

Petitioner's Demonstratives

Forte Biosciences, Inc. v. University of Massachusetts

PGR2023-00014

U.S. Patent No. 11,278,505

Instituted Grounds

Claims	Challenge
1-5	35 USC § 112(a) Written Description
1-5	35 USC § 112(a) Enablement
1-5	35 USC § 103 Obvious over Xing and Harris

What is claimed is:

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

Pet., 1-5, 23, 48, 64; Paper 10, 2, 34.

Well Qualified Experts

Dr. Abul Abbas

Decades of experience researching cellular interactions in immune response, tolerance and autoimmunity, cytokines, and lymphocyte apoptosis.

Major focus of research for many years has been IL-2 signaling via the CD122/CD132 $\beta\gamma$ receptor complex and its role in regulating T cells.

Distinguished Fellow of the American Association of Immunologists

A portrait photograph of Dr. Abul K. Abbas, an older man with glasses, wearing a light blue button-down shirt, smiling slightly. He is seated in an office with a framed picture on the wall behind him.

Abul K. Abbas, MBBS

Professor Emeritus

Pathology

Specialty Areas

Immunology
Immunopathology

UCSF
Pathology, Box 0511
513 Parnassus Avenue, Room HSW-450A
San Francisco, CA 94143
United States

EX1002; EX1003; Pet., 5; EX2074; POR, 8; EX2005, ¶60; EX1046, 129:16-130:10.

Well Qualified Experts

Dr. R. Todd Plott, MD

Decades of experience treating autoimmune diseases including vitiligo.



R. Todd Plott, M.D.

Epiphany Dermatology:

Chief Medical Officer,

Member of Board of Directors

Market Medical Director, DFW area.

Private Practice Dermatologist.

EX1004, ¶¶1-8; EX1005; Pet., 5.

Ground 1: Written Description

Written Description for a Genus Requires:

Representative number of species or common structural features

scientific and technologic knowledge already in existence”). In the case of a claim to a genus, the Federal Circuit has held that “a sufficient description of the genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Ariad*, 598 F.3d at 1350.

“[F]unctional claim language can meet the written description requirement when the art has established a correlation between structure and function.”

Id.

Paper 10, 15.

Paper 10 (ID), 15; Pet., 23-25, 36-37; Pet., 39; EX1002, ¶62; EX1004, ¶44.

Written Description for a Genus Requires:

More than a wish, a plan, a hunting license, or a research hypothesis

- Specification “failed to provide an adequate written description as it amounted to no **more than a ‘wish’ or ‘plan’** for obtaining the [invention] rather than a description of the [invention] itself.
- “A patent is **not a hunting license**. It is not a reward for the search, but compensation for its successful conclusion.”
- **Research hypotheses do not qualify** for patent protection....[C]laims to research plans also impose costs on downstream research, discouraging later invention. The goal is to get the right balance, and the written description doctrine does so by giving the incentive to actual invention and not “attempt[s] to preempt the future before it has arrived.”

Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1350, 1353 (Fed. Cir. 2010) (en banc).

Paper 10, 15; Pet., 23-25, 36-37; Pet., 39; EX1002, ¶62; EX1004, ¶44.

Written Description Requirement:

Applies equally to method claims as compound claims

We do not agree. The present case is similar to *University of Rochester v G.D. Searle & Co., Inc.*, 358 F.3d 916, 925–926 (Fed. Cir. 2004) where the patentee argued that holdings in precedential case law was limited to composition of matter claims, whereas the disputed claim was directed to a method. The CAFC held that argument to be “a semantic distinction without a difference.” *Univ. of Rochester*, 249 F.Supp.2d at 228. The Court held that “[r]egardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.”

Paper 10, 18.

Paper 10 (ID), 18; Pet., 23-25, 36-37.

Written Description Law: Fact-Intensive Inquiry

The Board's findings for the salient facts are now undisputed

Here, the specification only provides a single working example using an Fc-diminished ChMBC7 mouse antibody to the beta subunit of the IL-15 receptor (i.e., IL-15R β) and a recitation of 20 individual inhibitors known in the prior art. *See* Ex. 1001, 7:34–8:37, 33:1–34:45. Patent Owner argues that this disclosure of a “large variety and number of species that ‘might be used to achieve’ vitiligo treatment is significantly more than what has been found sufficient” in other cases to support written description of a claimed method. *See* Prelim. Resp. 24 (citing *Ajinomoto Co. v. Int’l Trade Comm’n*, 932 F.3d 1342, 1359 (Fed. Cir. 2017); *UroPep*, 276 F. Supp. 3d at 649.). Patent Owner’s argument is unpersuasive for at least two reasons.

First, satisfaction of the written description standard is fact-intensive and is determined on a case-by-case basis; the Federal Circuit has declined to “set out any bright-line rules governing, for example, the number of species that must be disclosed to describe a genus claim.” *Ariad Pharm.*,

Paper 10, 19.

Single Working Example

- ChMBC7 antibody
- Targeting someplace on CD122 receptor subunit

Recitation of 20 individual inhibitors in the specification is no cure for what is **not** disclosed

Written Description Law: Fact-Intensive Inquiry

The Board's findings for the salient facts are now undisputed

Second, the '505 patent fails to explain why the Fc-diminished ChMBC7 antibody would be representative of the different inhibitors recited in the specification (*see* Ex. 1001, 7:34–8:37), and never explains whether and why the enumerated molecules would be representative of all other compounds that can inhibit IL-15 or the IL-15 receptor. The specification also fails to explain adequately what structural features of small molecules, peptides, antibodies, or nucleic acids are necessary or sufficient to perform the claimed method. Nor is there evidence presented in the current record that such information was generally known in art.

Paper 10, 19.

No explanation why ChMBC7 representative of recited inhibitors and all other compounds that can inhibit IL-15 or the IL-15 receptor

No explanation what structural features are necessary or sufficient to perform the claimed method.

- Not in the specification
- Not identified as generally known in the art.

Paper 10 (ID), 19; Pet., 27-35, 36-39; Pet. Reply, 4-8, 13-14.

Written Description Law: Fact-Intensive Inquiry

True At Institution

Confirmed at Trial

- | | | |
|---|---|---|
| ✓ | Single Working Example | ✓ |
| | <ul style="list-style-type: none">• ChMBC7 antibody• Targeting someplace on CD122 receptor subunit | |
| ✓ | No explanation why ChMBC7 representative of recited inhibitors and all other compounds that can inhibit IL-15 or the IL-15 receptor | ✓ |
| ✓ | No explanation what structural features are necessary or sufficient to perform the claimed method. | ✓ |
| ✓ | <ul style="list-style-type: none">• Not in the specification | ✓ |
| ✓ | <ul style="list-style-type: none">• Not identified as generally known in the art. | ✓ |
| ✓ | Recitation of 20 individual inhibitors in the specification is no cure for what is not disclosed | ✓ |

Pet., 1-2, 23-26, 31, 48-53, 64-65; Pet. Reply, 4-9; 12-14; Paper 10, 19-20.

Ground 2: Enablement

Enablement Requirement:

Amgen: Enablement of the entire class required for method claims

§ 112(a). If a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent's specification must enable a person skilled in the art to make and use the entire class. *Amgen v. Sanofi*, No. 21-757, 598 U.S. [REDACTED] (May 18, 2023) (citing *Holland Furniture Co. v. Perkins Glue Co.*, 277 U. S. 245 (1928)). Specifically, the

Paper 10, 20-21.

Paper 10 (ID), 20-21; Pet., 48-51; Pet. Reply, 4-9, 12-14, 17-18.

Enablement Requirement:

Wyeth: Must enable full scope of **method claims** using even an existing class

Furniture Co. v. Perkins Glue Co., 277 U. S. 245 (1928)). Specifically, the specification must enable the full scope of the invention without undue experimentation. *Wyeth and Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (The enablement requirement asks whether “the specification teach[es] those in the art to make and use the invention without undue experimentation.”). This is true even for method claims that are directed to a new use of an existing class of compounds. *Wyeth*, 720 F.3d at 1385.

Paper 10, 21.

Enablement Requirement:

More than just a starting point for iterative research

A claim is not enabled where the specification discloses only a starting point for further iterative research in an unpredictable and poorly understood field. *Wyeth*, 720 F.3d at 1386; *Enzo Life Sciences v. Roche Molecular Sys.*, 928 F.3d 1340, 1345-46 (Fed. Cir. 2019) (where claims require both a particular structure and functionality, no enablement where specification fails to teach which of the many embodiments of the broad claims would exhibit that required functionality of being both hybridizable and detectable upon hybridization). In analyzing undue experimentation, we

Paper 10, 21.

Paper 10 (ID), 21; Pet., 48-52; Pet. Reply, 4-9.

Enablement Requirement:

Amgen:

No enablement for entire ***antibody genus*** even when ***limited to tested epitope***

LDL cholesterol from the blood stream. *Id.* at 4. The patents claimed an “the **entire genus**” of **antibodies** that (1) **“bind to specific amino acid residues on PCSK9,”** and (2) **“block PCSK9 from binding to [LDL receptors].”** *Id.* at 5. The patent specifications **described the relevant antibody by its unique amino acid sequence** and specifically identified the amino acid sequences **of 26 antibodies** that perform the two claimed functions. *Id.* The specification also described two methods for making other antibodies that performed the claimed binding and blocking function. *Id.* at 5–6.

The Court found that patentee’s specifications enabled the 26 exemplary antibodies identified by their amino acid sequences. *Id.* at 15. But found that the patent **failed to enable the broader scope of the claims beyond those specifically disclosed exemplary antibodies.** *Id.*

Paper 10, 24-25.

Salient Enablement Facts Undisputed

Extremely Broad Genus Claims:

Claims 1 and 3–5 of the '505 patent recite methods for treating vitiligo using the entire class of IL-15 inhibitors or the entire class of IL-15 receptor inhibitors. *See* Ex. 1001, 44:12–26. Claim 2 is slightly narrower and limits the inhibitors of claim 1 to “a small molecule inhibitor, an antibody, a peptide inhibitor, or an inhibitory nucleic acid targeting IL-15 or the IL-15 receptor.” *Id.* at 44:18–20. The enablement of such broad “genus claims” was addressed recently by the Supreme Court in *Amgen v. Sanofi*, No. 21-757, 598 U.S. at [REDACTED] (May 18, 2023).

Paper 10, 24.

Paper 10, 24; Pet., 48-51, 54-58, 59-61; Pet. Reply, 3, 11-12, 17-18.

Salient Enablement Facts Undisputed

Entire class of treatment

Functional claims

Two classes of inhibitors

Large variety and number of species that might be used

Neither claims nor specification:

- provide any structural requirement
- Explain how inhibitors structurally related

The facts of the present case are similar to the *Amgen* case. Here, Patent Owner attempts to claim an entire class of treatment based on the function of two classes of inhibitors: inhibitors of IL-15 and inhibitors of the IL-15 receptor. As the Supreme Court in the *Amgen* case stated “the more a party claims, the broader the monopoly it demands, the more it must enable.” *Id.* at 16. Patent Owner explains that the ’505 patent encompasses a “large variety and number of species that ‘might be used to achieve’ vitiligo treatment. Prelim. Resp. 25. In fact, the ’505 patent lists such divergent inhibitors as antibodies, benzoic acid derivatives, and small molecules such as cis-imidazoline analogs and trifluoroacetate. *See* Ex. 1001, 7:34–8:37.

Yet, unlike in *Amgen*, neither the claims nor the specification, provide any structural requirement for the claimed inhibitor. Nor does the ’505 patent explain how these inhibitors are related structurally so that such inhibitors could be identified at an operational level. Specifically, the

Paper 10, 25-26.

Salient Enablement Facts Undisputed

No Sequence

No Structure

No Binding site

No explanation how
binding/blocking of
ChMBC7 is
representative

No demonstration
ChMBC7 targets only IL-
15 signaling

inhibitors could be identified at an operational level. Specifically, the specification here does not provide (1) the sequence or structure that corresponds to the exemplary inhibitor, (2) a purported binding site on the exemplary inhibitor that would correspond to other inhibitors that fall within the scope of the claims, or (3) how the exemplary inhibitor binding to/blocking of IL-15 receptor is representative of the binding/blocking by the 20 inhibitors listed in the specification. *See* Ex. 1001, 7:34–8:37. Moreover, the '505 patent discloses that the beta subunit “is a shared receptor for both IL-2 and IL-15.” *Id.* at 6:3–4. The specification, however, does not explain how the disclosed antibody targets only the IL-15 receptor signaling pathway or why the invention is limited to only IL-15 and IL-15 receptor and not IL-2.

Paper 10, 26.

Paper 10, 26; Pet., 2-3, 54-58, 59-60, 62-63; Pet. Reply, 1, 6-8, 13-14.

Enablement Requires More

True At Institution

Confirmed at Trial

- | | | |
|---|--|---|
| ✓ | Very broad genus claims | ✓ |
| ✓ | Functionally defined | ✓ |
| ✓ | Large variety and number of species that might be used | ✓ |
| | Neither claims nor specification: | |
| ✓ | • Provide any structural requirement | ✓ |
| ✓ | • Explain how inhibitors structurally related | ✓ |
| ✓ | • Provides sequence or structure of ChMBC7 | ✓ |
| ✓ | • Provides binding site | ✓ |
| ✓ | • Explains how ChMBC7 binding/blocking is representative of entire genus | ✓ |
| ✓ | • Demonstrates ChMBC7 targets only IL-15 signaling | ✓ |

Pet., 3-4, 51-52, 54-58, 59-61, 61-63; Pet. Reply, 2-3, 11-12, 12-14; Paper 10, 19, 24-25.

Enablement is lacking under Amgen

As the Board recognized, the facts are similar to *Amgen*: PO claims an entire class of treatment based on the function of two classes of inhibitors.

- But, unlike *Amgen*—where enablement was found for antibodies identified by sequence—the '505 patent fails to provide any structural guidance.
- **No enablement for even the exemplary antibody.**
- **No enablement for antibodies generally.**
- No enablement for the full genus.

Specification does not provide:

- Sequence, structure, or binding epitope of the exemplary inhibitor.
- Purported binding site of exemplary inhibitor corresponding to genus.
- Explanation of how exemplary inhibitor is representative of inhibitors mentioned in specification.
- Explanation of how its antibody selectively targets IL-15 over IL-2 when they share a receptor.

Pet. 48-53; Paper 10, 24-27; *Amgen v. Sanofi*, No. 21-757, 598 U.S. at ____ (May 18, 2023).

Section 112 Challenges Overview

Extremely Broad Claims:

Multiple, Disparate Types of Inhibition

receiving treatment. For example, the claims encompass using any inhibitor of IL-15 or IL-15R (including any of the IL15R α , CD122/ β , or CD132/ γ subunits) and do not even require that the inhibitor physically interact with any of these targets of inhibition. CD122/ β is shared by at least two signaling pathways (IL-2 and IL-15), and CD132/ γ is shared by at least six signaling pathways. The claims thus encompass multiple, disparate types of inhibition.

Pet., 2.

Pet., 2-3, 35-36, 54-58.

Extremely Broad Claims

No (claims 1, 3-5) or almost no (claim 2) structural requirements

- Includes several very broad sub-genera
 - Antibodies
 - Small molecules
 - Peptides
 - Inhibitory Nucleic Acids (i.e., no physical interaction with IL-15 or IL-15R)
- Includes several very broad sub-genera
 - IL-15 inhibitors
 - Inhibitors of the IL-15 Receptor – any subunit: α , β (CD122), or γ (CD132)
 - Dimeric receptor ($\beta\gamma$)
 - Trimeric receptor ($\alpha\beta\gamma$)

Defined purely functionally

- The **number** and **nature** of the compounds implicated is **so large as to be incalculable**.

Pet., 2, 36-39, 54-58; EX1002, ¶¶83-87, 91.

Extremely Broad Claims

Many different genera of inhibition

- Block IL-15 from α
- Block IL-15 alone or + IL-2 from β
- Block IL-15 alone or + 5 from γ
 - IL-2
 - IL-4
 - IL-7
 - IL-9
 - IL-21
- Block IL-15 from β and γ
- Block IL-15 from α , β , and γ
- Block α from β
- Block α from γ
- Block β from γ
- Silence or reduce IL-15
- Silence or reduce α
- Silence or reduce β
- Silence or reduce γ
- Block *cis* only, *trans* only, or both
- Block trimeric, dimeric, or both
- Block downstream effects of IL-15

Pet., 2, 36-39, 54-58; EX1002, ¶¶83-87; Pet. Reply, 4-5; EX1047, ¶¶58-62; EX1046, 162:12-163:25, 165:11-16, 170:25-173:2, 219:24-222:8.

Extremely Broad Claims

Differential Effects

- Different subunits implicate different upstream and downstream pathways
- CD132 inhibition implicates 6 different pathways
 - Inhibits JAK3/STAT5 signaling
 - CD132 knockout results in severe immunodeficiency
- CD122 inhibition implicates 2 different pathways
 - Inhibits JAK1/STAT1 signaling
 - Some CD122 inhibition blocks only trans signaling, only cis signaling, or both
 - CD122 knockout could block expression of Treg cells that help inhibit the autoimmune response that causes vitiligo
- Inhibiting the receptor is not representative of inhibiting IL-15
 - Anti-IL-15 mAbs can enhance IL-15 signaling
 - Soluble IL-15R α can both inhibit and enhance IL-15 signaling

Pet., 30-35, 55-56; EX1002, ¶¶66-69, 70-81; Pet. Reply, 4-9; EX1047, ¶¶10-11, 18, 25-26, 50, 54-55; EX1040, 2; EX1048, 3.

Very Narrow Working Example

The patent does not describe the sequence or structure that corresponds to this antibody code name, does not describe the epitope where this antibody binds CD122 or explain how it inhibits $\beta\gamma$ signaling (e.g., *cis*- and/or *trans*-presentation), and provides no evidence that this antibody specifically inhibits IL-15 signaling (e.g., as opposed to inhibiting IL-2 signaling) or that an Fc-intact

Pet., 27.

Pet., 27, 37, 46-47, 56-61; Pet. Reply, 12-14; EX1002, ¶¶37, 64, 70.

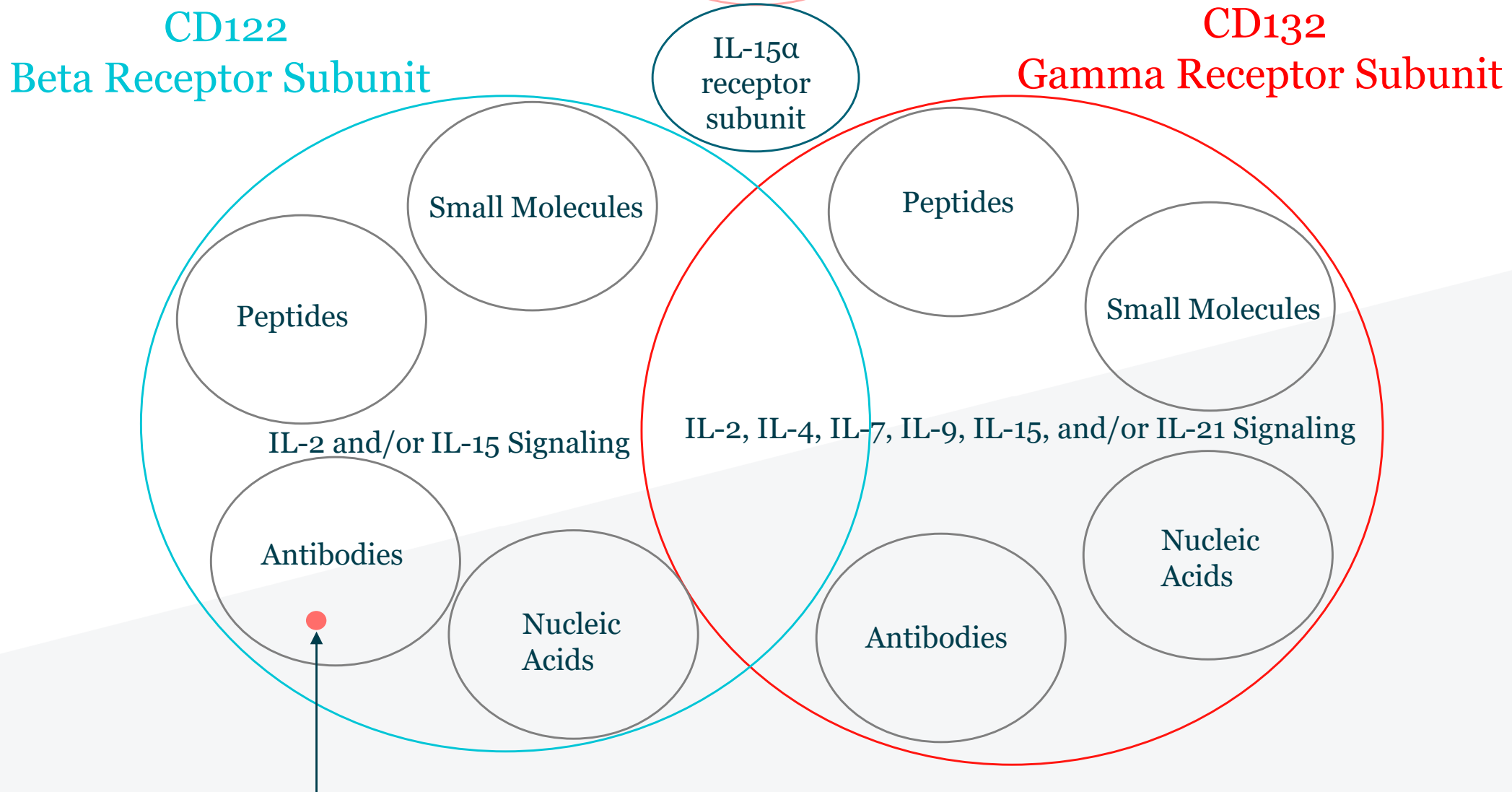
Very Narrow Working Example

antibody inhibition of CD122. But the specification does not disclose the sequence or structure the corresponds to the code name ChMBC7, or even the species of CD122 inhibition performed by ChMBC7. It is merely identified by a code name. EX1002, ¶89. As discussed above in Sections I.A.i, iii and VII.B, CD122 inhibition can inhibit various types of IL-2 signaling, of IL-15 signaling, or both, with varying biological consequences. But the specification does not disclose what species or combination of species of CD122 inhibition were employed to achieve the reported effects. The '505 patent assumes that ChMBC7 inhibits IL-15 binding

Pet., 59.

Pet., 59-61, 27, 37, 46-47; EX1002, ¶¶64, 88-89.

Inhibitor Targets: Broad Claims vs. Narrow Data



Fc-diminished chimeric rat/mouse ChMBC7 anti-CD122 antibody

Pet. 54-61.

Section 112: Broad and Diverse, Functional Genus Claims

Extremely broad claim breadth:

Encompass every inhibitor of IL-15, IL-15R α , β -subunit (CD122, shared with IL-2)

Q So going back to Claim 1. When it says an inhibitor of the IL-15 receptor, do you agree that that includes inhibitors of IL-15 receptor alpha?

A Yes.

Q When Claim 1 says inhibitor of the IL-15 receptor, do you agree that that includes inhibitors of IL-15 receptor beta?

A Yes.

Q And that is also called IL-2 receptor beta?

A Yes.

Q It is also called CD122. Correct?

A Yes.

EX1046 (Damsky Deposition), 170:25-171:12.

Extremely broad claim breadth:

Also encompasses every inhibitor of the γ -subunit (CD132, shared with 6 cytokines)

Q You agree that when Claim 1 recites inhibitor of the IL-15 receptor, that also includes inhibitors of IL-15 receptor gamma?

A Yes.

Q Which is the same as IL-15 -- sorry -- which is the same as IL-4 receptor gamma?

A It is usually referred to as IL-2 receptor gamma.

Q But it could also be called IL-4 receptor gamma?

A I have never seen it referred to like that, but I suppose someone could call it that if they wanted to.

Q Same answer for IL-7?

A If someone wanted to call it that, they could.

Q And IL-9?

A Yes, IL-9 also use that receptor.

Q And IL-21?

A Yes.

Q That is why they call it gamma C, it is gamma common because it is the same receptor for all six of those cytokines. Correct?

A Is that six? Yes.

Q And for each of those, for the gamma -- so I guess we can call gamma also CD132. Right?

A Correct, yes.

EX1046 (Damsky Deposition), 171:13-172:14.

Extremely broad claim breadth:

Encompasses inhibitors of both the dimeric and trimeric IL-15 receptors

So there is both a heterodimeric IL-15 receptor that can be expressed on a T-cell.

Correct?

A Beta gamma, yes.

Q There is also a heterotrimeric IL-15 receptor that can be expressed on a single cell membrane. Correct?

A Yes. But it is not thought to be the predominant mode of signaling, but yes.

Q So in that case for the heterotrimeric receptor that's on a single cell that's alpha, beta and gamma that are associated together on the same cell membrane. Correct?

A Yes, that is my understanding.

Q Okay. And then going back to the claim. In Claim 1, when it says inhibitor of the IL-15 receptor -- when it says the IL-15 receptor, does that include all iterations of the IL-15 receptor or only some of them?

A All of them.

EX1046 (Damsky Deposition), 162:22-163:10, 165:11-16.

Extremely broad claim breadth:

Claims are *much broader* than in Amgen

and let me know. In Claim 1, it could be an antibody. Correct?

A Yes.

Q Claim 1 is not limited to an antibody. Correct?

A Correct.

Q In Claim 1, the inhibitor could be a peptide inhibitor. Correct?

A Yes.

EX1046 (Damsky Deposition), 173:6-14.

Q Yeah. So in Claim 2, it says that the -- the inhibitory nucleic acid must target either IL-15 or the IL-15 receptor. Correct?

A Yes.

Q And you agree that when it talks about targeting the IL-15 receptor, it could be targeting the alpha receptor. Correct?

A Yes.

Q It could be targeting the beta receptor. Correct?

A Yes.

Q It could be targeting the gamma receptor. Correct?

A Yes.

EX1046 (Damsky Deposition), 174:13-175:1.

Extremely Broad Claims

What is claimed is:

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.

Independent claim 1 is unbounded: any potential inhibitor of IL-15 activity.

For example, **any**:

- Small molecule inhibitor of IL-15
- Small molecule inhibitor of IL-15R α .
- Small molecule inhibitor of IL-2/IL-15R β
- Small molecule inhibitor of γ /CD132
- Small molecules binding IL-15R α with concomitant blocking of IL-2R β , and γ /CD132.
- Antibodies binding IL-15
- Antibodies binding IL-15R α
- Antibodies binding IL-2/IL-15R β .
- Antibodies binding γ /CD132.
- Nucleic acids targeting IL-15
- Nucleic acids targeting IL-15R α
- Nucleic acids targeting IL-2/IL-15R β
- Nucleic acids targeting γ /CD132
- Nucleic acids targeting IL-15 mRNAs
- Nucleic acids targeting IL-15 α mRNAs
- Nucleic acids targeting IL-2/IL-15R β mRNAs
- Nucleic acids targeting γ /CD132 mRNAs
- Soluble IL-15 receptor subunit
- Muteins binding IL-15
- Muteins binding IL-15R α
- Muteins binding IL-2/IL-15R β
- Muteins binding γ /CD132
- Mutant IL-15/FC- γ 2a fusion proteins.
- Peptides binding IL-15
- Peptides binding IL-15R α chain.
- Peptides binding IL-2/IL-15R β
- Peptides binding γ /CD132
- Molecules that inhibit IL-15-induced cellular responses (e.g., cefazolin, Y-320, IL-17, JAK/STAT).

Pet., 23-26; Pet. Reply, 4-11, 12-14 EX1001, 7:34-8:37, Claim 1; EX2005, Appendix.

Trial Confirmed Claims Encompass Disparate Effects

The claims encompass inhibiting any one of various types of IL-15 signaling and various versions of the receptor, implicating different results. More than a dozen different genera of inhibition are covered.

Inhibition is complicated and unpredictable. Some inhibitors also were capable of **enhancing** forms of IL-15 signaling.

IL-15 receptor, including newly discovered inhibitors, is incorrect. Dr. Damsky's own deposition testimony illustrates that cytokine signaling, including IL-15 signaling and inhibition thereof, was complex and unpredictable. As illustrated by the same references cited by Dr. Damsky, the effects of a given molecule varied widely depending on its target (e.g., IL-15 vs. IL-15R α vs. IL-15R β vs. IL-15R γ), the variety of IL-15 receptor(s) implicated, the location (i.e., epitope) where the molecule interacts with a given target, and the nature of the specific molecule being used. Indeed, molecules shown to block the interaction of IL-15 with

EX1047 (Plott Reply Declaration), ¶10.

Pet., 30-35; Pet. Reply, 4-9; EX1047, ¶10.

Section 112: Narrow and Limited Working Example

Sole working example

Single working example: ChMBC7 antibody targeting CD122 receptor subunit

Q So in the experiments where they administer an IL-15 or IL-15R receptor in the '505 patent, they are always using the ChMBC7 antibody. Correct?

A Yes.

EX1046 (Damsky Deposition), 225:8-12.

Q Okay. And whether or not the antibodies prevent the binding or not depends on the epitope where the antibodies bind. Correct?

A In general, yes.

Q Okay. So sometimes the antibody that binds to the molecule blocks the interaction, sometimes it doesn't. Correct?

MR. FELDSTEIN: Object to form.

Beyond the scope.

THE WITNESS: There may be examples where it doesn't block signaling.

EX1046 (Damsky Deposition), 207:11-21.

Pet., 59-61; Pet. Reply, 13-14; EX1046, 224:18-225:12, 207:11-21, 225:25-226:8, 230:3-5, 230:6-13.

Limited Disclosure

No Sequence, No Structure, No Epitope.

EX1046 (Damsky Deposition),
225:25-226:8.

So you agree that the '505 patent doesn't tell us the sequence of the ChMBC7 antibody. Correct?

A Yes, correct.

Q And you haven't identified any document incorporated by reference in the '505 patent that -- that you think provides that sequence. Correct?

A Not the specific sequence, but it was known to inhibit IL-15 signaling.

EX1046 (Damsky Deposition),
230:3-5.

Q Same question for the secondary structure. Is your answer the same?

A Yes.

EX1046 (Damsky Deposition),
230:11-13.

Q Does the '505 patent disclose the epitope that ChMBC7 binds to?

A No.

Pet., 51-52, 54, 59-61; Pet. Reply, 13-14; EX1046, 224:18-225:12, 225:25-226:8, 230:3-5, 230:6-13.

Sole working example is narrow and limited

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

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

EX1002 (Abbas Declaration), ¶64.

- Native immune system depleted
- Injected with melanocyte-targeting CD8⁺ T cells from PMEL transgenic mice.
- ChMBC7 mouse CD122 antibody.

Pet., 3-4, 35-36, 48, 59-61; EX1002, ¶64.

Sole working example is narrow and limited

biopsies obtained from human patient study “subjects”). The depigmentation lesions induced in mice in the ’505 patent by priming CD8⁺ effector T cells to attack melanocytes and transferring them to the mice are not representative of natural or spontaneous vitiligo in a human patient. Transferring activated and targeted CD8⁺ effector cells into the body is not how vitiligo naturally or spontaneously develops in a human patient. The ’505 patent’s experiments provide a POSA with little to no understanding of what might happen when using an IL-15 inhibitor or an IL-15R inhibitor in humans having vitiligo lesions. The ’505 patent merely invites a POSA to undertake a research project in treating natural or spontaneous vitiligo outside the mouse model. It does not convey invention of using IL-15 or IL-15R inhibition to treat a human patient who has a vitiligo lesion.

EX1002, ¶62.

Pet., 29, 39-41, 50-51, 57-58, 59-63; EX1002, ¶¶62-63, 83-85.

The '505 Patent's (many) deficiencies

- Black box disclosure is prohibitively limiting.
 - Specification's sole working example: ChMBC7 in Harris mice.
 - No other antibody, small molecule, protein, etc., were evaluated.

THE WITNESS: Because they work in completely different ways. The antibody blocks the receptor. The interfering RNA blocks the expression of the receptor. We have no idea whether they'll have the same effect or not.

EX2007 (Dr. Abbas Deposition), 93:16-97:25

- Recitation of additional molecules cannot fix the specification.
 - Patent fails to show ChMBC7 inhibition is representative of genus.
 - Fails to demonstrate what structural features are necessary or sufficient to perform the claimed method.

Pet., 16, 30; Pet. Reply, 12-17; Paper 10 (ID), 19, 25-26.

The '505 Patent's (many) deficiencies

- Other inhibitors cannot salvage the claims. The specification fails to disclose:
 - Any structural requirement for the claimed inhibitors
 - The sequence or structure corresponding with ChMBC7
 - The binding site for ChMBC7
 - How ChMBC7 binds to or blocks IL-15 receptors and how this is representative of the full genus
 - How ChMBC7 targets only IL-15 signaling (rather than, e.g., IL-2).

53. The specification of the '505 patent is essentially a black box (so far as which aspects of IL-15 signaling it inhibits and how it operates), leaving the reader to guess through trial and error which molecules might operate similarly to ChMBC7 and which do not. Dr. Damsky attempts to sidestep this problem by

EX1047 (Plott Reply Declaration), ¶53.

Pet., 48-53; Pet. Reply, 12-17; Paper 10 (ID), 25-26.

Testing one compound in Harris mouse model does not save Patent Owner's broad claims

The '505 patent never evaluated the effects of IL-15 or IL-15R inhibitors in natural or spontaneous vitiligo.

- Small subsets of patients do not represent a treatment genus. *United*, 1370-71.
- The Harris mouse model is of limited value: it produces vitiligo lesions using simplified pathogenesis (radiation-induced immunodeficiency + PMEL-targeting CD8+ T cell transfer)
- Harris model not illustrative of depigmentation in natural vitiligo.
- There are numerous causes of vitiligo with no singularly true mechanism; pathogenesis was elusive.

THE WITNESS: It's improper to extrapolate from this mouse model to the human situation -- to the human disease.

EX2007 (Abbas Deposition), 38:2-8.

Pet., 2-4, 3-41, 57-58, 59-61; Pet. Reply, 12-17; *United Therapeutics Corp. v. Liquidia Techs.*, 74 F.4th 1360 (Fed. Cir. 2023)

Trial and Error Process

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

EX1004 (Plott Declaration), ¶36.

Pet., 5-6, 53-63; EX1004, ¶¶33-36; EX1002, ¶¶41-42.

Trial and Error Process

Q I am going to go ahead and play the video.

(Video played as follows:)

DR. DAMSKY: There is a proof of concept study that is underway now looking at IL-15 blockade in patients with vitiligo. And we have all got our fingers crossed that it is going to work.

* * *

EX1046 (Damsky Deposition),
234:20-236:11.

DR. DAMSKY: The point about IL-15 and memory I think is an interesting one, because one can conceive of if you were able to turn off that memory response, that you may not be only looking at treatment for vitiligo, but you -- maybe you're looking at long-lasting treatment.

BY MR. MILLS:

Q So do you dispute that you said those words to Dr. Desai on December 14th, 2021?

* * *

THE WITNESS: If that is the date. I can't see it. No. No.

BY MR. MILLS:

Q Thank you.

Pet. Reply, 9; EX1046, 232:5-236:11; EX1047, ¶11; EX1046, 234:20-236:11.

Indeterminate Genus: Not Just the Claimed Targets

There was no recognized genus

Dr. Damsky and the '505 patent: **Anything** that inhibits a biological effect (IL-15-induced cellular response) of IL-15 or its receptor

described in WO2014191823 A1. In some embodiments, the therapeutic molecule to be administered comprises a small molecule inhibitor of IL-15-induced cellular responses, e.g., cefazolin as described in US20160235762 A1 and Y-320 (Ushio, 2008). In some embodiments, the therapeutic mol-

EX1001, 7:40-44.

Q I want to focus on the words "an inhibitor of IL-15."

A Uh-huh.

Q What is that -- what does it mean, an inhibitor of IL-15?

* * *

THE WITNESS: My summary would be that it inhibits the biologic effect of IL-15 or its receptor.

BY MR. MILLS:

Q Is JAK signaling a biological effect of IL-15?

A It can be.

EX1046 (Damsky Deposition), 156:9-21.

Pet. Reply, 11-12; EX1047, ¶¶65-68; EX1046, 156:9-21; EX1001, 7:40-44.

Inhibitors of IL-15-induced cellular responses

The patent considered Y-320, Ro26-4550, SP4206, ABT-737, Nutline-2 and Compound 3 to be IL-15 inhibitors even though they act on different targets.

68. On the other extreme, Dr. Damsky also appears to include within the scope of the claim the use of molecules whose predominant mode of action is not through any direct action on IL-15 or the IL-15 receptors. For example, the '505 patent sweeps in compounds that inhibit microbial activity, IL-2, IL-17, Bcl-xL, or MDM2. EX1001, 7:40-45 (citing EX2015 for cefazolin and Ushio 2008, EX2016, for Y-320), 7:60-64 (citing EX2022 for Ro26-4550, SP4206, ABT-737, Nutlin-2, and compound 3); EX1046, 259:7-261:19 (ABT-737 and Nutlin-2 inhibit Bcl-xL and MDM2, respectively, neither of which are directly a component of the IL-15 or IL-2 receptors); EX2022, 36 (Ro26-4550 inhibits IL-2:IL-2R α interaction), 41 (SP4206 and compound 3 are IL-2 antagonists), 46-47 (ABT-737 and Nutlin-2 inhibit Bcl-xL and MDM2).

EX1047 (Plott Reply Declaration), ¶68.

Pet. Reply, 11-12; EX2005, ¶71; EX1047, ¶68.

Inhibitors of IL-15-induced cellular responses

Though Dr. Damsky considered the broad-spectrum antibiotic Cefazolin to be an IL-15 inhibitor, he was unable to answer whether administering Cefazolin to a patient diagnosed with vitiligo would satisfy the claims.

Q So Cefazolin is, in your opinion, an IL-15 inhibitor. Correct?

A Yes.

Q Cefazolin also is an IL-2 inhibitor. Correct?

A Based on these experiments, it is to a lesser extent, yes.

Q It also has a third functionality for which it is much more famous, and that's inhibiting activity of bacteria. Is that correct?

A That would be the predominant clinical use.

EX1046 (Damsky Deposition), 254:4-15

Q So the question is, does it satisfy the two steps of the claim? So that -- you identify that the patient has vitiligo and then you administer the Cefazolin. Does that satisfy the steps of the claim?

* * *

THE WITNESS: I am not sure.

EX1046 (Damsky Deposition), 254:16-255:11

Pet. Reply, 10-12; EX2005, ¶71; EX1001, 7:40-44; EX1047, ¶69; EX1046, 254:4-255:11.

Inhibitors of IL-15-induced cellular responses

Dr. Damsky was unable to answer whether prior art JAK 1/3 Inhibitor tofacitinib falls within the claimed class.

Q Tofacitinib inhibits JAK1 and 3. Is that correct?

A And, to some extent, 2, yes.

Q Let's ask the questions about tofacitinib. Is tofacitinib an inhibitor of IL-15 within the meaning of Claim 1?

THE WITNESS: It is really complicated. I don't know that we can assume that. I think the field would suggest that the predominant mode of action was through interferon gamma.

Q So you agree that JAK1, 3 signaling is a downstream effect of IL-15. Correct?

A Yes, but the inhibitory concentrations of each JAK inhibitor for various cytokines downstream of various JAKs is variable.

Q So as you sit here today, your testimony is that tofacitinib may or may not be an inhibitor of IL-15?

THE WITNESS: I think it is hard to have a generic discussion. It would depend on the context.

BY MR. MILLS:

Q On what context would it depend?

A Which JAK inhibitor.

Q I think we were talking about tofacitinib.

A Tofacitinib, what dose it was used at.

Q Can you definitively rule out tofacitinib as qualifying under the category of inhibitor of IL-15 as used in Claim 1 of the '505 patent?

THE WITNESS: I would just say IL-15 was known to use the JAK-STAT pathway. It would have to be evaluated.

EX1046 (Damsky Deposition), 158:12-160:20

Pet. Reply, 8-9, 10, 11-12; EX1046, 158:12-160:20.

There was no recognized genus

Dr. Damsky, can you tell by looking at a molecule whether it is an IL-15 inhibitor?

A When you say look at it, you are referring to the chemical structure?

Q Right.

A No.

EX1046 (Damsky Deposition), 236:12-24

Q Okay. What assay is left? So we have done the binding assay. We have done an in vitro assay. It is highly suggestive. But at this point, we are still not sure whether it is an inhibitor within the scope of Claim 1. So what else do we do to tell us whether it is an inhibitor within the scope of Claim 1?

A I mean, I think people would approach it in a variety of directions. I wouldn't say there is an absolute standard.

EX1046 (Damsky Deposition), 197:12-21

Structure Is Not Enough

No absolute standard for determining whether a molecule that blocks in binding and in vitro proliferation assays are encompassed by the claims.

Pet. Reply, 11-12; EX1046, 197:12-21, 236:12-24.

Section 112: The Wands Factors

Undue experimentation under Wands

Consistent with *Amgen*, the eight *Wands* factors support finding a lack of enablement.

- ☐ Factors 4 and 5: nature of claims and state of the art.
- ☐ Factor 8: breadth of the claims.
- ☐ Factors 2 and 3: guidance and working examples.
- ☐ Factors 1 and 7: experimentation necessary and unpredictability of the art.
- ☐ Factor 6: relative skill of those in the art.

Pet., 53-63.

Undue experimentation under Wands

☑ Factors 4 and 5: nature of claims and state of the art.

Complex claims: treating vitiligo across genus of subjects with inhibitors of unpredictable, biologically complicated cytokine signaling pathways.

State of art as of the critical date:
nascent.

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

EX1004 (Plott Declaration), ¶59.

84. Treating vitiligo in subjects ranging from mouse models to actual humans with vitiligo was very complex and unpredictable at the critical date. The idea of using cytokine signaling to treat vitiligo was just at its very earliest of stages (e.g., mouse models in which vitiligo-like lesions were induced by priming CD8⁺ effector T cells to attack melanocytes and implanting them into the mouse). Moreover, cytokine signaling pathways were complex, biologically unpredictable, and often misunderstood.

EX1002 (Abbas Declaration), ¶84.

Pet., 53-54.

Undue experimentation under Wands

☑ Factor 8: breadth of the claims.

Extremely broad claims cover:

- Multiple sub-genera of **inhibitory pathways** (IL-15, IL-15R α , CD122, CD132)
- Multiple genera of **type of potential inhibitors**
- Broad and disparate genus of **subjects** implicated
- As little as **1% inhibition**
- No requirement to preferentially, exclusively, **specifically, or physically inhibit** IL-15 or IL-15R (as opposed to e.g. IL-2)

57. The claims are very broad at least because they encompass treating natural or spontaneous vitiligo, which are complex diseases, in addition to simply treating the depigmentation lesions in the mouse model described in the '505 patent. They also were broad because they claim all inhibitors of IL-15 or IL-15 receptor, when a POSA would not extrapolate from their mouse study to the entire class of IL-15/IL-15 receptor inhibition. There was no consensus among practitioners that there was a class wide property of IL-15 and IL-15 receptor inhibitors for treating vitiligo.

EX1004 (Plott Declaration), ¶57.

Pet., 54-58; EX1046, 246:14-21; EX1047, ¶51; EX1002 (Abbas Declaration), ¶¶85-87; Pet. Reply, 14.

Undue experimentation under Wands

☑ Factor 8: breadth of the claims.

85. The claims of the '505 patent are much broader than what the applicant can claim to have invented. As explained above, the claims encompass administration to any subject, including humans having natural or spontaneous vitiligo, but the specification only discloses administering the mouse CD122

86. As I also explained above, the claims are very broad because they encompass inhibition of any of the IL-15R α , CD122, or CD132 subunits in a variety of different ways. As I explained above, each of these four sub-genera of

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

EX1002 (Abbas Declaration), ¶¶85-87.

Pet., 54-58.

Undue experimentation under Wands

☑ Factors 2 and 3: guidance and working examples.

Sparse guidance: merely raises research question of whether any form of inhibitor other than ChMBC7 could treat vitiligo.

Sole working example: mice induced with vitiligo-like lesions by priming CD8⁺ effector T cells to attack melanocytes.

Sole working example: mice treated with ChMBC7 antibody: unknown sequence, structure, or means of inhibition.

natural or spontaneous vitiligo in a human patient. Transferring activated and targeted CD8⁺ effector cells into the body is not how vitiligo naturally or spontaneously develops in a human patient. The '505 patent's experiments provide a POSA with little to no understanding of what might happen when using an IL-15 inhibitor or an IL-15R inhibitor in humans having vitiligo lesions. The '505 patent merely invites a POSA to undertake a research project in treating natural or spontaneous vitiligo outside the mouse model. It does not convey invention of using IL-15 or IL-15R inhibition to treat a human patient who has a vitiligo lesion.

EX1002 (Abbas Declaration), ¶62.

Pet., 59-61.

Undue experimentation under Wands

- ☑ Factors 2 and 3: guidance and working examples.

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

EX1004 (Plott Declaration), ¶58.

Pet., 59-61.

Undue experimentation under Wands

☑ Factors 1 and 7: experimentation necessary and unpredictability of the art.

Experimentation necessary: no evidence given for what combination of characteristics of ChMBC7 make it useful for treating induced mouse lesions: **must individually test** potential inhibitors.

Unpredictability: even small structural changes can have a large and disparate effect on biological function.

Trial and error: the only way to iteratively screen through compounds to determine whether they work.

90. Because the specification provides no evidence as to what specifically made it useful for treating CD8⁺T cell-induced depigmentation lesions in mice, the only way to determine whether other forms of inhibition claimed by the '505 patent would achieve the desired result even in the mouse would be to individually test them. Even very small changes to the structure of a compound (e.g., small molecule or antibody) can have very large and disparate effects on biological function. Accordingly, a POSA would have to synthesize and screen each new candidate compound through an iterative, trial-and-error process to determine whether they work or not. Even testing the candidate compounds identified in the specification would take months,

EX1002 (Abbas Declaration), ¶90.

Pet., 61-63.

Undue experimentation under Wands

□ (neutral) Factor 6: relative skill of those in the art.

POSA: high level of education and experience.

However: that knowledge, training, and experience would not overcome the lack of guidance, complexity of the invention, nascency of the field, unpredictability of the art, and overly broad claims.

93. A POSA's education, knowledge, training, and experience would not provide the guidance necessary to overcome the lack of guidance in the specification, the complexity of the invention, the nascency of the field, and the unpredictability of the art, and enable them to make a use the broad and functionally defined genus in the claims.

EX1002 (Abbas Declaration), ¶93.

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

EX1004 (Plott Declaration), ¶61.

Pet., 63.

Undue experimentation under Wands

Consistent with *Amgen*, the eight *Wands* factors support finding a lack of enablement.

- ☒ Factors 4 and 5: nature of claims and state of the art.
- ☒ Factor 8: breadth of the claims.
- ☒ Factors 2 and 3: guidance and working examples.
- ☒ Factors 1 and 7: experimentation necessary and unpredictability of the art.
- ☐ (neutral) Factor 6: relative skill of those in the art.

Pet., 53-63.

Ground 3: Obviousness

Xing and Harris render the claims obvious

mouse model of alopecia areata. EX1002, ¶98. A POSA would have had good reason to administer Xing's CD122 antibody (i.e., TM-β1) in Harris's mouse model of vitiligo because Harris expressly suggests that preventing autoreactive CD8⁺ T cell accumulation in the skin has therapeutic potential for treating vitiligo. EX1002, ¶99. Furthermore, a POSA would have wanted to reduce the number of autoreactive CD8⁺ T cells because these cells were known to cause destruction of melanocytes in the mouse model. *E.g.*, EX1006, 1869 (explaining that autoreactive CD8⁺ T cells have a "direct role...in melanocyte destruction"), 1870 (explaining that "prevent[ing] CD8⁺ T cell accumulation in the skin" has "therapeutic potential" for vitiligo); *see also* EX1008, 786 ("CD8⁺ T cells are both necessary and sufficient for melanocyte destruction in vitiligo...."), 787 ("[C]ytotoxic CD8⁺ T cells[] play[] a key role in the destruction of melanocytes in vitiligo (21) and hair loss in alopecia areata."); EX1002, ¶100.

Pet., 67.

Xing (EX1007):
administering TM-β1
CD122 antibody
prevented accumulation
and maintenance of
autoreactive CD8⁺
cytotoxic T cells in
mouse skin.

Harris (EX1006):
simplified mouse model in
which PMEL-targeting
autoreactive CD8⁺
cytotoxic T cells are
necessary and sufficient
for vitiligo lesions.

Pet., 64-74, 67; Pet. Reply, 22-23; EX1007; EX1008.

Obvious to treat Harris Mice with TM- β 1 antibody

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

99. In my opinion, a POSA would have been motivated to evaluate Xing's CD122 antibody (i.e., TM- β 1) in the mouse model of vitiligo because Harris expressly suggests that preventing autoreactive CD8⁺ T cell accumulation in the skin has therapeutic potential for treating vitiligo.

EX1002 (Abbas Declaration), ¶¶98-99.

Pet., 64-74; Pet. Reply, 22-23.

Obvious to treat Harris Mice with TM-β1 antibody

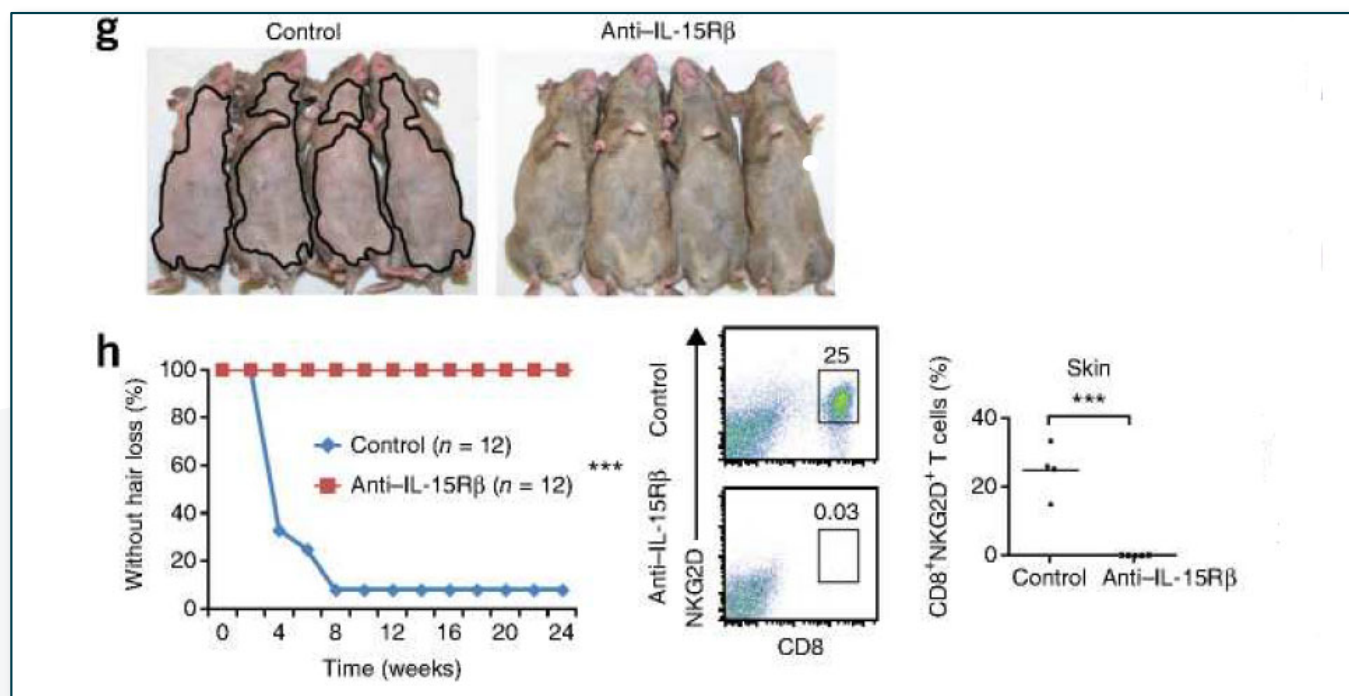
34. The use of specific CD122 antibodies in a CD8⁺-dependent mouse model of autoimmune skin lesions to treat autoimmune skin lesions by depleting CD8⁺ T cells was known in the art (e.g., EX1007) and also was obvious to a person of ordinary skill in the art (POSA) at the relevant time. Because the transference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

EX1004 (Plott Declaration), ¶34.

Pet., 64-74; Pet. Reply, 22-23.

Xing Discloses TM- β 1 CD8+ T cell Effect in Mouse Skin

- IL-15 is implicated in both the induction and maintenance of autoreactive CD8+ T cells.
- AA induced by placing skin grafts from mice with spontaneous AA onto the backs of unaffected C3H/HeJ mice.
- Blocking antibodies to IL-2 or IL-15R β (TM- β 1) prevented AA in grafted mice, blocked the accumulation of CD8+NKG2D+ T cells in the skin and abrogated MHC upregulation

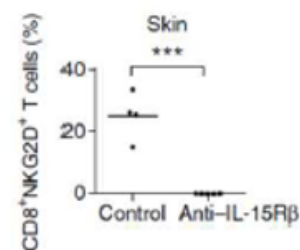


EX1007 (Xing), Fig. 2

EX1007, 3-4, 8 & Fig. 2; Pet., 64-74; see also EX1002, ¶104; EX1027 (Trm).

Obvious to treat Harris Mice with TM- β 1 antibody

101. Xing teaches that administration of the TM- β 1 antibody to mice reduces the number of CD8⁺ T cells in the skin. EX1007, Abstract, 4, 8, Figure 2h (reproduced in part herein), i. Accordingly, it is my opinion that a POSA would have been motivated to treat the mice lesions with TM- β 1 to reduce the autoreactive Trm cells in the skin that cause the melanocyte destruction in the mouse model.



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

EX1002 (Abbas Declaration), ¶¶101-02.

Obvious to treat Harris Mice with TM- β 1 antibody

THE WITNESS: It's relevant because in the Harris mouse model, the only T cells that are present are the CD8 T cells. That's what's being put into the mouse. So if you get rid of them, you'll cure the disease. To me, this is a -- this is a completely predictable result.

EX2007 (Abbas Deposition), 93:9-14;
see also EX1002, ¶36.

Q If we are talking about PMEL antigen specific CD8 positive T cells, are those T regulatory cells?

A No.

EX1046 (Damsky Deposition), 169:22-170:3.

2005) to induce vitiligo in our system. Naïve CD8⁺ T cells from the spleens of PMEL TCR transgenic mice were purified by negative selection, and one million cells were transferred intravenously into sublethally irradiated (500 rads) Krt14-Kitl* hosts. To track PMEL CD8⁺ T cells after transfer, PMEL TCR

EX1006 (Harris), 1870.

Pet., 64-74; EX1002, ¶¶98-99; Pet. Reply, 8, 23; EX1047, ¶45; EX1006, 1870.

No Secondary Considerations

- Patent never demonstrates lesion reversal natural or spontaneous vitiligo
 - No satisfaction of long-felt need
 - No commercial success
- Claims do not recite durable repigmentation
- Harris mice simplified cause (CD8+ T cells) so durably reversing with TM- β 1 was expected
- Dr. Damsky said repigmentation is natural when the cause of the vitiligo is addressed (EX1046, 121:17-128:2)
- No copying of a black box

Pet. Reply, 12-14, 24-25; Pet., 15-17, 59, 64-65.