5., Petitioner's challenge to claim 2 fails as well because the categories of inhibitors recited in claim 2 are specifically exemplified in the '505 patent and known in the prior art. *Supra* §II.A.3.a), II.A.3.b); EX2005, ¶181.

2. Claims 3-5

For the same reasons set forth above in §VIII.C.1.-VIII.C.5., Petitioner fails to demonstrate nonenablement of claims 3-5. Further, the methods of administration required by those claims are enabled by the specification, and a POSA would appreciate that each was common practice, as Petitioner's own declarants acknowledge. EX1001, 2:9-11, 20:30-54; EX1004, ¶29; EX2005, ¶182.

IX. PETITIONER FAILS TO ESTABLISH THAT CLAIMS 1-5 WOULD HAVE BEEN OBVIOUS OVER *XING* AND *HARRIS*

As the Board noted, Petitioner's obviousness 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." ID, 33-34. Petitioner's rationale for combining models of different diseases from *Xing* (AA) and *Harris* (vitiligo) further fails to account for the absence of evidence that IL-15

signaling inhibition would treat vitiligo, the art's focus on IFN- γ mechanisms for vitiligo, and known inter-disease differences. What was allegedly obvious to Petitioner's declarants—who failed to consider the specific subsets of CD8⁺ T cells, difference between prevention versus depletion, and inter-disease variability—cannot be reconciled with the art.

Petitioner fails to establish a motivation or a reasonable expectation of success for claims 1-5. EX2005, ¶¶183-212. Petitioner further failed to address known objective indicia of nonobviousness, including its own copying of the claimed method to target what it describes as a long-felt need for vitiligo treatment in an estimated \$1.2 billion market. *Id.*, ¶¶213-223.

A. No Motivation to Inhibit IL-15 Signaling for Vitiligo

1. Petitioner Fails to Establish Any Known Link Between IL-15 Signaling Inhibition and Vitiligo Treatment

As of 2014, it was reported that “cytokines that drive vitiligo pathogenesis have not been well defined, although they are not likely shared with [psoriasis or related autoimmune] because biological treatments for psoriasis have been ineffective for vitiligo.” EX1020, 1. On this backdrop of vitiligo's uncertain pathogenesis, IFN- γ was the cytokine of primary focus for vitiligo treatment prior to the discoveries reported in the '505 patent. *E.g.*, EX1021, 5 (“IFN- γ playing a central role in disease pathogenesis”); EX1023, 1 (“IFN- γ signaling might be an effective

new treatment strategy.”); EX2007, 50:16-51:21 (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.”); EX2005, ¶¶31-32, 184-186. Additionally, JAK inhibitors targeting the IFN- γ response were also being considered for the treatment of vitiligo. EX2005, ¶¶183-186; *supra* §II.B.1.; *e.g.*, EX1006, 6; EX1021, 5.

Petitioner’s attempt to “cobble[] together” (ID, 33) distinct teachings from *Xing* for AA with *Harris* for vitiligo ignores the vitiligo state of the art and its focus on IFN- γ . EX2005, ¶¶185-186. Inconsistent with Petitioner’s proposal to export an IL-15R inhibitor from *Xing* into *Harris*, neither the Petition nor its declarants cite any prior art teaching that IL-15 signaling inhibition would treat vitiligo. EX2005, ¶¶196-201. Dr. Abbas likewise admitted he was unaware of any such experiments. EX2007, 52:6-10. Instead, Petitioner cites numerous references linking IL-15 signaling inhibition for the treatment of *other* autoimmune conditions—to the notable exception of vitiligo. *E.g.*, EX1011, 4:25-34; EX1012, 1; EX1031, 4-7; *see also* EX2012, 1. This evidence is not even sufficient to support an obvious-to-try contention as “the possible approaches to solving the problem were not known or finite, and the solution was not predictable.” *Leo Pharm. Prods. Ltd. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013).

**2. Petitioner Fails to Establish Any Reason to Modify
Harris in View of *Xing***

The inbred C3H/HeJ mouse model used in *Xing* that spontaneously developed autoimmune diseases was well-known—dating back to as early as 1994. EX2007, 7:7-14; EX2005, ¶¶187-188; EX2034, 1; EX2091; EX2092; EX2093; EX2094. Other than its own forced combination of *Xing* and *Harris*, Petitioner does not identify any instance of the C3H/HeJ mouse model being used as a model or surrogate for vitiligo. Indeed, there is no evidence that the C3H/HeJ mouse model can even develop vitiligo, much less that it can be relied upon to guide vitiligo treatment. EX2007, 10:21-11:10; EX2005, ¶¶185, 189-195; *see St. Jude Med., Inc. v. Access Closure, Inc.*, 729 F.3d 1369, 1381 (Fed. Cir. 2013) (affirming nonobvious because a POSA would not have viewed the prior art “as complementary devices to achieve the positioning benefit of St. Jude’s claimed invention”).

Petitioner’s oversimplified analysis ignores key differences in the subset and specificity of CD8⁺ T cells disclosed in *Harris* and *Xing*. EX2005, ¶¶187-192. These unaddressed differences undermine Petitioner’s proposed modification and alleged expectation of success.

Xing’s C3H/HeJ mouse model uses specialized CD8⁺NKG2D⁺ T cells that “infiltrate the epithelial layers of the hair follicle, which overexpress the NKG2DLs... analogous to what has been observed in skin biopsies.” EX1007, 1. As Dr. Damsky explains, this specific subset of CD8⁺ T cells are a hybrid of NK and T

cells, and are distinct from the PMEL CD8⁺ T cells used in the *Harris* mouse model. EX2005, ¶¶189-190. Whereas the CD8⁺ T cells in *Harris* target a specific melanocyte antigen (PMEL), the CD8⁺NKG2D⁺ T cells in *Xing* had no known specificity and were “unlikely” to be PMEL-specific. EX2007, 45:4-25.

Given these ignored differences, Petitioner fails to establish that a POSA would have been motivated to rely on results in *Xing*’s AA mouse model with CD8⁺NKG2D⁺ T cells as a guide for potential vitiligo treatment related to PMEL CD8⁺ T cells used in the *Harris* mouse model. EX2005, ¶187; *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367-68 (Fed. Cir. 2016) (finding no motivation to combine where there was no expectation of achieving property underlying petitioner’s motivation argument); *supra* §II.B.3.

Petitioner’s rationale also misunderstands and mischaracterizes 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. EX2005, ¶¶192-193. *Xing* teaches that the anti-IL-15R antibody “prevented” AA in grafted mice and “**blocked the accumulation** of CD8⁺NKG2D⁺ T cells.” EX1007, 4. It was thus false and misleading for Petitioner’s declarant to assert that *Xing* discloses “**depleting** CD8⁺ T cells.” See EX1004, ¶34; EX2005, ¶192. *Xing* further differentiates between “interventions aimed at either preventing or reversing disease” and concludes that the anti-IL-15R antibody—unlike JAK inhibitors—was

not “able to reverse established AA.” EX1007, 4. Nothing in Petitioner’s oversimplified analysis addresses why a POSA would have been motivated to use *Xing*’s CD122 antibody that failed to reverse established AA in the *Harris* model for vitiligo having established disease based on excess PMEL CD8⁺ T cells *already present* in the skin. EX2005, ¶192.

Although the specific site of action of each disease is necessarily a significant factor, Petitioner does not address that vitiligo and AA affect different layers of the skin. EX2005, ¶¶194-195. Notably, *Xing* provides no evidence of IL-15 expression in the upper layers of the skin where melanocytes reside. *Id.* Figure 2h of *Xing* at most shows that an anti-IL-15R antibody reduced the frequency of CD8⁺NKGD2⁺ T cells in the *skin affected by AA*, as indicated by the immunohistochemical staining in Figure 2i focusing on skin around the hair follicle. EX1007, 3 (Figs. 2h, 2i); *see also* EX2035, 11-12, 17, 28 (discussing analyses of AA skin from mice and immunostaining from treated mice around the hair follicle). Relatedly, *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. EX2005, ¶194; *see also* EX1007, 6; EX2035, 20-21 (Suppl. Fig. 5a).

Petitioner's failure to address these key differences thus precludes any motivation or expectation of success to extrapolate from AA in *Xing* to vitiligo in *Harris*.

B. No Reasonable Expectation of Success

Other than conclusory declarant opinions, Petitioner cites no basis for extrapolating *Xing*'s limited results with an IL-15R inhibitor in AA to establish a reasonable expectation of success for treatment of vitiligo in *Harris*. See Pet., 69; EX2005, ¶¶202-212; see *Novartis Pharms. Corp. v. W.-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1061 (Fed. Cir. 2019).

First, Petitioner fails to even address *Xing*'s report that the anti-IL-15R antibody was *not* “*able to reverse* established” disease. EX1007, 4. And, as discussed above, Petitioner and its declarants misread *Xing*, which only reports that the anti-IL-15R antibody *prevented accumulation* of CD8⁺NKG2D⁺ T cells in the skin and *does not report depletion* of CD8⁺ T cells already accumulated in the skin. Given that the *Harris* mouse model is premised on 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. EX2005, ¶¶203-205.

Second, as the Board noted, “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.” ID, 33; EX2005, ¶¶204. As Dr. Damsky explains, a POSA might 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 given that it was found insufficient to break the feed-forward loop and regrow hair. EX2005, ¶¶198-200, 204-205.

Moreover, *Xing*’s results with IL-15 are consistent with its recognized role in the NKG2D signaling pathway. EX1007; EX2012; EX2005, ¶206. Petitioner, however, fails to establish any recognized role of IL-15 with respect to *Harris*’s PMEL CD8⁺ T cells or any basis to expect the same results as with CD8⁺NKG2D⁺ T cells. EX2005, ¶207. Petitioner thus failed to establish a reasonable expectation of successfully treating PMEL CD8⁺ T cell-dependent vitiligo in *Harris* via IL-15 signaling inhibition based on results from *Xing*’s study of CD8⁺NKG2D⁺ T cells. EX2005, ¶208.

Finally, Petitioner cites to *Cheuk* (EX1027), but it also fails to support a reasonable expectation of success. *See* Pet., 69, 78. As a preliminary matter, *Cheuk* focuses on CD49 expression and not IL-15 expression, and for this reason does not

support an expectation of success based on IL-15 signaling inhibition. EX2005, ¶¶209-212; *see* Pet., 78. Moreover, rather than support intra-disease extrapolations, *Cheuk* reported *disease-based differences* in CD49a expression, specifically in vitiligo (CD49a⁺) versus psoriasis (CD49a⁻), revealing “a functional specialization of distinct skin Trm cell subsets in health and disease,” and an expectation that the diseases “involve the contribution of functionally different subsets” of Trm cells. EX1027, 2, 4. POSAs recognized that the same “functional dichotomy” may hold true for other skin and autoimmune diseases, including vitiligo and AA. EX1027, 4; EX2005, ¶¶210-211.

By 2017, the effects seen with one autoimmune disease driven by a subset of T cells could therefore not be extrapolated to a different autoimmune disease with a functionally different subset of T cells. EX2005, ¶212. Rather than supporting an expectation of success for extrapolation from AA to vitiligo, *Cheuk* points in the opposite direction, emphasizing the structural and functional differences between healthy and distinct immune-mediated skin diseases, and further precludes any extenuation of success for extrapolating results from *Xing* to vitiligo. EX2005, ¶212; EX2007, 47:1-8 (*Cheuk* reports a vitiligo correlation with IL-15, but does not show IL-15 causation).

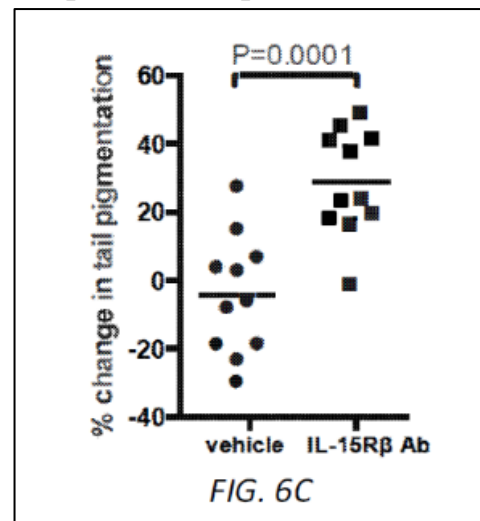
**C. Objective Indicia Not Addressed by Petitioner Further
Support Nonobviousness**

Petitioner further failed to establish a threshold showing of unpatentability as it contravened the requirement that objective evidence of nonobviousness “*must be considered*” in every case where present.” *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc). Here, the objective evidence establishes nonobviousness. EX2005, ¶213.

1. Unexpected Results Demonstrate Nonobviousness

Addressed only in passing in the Petition, Petitioner fails to materially address the unexpected result of “durable” treatment to satisfy the long-felt but unmet need described in the ’505 patent beyond recognizing that this *unexpected result* was a basis for allowance and that the claims do not require this effect. Pet., 17, 75. As Petitioner acknowledged, the Examiner expressly considered and relied upon this evidence. EX1010, 15, 38; Pet., 75; *see also Merial Ltd. v. Virbac*, IPR2014-01279, Paper 13 at 27 (PTAB Jan. 22, 2015) (concluding petitioner “was aware of the unexpected results showing which the Examiner found persuasive” and “[petitioner] should have addressed [the] unexpected results in the first instance”).

More specifically, the specification reports data from *in vivo* testing in a working example embodying the claimed method, demonstrating that treatment of vitiligo with an inhibitor of the IL-15 signaling pathway resulted in ***durable repigmentation*** even after discontinuation of treatment. *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 (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)”). That is, more than just halting the progression of vitiligo, the method resulted in disease reversal (repigmentation) with



“longstanding effects after a limited treatment course.” EX1001, 33:64-67; EX2005, ¶¶219-220.

The specification further explains why the demonstrated effect is a property of—and therefore has nexus and is commensurate in scope with—the claimed method of inhibiting IL-15 or IL-15R as not limited to the exemplary antibody tested. *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”), 33:64-67 (data “suggests that targeting IL-15 in the skin in vitiligo, unlike existing therapies, could provide a durable treatment option”).

The '505 patent's unexpected results are also opposite of what was seen in *Xing* for AA, where neither disease reversal nor durability was achieved using *Xing*'s IL-15R inhibitor for AA. EX1007, 4, 6; EX2005, ¶218. Petitioner failed to substantively address these differences in *Xing* and thereby necessarily failed to meet its burden to establish unpatentability. *See* Pet., 64-74.

2. Long-Felt Need, Recognized Commercial Value, and Copying

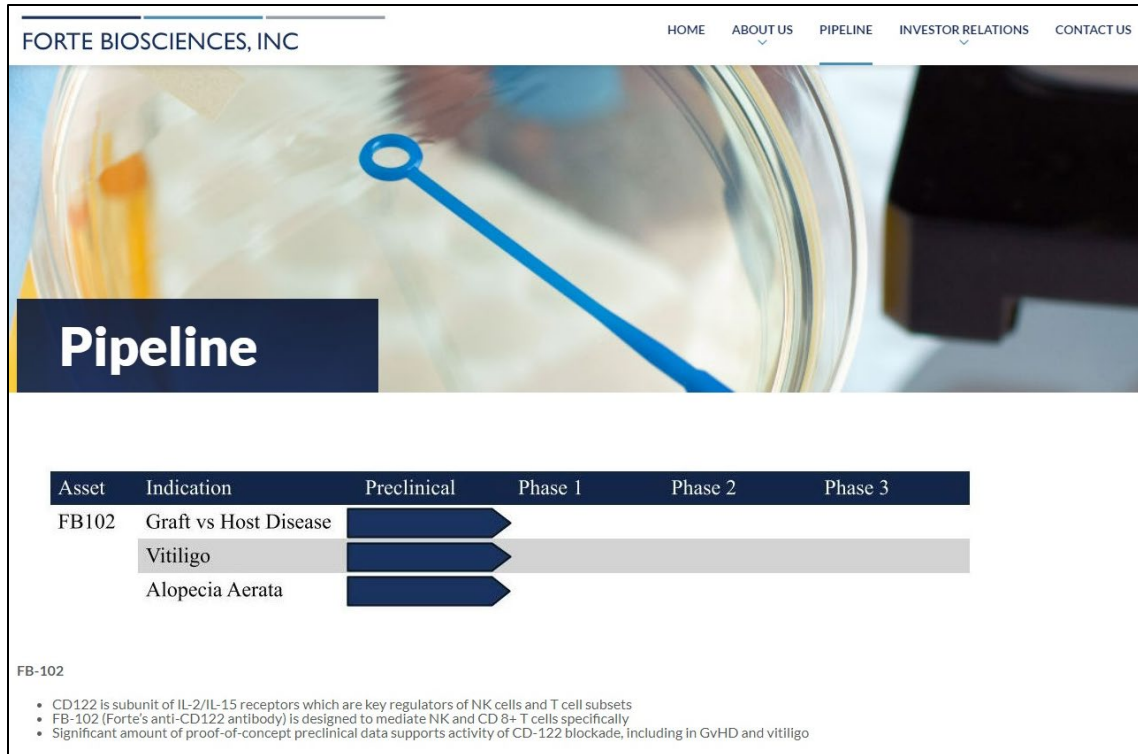
Petitioner's own admissions and actions are particularly persuasive evidence of objective indicia of nonobviousness. *E.g.*, *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1336 (Fed. Cir. 2016) (“The fact that a competitor copied technology suggests it would not have been obvious.”).

First, Petitioner itself identified a “***LARGE UNMET NEED IN VITILIGO.***” EX2004, 33; *see also* EX1004, ¶48 (“[V]itiligo... was not a mature or well-developed field of treatment.”); EX2008, 20:12-22 (“In the clinic in 2017, it was not a common thing to use a molecule or an antibody to treat a skin disease.”), 48:17-24 (not aware of any publications that show durable reversal of treatment of vitiligo), 69:2-6 (“Q: Are you aware of any that were in clinical development as of 2017?...”).

A: In 2017 I was not aware....”). Petitioner’s investor presentation is consistent with the long-felt need reflected in the art as of 2017. EX2001, 2 (“There are currently no FDA-approved treatments for vitiligo, and standard off-label treatments are limited in efficacy.”); EX2060, 8 (“[S]uccessful treatment strategies should be able to reverse established disease through repigmentation, rather than simply prevent it.”). The claimed method of the ’505 patent meets this need. EX2005, ¶¶214-217; EX2009, 3, 8; EX2062, 1; EX2095; EX2060, 1; EX2099, 15; EX2100, 3; EX2098, 1.

Petitioner further *recognized* the commercial potential of Patent Owner’s work and *praised* the commercial value of Patent Owner’s CD-122 antibody, arguing its own “FB-102 is more advanced..., highlighting significant current value.” EX2004, 27 (“\$70[M] upfront and \$1.4 billion in milestones”), 26 (“FB-102 has significant intermediate and long term value based on [PO’s] acquisition[.]...”); *see also Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1365 (Fed. Cir. 2017) (“[I]ndustry recognition of the significance and value of the claimed invention weighs in favor of nonobviousness.”).

Relying on the large unmet need in treating vitiligo and a market estimated value of \$1.2 billion in 2018 (EX2004, 33), Petitioner then *copied* the claimed method by developing “FB-102, [which] targets CD-122, a subunit of the... IL-15 receptor,” for vitiligo (EX2003, 1). EX2005, ¶¶222-223.



EX2045. Because Petitioner’s FB-102 inhibits “CD-122, a subunit of the... IL-15 receptor,” and “shows activity in vitiligo,” use of FB-102 to treat vitiligo in a selected subject is an embodiment of the ’505 patent and there is a presumption of nexus for objective indicia. EX1003, 1; *Volvo Penta of the Ams., LLC v. Brunswick Corp.*, No. 2022-1765, 2023 WL 5440530, at *5 (Fed. Cir. Aug. 24, 2023).

X. CONCLUSION

For these reasons, Petitioner has failed to prove that any challenged claim is unpatentable for lack of written description, enablement, or obviousness by a preponderance of the evidence. The Board should find that claims 1-5 of the ’505 patent are not unpatentable.

Respectfully submitted,

Dated: October 3, 2023

/Mark J. Feldstein/

Mark J. Feldstein

Reg. No. 46,693

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I, Mark J. Feldstein, certify that **PATENT OWNER'S RESPONSE** contains 17,383 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

Dated: October 3, 2023

/Mark J. Feldstein/

Mark J. Feldstein

Reg. No. 46,693

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Response** was served electronically via email on October 3, 2023, in its entirety on the following:

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Dated: October 3, 2023

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