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Paper No. 14
Entered: February 15, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANOFI-AVENTIS U.S. LLC, GENZYME CORP., and
REGENERON PHARMACEUTICALS, INC.,
Petitioner,

v.

IMMUNEX CORPORATION,
Patent Owner.

Case IPR2017-01884
Patent 8,679,487 B2

Before JAMES T. MOORE, GRACE KARAFFA OBERMANN, and TINA E. HULSE, *Administrative Patent Judges*.

HULSE, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Sanofi-Aventis U.S. LLC, Genzyme Corp., and Regeneron Pharmaceuticals, Inc. (collectively, "Petitioner") filed a Petition requesting an *inter partes* review of claims 1–17 of U.S. Patent No. 8,679,487 B2 (Ex. 1001, "the '487 patent"). Paper 1 ("Pet."). Immunex Corporation ("Patent Owner") filed a Preliminary Response to the Petition. Paper 10 ("Prelim. Resp."). With our authorization, Petitioner filed a Reply to the Preliminary Response (Paper 12, "Reply"), and Patent Owner filed a Surreply (Paper 13, "Surreply").

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon considering the Petition and Preliminary Response, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–17 of the '487 patent. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

Patent Owner has asserted the '487 patent against Petitioner in a pending lawsuit styled *Immunex Corp. v. Sanofi*, No. 17-cv-02613 (C.D. Cal., filed Apr. 5, 2017). Pet. 4; Paper 7, 2.

Petitioner has also filed a petition for *inter partes* review of the '487 patent on different grounds in IPR2017-01879. Pet. 4; Paper 7, 2.

Patent Owner also identifies certain applications and patents that "claim or may claim the benefit of the priority of the filing date of [the '487 patent]." Paper 7, 1–2.

B. The ’487 Patent

The ’487 patent relates to compositions and methods for treating certain conditions induced by interleukin-4 (IL-4) by administering an IL-4 antagonist to a patient with such a condition. Ex. 1001, 3:9–14. IL-4 has a broad spectrum of biological activities, including growth of co-stimulation of T cells, mast cells, granulocytes, megakaryocytes, and erythrocytes. *Id.* at 1:29–36. IL-4 binds to specific cell surface receptors called interleukin-4 receptors (IL-4R). *Id.* at 1:49–51. Binding of IL-4 to IL-4R results in transduction of a biological signal to cells, such as various immune effector cells. *Id.* IL-4 has been implicated in a number of disorders, including allergy and asthma. *Id.* at 2:1–2, 4:11–31.

Different IL-4 antagonists may act at different sites or by different mechanisms of action. *Id.* at 10:47–48. According to the ’487 patent, examples include antagonists that interfere with binding of IL-4 to cell surface receptors or that inhibit signal transduction. *Id.* at 10:48–50. The site of action may be intracellular, on a cell surface, or extracellular. *Id.* at 10:50–53. Antagonists may bind to either IL-4 or to the receptor. *Id.* at 10:53–54. Examples of IL-4 antagonists include IL-4 receptors, antibodies that bind to IL-4 or IL-4R, other IL-4 binding molecules, and IL-4 muteins. *Id.* at 10:36–38.

Blocking antibodies that interfere with the binding of IL-4 to IL-4R may be raised against either IL-4 or IL-4R. The antibodies can be screened in conventional assays for their ability to interfere with binding of IL-4 to IL-4R. *Id.* at 18:40–45. Because it has been found that IL-4R is a component of certain multi-subunit IL-13 receptor complexes, some antibodies raised against IL-4R may interfere with the binding of IL-13 to those complexes. *Id.* at 18:50–57. Those antibodies may inhibit both IL-4

induced biological activity and IL-13 induced activity and therefore may be used in treating conditions induced by either or both cytokines. *Id.* at 18:58–62. Such conditions include IgE-mediated conditions, asthma, allergic conditions, allergic rhinitis, and dermatitis. *Id.* at 18:62–65.

The ’487 patent identifies examples of IL-4R human monoclonal antibodies (MAbs) produced by immunizing transgenic mice. The examples are designated MAbs 6-2, 12B5, 63, 1B7, 5A1, and 27A1. *Id.* at 21:6–11. MAbs 12B5, 63, and 1B7 are preferred fully human antibodies capable of inhibiting activity of both IL-4 and IL-13. *Id.* at 21:11–15.

The ’487 patent presents the encoded amino acid sequence of the variable region of the light chain Mab 12B5 in SEQ ID NO:10, and of the variable region of the heavy chain in SEQ ID NO:12. *Id.* at 22:36–41.

C. Illustrative Claim

Petitioner challenges claims 1–17 of the ’487 patent, of which claim 1 is the only independent claims. Claim 1 is illustrative and is reproduced below:

> 1. An isolated human antibody that competes with a reference antibody for binding to human IL-4 interleukin-4 (IL-4) receptor, wherein the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12.

Ex. 1001, 77:26–31.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–17 of the '487 patent on the following grounds:

References	Basis	Claims challenged
Hart[1] and Schering-Plough[2]	§ 103(a)	1–17
Hart, Schering-Plough, and Hoogenboom[3]	§ 103(a)	1–17

Petitioner relies on the Declaration of Gerard Zurawski, Ph.D. (Ex. 1400) to support its challenge.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art would have had at least a Ph.D. or an M.D. with research experience in immunology, biochemistry, cell biology, molecular biology, or a related field or at least 2–3 years of professional experience in one or more of those fields. Pet. 35. According to Petitioner, such a person would have had an understanding of "how one generates antibodies to a chosen antigen from animals (*e.g.*, mice), and how one isolates human antibodies by generating human antibodies directly from transgenic animals or transforming animal antibodies into human antibodies." *Id.* (citing Ex. 1400 ¶ 27).

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[1] Hart et al., *Diminished Responses to IL-13 by Human Monocytes Differentiated* in vitro*: Role of the IL13Rα1 chain and STAT6*, 29 EUR. J. IMMUNOL. 2087–97 (1999) ("Hart," Ex. 1204).
[2] Galizzi et al, EP 0 604 693 A1, published July 6, 1994 ("Schering-Plough," Ex. 1007).
[3] Hoogenboom, et al. US 5,565,332, issued Oct. 15, 1996 ("Hoogenboom," Ex. 1402).

Patent Owner contends that a person of ordinary skill in the field of immunology would have had skills relating to that field, including the design and generation of antibodies, knowledge of laboratory techniques and strategies used in immunology research and their practical applications. Prelim. Resp. 38 (citing Ex. 2101 ¶ 14). Patent Owner further asserts that a person of ordinary skill in the art would have typically had an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, or a related discipline, with at least two years of experience in the field. *Id.*

On this record, we do not discern a substantive difference between the parties' definitions of the level of ordinary skill in the art, which we find to be high as stated. Neither declarant indicates that any proffered opinion would change, moreover, depending on the level of ordinary skill in that art. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we generally give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the

time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "human"

Each of the claims of the '487 patent recites an isolated "human antibody." According to Petitioner, the broadest reasonable interpretation of "human" is "partially or fully human." Pet. 20–21. Patent Owner disagrees, asserting that construing "human" to mean "partially or fully human" is unreasonably broad in light of the intrinsic evidence. Prelim. Resp. 39–45. Patent Owner contends that "human" should be construed to mean "antibodies in which the amino acid sequence is consistent with the amino acid sequences of antibodies produced by the human immune system." *Id.* at 40 (citing Ex. 2101 ¶¶ 15–19).

On this record, we find Petitioner has the better position. Both parties argue the '487 patent specification supports their respective constructions. In reviewing the '487 patent, we find the specification uses the term "human antibodies" to refer interchangeably to "fully human" antibodies specifically, and to a broader category of antibodies that are partially or fully human. For example, Patent Owner is correct that the abstract refers to "human antibodies" that are "generated by procedures involving immunization of transgenic mice." Prelim. Resp. 40–41 (citing Ex. 1001, Abstract). The specification also states that anti-IL-5 antibodies can be "a human or humanized anti-IL-5 monoclonal antibody." Ex. 1001, 31:31–33.

As Petitioner notes, however, the specification teaches that "[a]ntibodies of the invention include, but are not limited to, partially human (preferably fully human) monoclonal antibodies." Pet. 20 (quoting

Ex. 1001, 20:57–59); *see also* Ex. 1001, 21:1–2 ("The desired antibodies are at least partially human, and preferably fully human."). Patent Owner argues that the language cited by Petitioner only demonstrates that the specification contemplated antibodies with "varying degrees of human-derived sequence content" and "does not indicate that the term 'human antibody' without any modifier should mean anything other than the plain and ordinary meaning of 'human antibody.'" Prelim. Resp. 43–44.

We disagree based on the record presented at this stage of the proceeding. We note that the specification also states: "Procedures have been developed for generating *human antibodies* in non-human animals. The antibodies may be partially human, or preferably completely human." Ex. 1001, 19:41–44 (emphasis added). Thus, at least in this instance, the specification broadly teaches that the "human antibodies" generated can be "partially human" or "completely human."

Patent Owner also cites dependent claim 39 from the prosecution history of the parent application of the '487 patent, which recites "wherein said isolated antibody is a human, partially human, humanized, or chimeric antibody." Prelim. Resp. 42–43 (citing Ex. 2105, 139 (claim 39 of U.S. App. No. 12/291,702)). According to Patent Owner, this demonstrates that "human antibodies" are a distinct category from "humanized antibodies." *Id.* at 43. We note, however, that Patent Owner has also asserted that "humanized antibodies are only partially human antibodies." Prelim. Resp. 41. Thus, if "humanized antibodies" are "partially human antibodies," the distinction between the various categories of antibodies recited in claim 39 becomes less clear. In view of that lack of clarity, we are not persuaded on this record that the cited portion of the prosecution history of

the parent application supports an adoption of the narrower construction of "human" advanced by Patent Owner.

Patent Owner also cites the testimony of its declarant, Dr. Wayne A. Marasco, M.D., Ph.D. as support, stating the convention in the field had been to refer to antibodies by their species of origin. Ex. 2101 ¶ 17. Patent Owner's extrinsic evidence, however, is less persuasive than the intrinsic evidence of the specification discussed above.

Accordingly, on this record, we determine that the broadest reasonable interpretation of the term "human antibody" includes both partially human and fully human antibodies.

2. "antibody"

Petitioner asserts the broadest reasonable interpretation of "antibody" as set forth in the '487 patent specification "encompass[es] both whole antibodies and antigen-binding fragments thereof." *Id.* at 22 (quoting Ex. 1001, 19:18–20). Patent Owner argues we should deny institution, as we did in IPR2017-01129, because Petitioner again fails to explain its inconsistent claim construction positions taken in district court litigation, including its assertion that 35 U.S.C. § 112 ¶ 6 should apply to the construction of "antibody." Prelim. Resp. 29–37.

Although we remain troubled by Petitioner's failure to notify us of its litigation position regarding whether § 112, ¶ 6 applies to the term "antibody," we decline to deny institution on this basis. We denied institution in the prior proceeding for a variety of reasons that, taken

together, justified denying the petition.[4] IPR2017-01129, slip op. at 14 (PTAB Oct. 4, 2017) (Paper 19).

Here, we find the '487 patent specification sets forth the definition of "antibody" with reasonable clarity, deliberateness, and precision. Specifically, the specification defines "the terms 'antibody' and 'monoclonal antibody' as used herein [to] encompass both whole antibodies and antigen-binding fragments thereof." Ex. 1001, 19:18–20.

Thus, on this specific record, we construe the term "antibody" consistently with the specification's express definition.

C. Whether to Exercise Our Discretion to Deny Institution

As an initial matter, Patent Owner argues that we should exercise our discretion under 35 U.S.C. §§ 314(a) or 325(d) to deny institution. For the reasons discussed below, we decline to do so under the facts of this case.

1. 35 U.S.C. § 314(a)

The Director has discretion whether to institute *inter partes* review under 35 U.S.C. § 314(a). *See* 35 U.S.C. § 314(a) (stating "[t]he Director *may not* authorize an inter partes review to be instituted . . . .") (emphasis added). As set forth in *General Plastic Industrial Co. v. Canon Kabushiki Kaisha*, IPR2016-01357 (PTAB Sept. 6, 2017) (Paper 19) (precedential), the Board has consistently considered a number of factors when determining whether to exercise that discretion. *Id.* at 15–16. Those seven factors include whether the same petitioner previously filed a petition directed to the

[4] Similarly, the panel in *Facebook, Inc. v. Sound View Innovations, LLC*, IPR2017-00998 (PTAB Sept. 5, 2017) (Paper 13) declined to institute trial in view of both the district court's determination that the challenged claim is indefinite and the petitioner's failure to inform the Board of its inconsistent § 112, ¶ 6 position before the district court. Slip op. at 18.

same claims of the same patent, whether the petitioner knew of the prior art asserted in the second petition when filing the first petition, and whether at the time of filing the second petition, the petitioner already received the patent owner's preliminary response to the first petition. *Id.* at 16. We noted, however, that there is no *per se* rule precluding the filing of follow-on petitions and that the list of factors to consider is non-exhaustive. *See id.* at 15–16; *see also id.* at 18 ("We recognize that there may be circumstances where multiple petitions by the same petitioner against the same claims of a patent should be permitted, and that such a determination is dependent on the facts at issue in the case.").

The instant Petition represents Petitioner's third challenge to the claims of the '487 patent. Petitioner filed its first petition on March 23, 2017, in IPR2017-01129 challenging claims 1–17 of the '487 patent. In that petition, Petitioner argued the claims of the '487 patent were anticipated by the prior art because the claims were not entitled to the benefit of their earliest effective filing date. We denied institution, finding Petitioner had not sufficiently made that showing. IPR2017-01129, slip op. at 14 (PTAB Oct. 4, 2017) (Paper 19). Four months after filing its first petition, on July 28, 2017, Petitioner filed the second petition in IPR2017-01879 ("IPR1879"), asserting claims 1–14, 16, and 17 are anticipated under 35 U.S.C. § 102(e). Three days after that, on July 31, 2017, Petitioner filed the instant Petition, asserting claims 1–17 are unpatentable as obvious under 35 U.S.C. § 103.

Patent Owner argues that each of the seven *General Plastic* factors favors denial of the Petition. Prelim. Resp. 8–23. For example, it is undisputed that Petitioner previously challenged the same claims of the same patent; knew of the primary references, Hart and Schering-Plough, before

filing the first petition; and had already received Patent Owner's preliminary response to the first petition at the time of filing this Petition (and responded to certain arguments in the instant Petition). Prelim. Resp. 8–16. Patent Owner also contends that Petitioner has failed to provide an adequate explanation for why it filed mulitple petitions. *Id.* at 16–18.

In response, Petitioner asserts that the '487 patent does not specify how to determine whether an antibody "competes with a reference antibody," as required by the claims. Reply 4–5. According to Petitioner, it was not until November 23, 2016, in a European Patent Office proceeding, that Patent Owner endorsed two competition assays disclosed in the prior art as methods for determining competition. *Id.* at 5; Ex. 1201, 12–13. Petitioner explains that it "immediately identified and retained experts, prepared the relevant antibodies and conducted relevant experiments. Petitioners were diligent in filing this Petition only eight days after the experiments were completed (and only three days after IPR2017-01879 Petition was filed)." Reply 5; Ex. 1400 ¶ 99.

Having considered each of the *General Plastic* factors and the facts and circumstances of this case, under the unique facts of this case we are not inclined to exercise our discretion to deny the Petition under § 314(a). We are persuaded that the grounds are sufficiently different in each petition that Petitioner did not appear to "strategically stage [its] prior art and arguments in multiple petitions, using [Patent Owner's preliminary response] as a roadmap, until a ground is found that results in the grant of review." *See General Plastic*, IPR2016-01357, slip op. at 17. We are also persuaded that the delayed filing of the latter two petitions to allow time for Petitioner to complete the competition testing was reasonable, particularly because it was not an issue in the first petition.

2. 35 U.S.C. § 325(d)

The Director also has discretion to decline to institute *inter partes* review if "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). Patent Owner argues that "the Office already decided that the claims are patentable in view of combinations of art relating to mouse anti-IL-4R antibodies with art disclosing methods of preparing human antibodies." Prelim. Resp. 23–29.

Petitioner notes that during prosecution, Patent Owner repeatedly argued that the Examiner had to provide evidence that the prior art antibodies compete with the '487 patent's reference antibody to maintain the anticipation rejection. Pet. 27–29; *see, e.g.*, Ex. 1002, 75–76 ("[I]t cannot be concluded that an antibody made according to [the asserted prior art] would *necessarily* compete for binding with the reference antibody of the rejected claims. Should this rejection be maintained, however, Applicants respectfully request that either documentary evidence . . . or an affidavit or declaration . . . supporting the assumption be provided."). Thus, Petitioner argues that the Board should not exercise its discretion under § 325(d) because the Office lacked the evidence submitted by Petitioner in this proceeding that Hart's Mab230 practices the "competes" limitation. Reply 3–4.

Having considered the prosecution history and the arguments of both sides, we are persuaded by Petitioner's reasoning. Because the Examiner did not have the benefit of Petitioner's additional experimental evidence relating to competition, we are not persuaded that the same or substantially the same prior art or arguments were previously presented to the Office. Nor was the evidence contained in Dr. Zurawski's declaration before the

Examiner. Accordingly, under the facts and circumstances of this case, we decline to exercise our discretion to deny institution under § 325(d).

D. Obviousness over Hart and Schering-Plough

Petitioner asserts that claims 1–17 of the '487 patent are unpatentable as obvious over Hart and Schering-Plough. Pet. 35–56. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 37–59. On this record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the challenged claims are unpatentable as obvious over Hart and Schering-Plough.

1. Hart (Ex. 1204)

Hart relates to a study of the signaling complexes induced by IL-4 and IL-13 in monocytes and monocyte-derived macrophages ("MDMac"). Ex. 1204, 2088, 2091. Hart describes the use of a murine anti-hIL-4R antibody called "MAb230," which was obtained commercially from R&D Systems. *Id.* at 2094. Hart describes MAb230 as "a neutralizing antibody to IL-4Rα." *Id.* Hart teaches that MAb230 inhibits both IL-4 and IL-13 signaling by blocking hIL-4Rα. *Id.* at 2092–93.

2. Schering-Plough (Ex. 1007)

Schering-Plough relates to "compounds and compositions useful for the detection, purification, measurement and/or inhibition of the human 130 kDa IL-4 receptor." Ex. 1007, Abstract. Schering-Plough recognizes that antibodies specific for the IL-4 receptor "could be therapeutic entities for allergy" given IL-4's role in the production of IgE. *Id.* at 2:18–22. Schering-Plough also recognizes that non-human monoclonal antibodies could be humanized and used for long term treatment of allergic disorders and may prevent the rejection of grafts. *Id.* at 2:20–23.

Accordingly, Schering-Plough describes a technique for making humanized versions of mouse anti-hIL-4R antibodies called "CDR grafting." *Id.* at 5:1–4. "[T]he CDRs [complementarity determining regions] from a rodent monoclonal antibody can be grafted onto a human antibody, thereby 'humanizing' the rodent antibody." *Id.* at 5:3–4.

3. Analysis

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

Regarding claim 1, Petitioner asserts that the combination of Hart and Schering-Plough teaches each limitation of the claims. For example, Hart teaches a murine anti-hIL-4R blocking antibody, MAb230, which Dr.

Zurawski asserts inherently "competes" with mAb 12B5. Pet. 35–36. According to Petitioner, Hart teaches every limitation of claim 1 except that it is a murine instead of a human antibody. *Id.* at 36. Petitioner argues that Schering-Plough's description of techniques for humanizing murine anti-hIL-4R blocking antibodies so they can be employed "for long term treatment of allergic disorders" supplies the missing limitation. *Id.* (quoting Ex. 1007, 2:18–22, 5:1–23, 6:30–34).

At this stage of the proceeding, we are persuaded that Petitioner has shown sufficiently that the combination of Hart and Schering-Plough teaches each limitation of claim 1. We have considered the arguments and evidence regarding claims 2–17 and find that Petitioner has made a sufficient showing that the combination of Hart and Schering-Plough teaches each limitation of those claims, as well. Pet. 48–56.

Petitioner further asserts an ordinary artisan would have had a reason to combine Hart and Schering-Plough because it was well known in the art that the ultimate goal of humanization is to decrease the immunogenicity of a non-human antibody while still maintaining its antigen binding specificity and affinity. *Id.* at 37 (citing Ex. 1400 ¶¶ 138, 142; Ex. 1413, 969). Thus, according to Petitioner, it would have been obvious to modify Hart's MAb230 with Schering-Plough's humanization techniques to derive a potential therapeutic for allergic diseases. *Id.* (citing Ex. 1007, 2:18–22; 5:1–23; Ex. 1400 ¶ 132). Petitioner further asserts a person of ordinary skill in the art would have had a reasonable expectation of success in combining the references, as humanization techniques were well-developed by May 1, 2001, and "skilled artisans would have reasonably expected to apply these techniques to transform MAb230 into a promising therapeutic with the same

specificity and relative affinity for hIL-4R." *Id.* at 45 (citing Ex. 1400 ¶¶ 56, 149; Ex. 1007, 5:5–8; Ex. 1405, 10033).

In response, Patent Owner argues we should deny instituting on this ground because the proper construction of "human antibody" does not include humanized antibodies (i.e., partial human antibodies). Prelim. Resp. 37–47. As explained above, however, on this record, we disagree with Patent Owner and accept Petitioner's proposed construction that "human antibody" includes partially and fully human antibodies.

Patent Owner also argues that Petitioner's arguments rely on impermissible hindsight to "pick MAb230 out of a sea of options and conclude that it would be used to develop a therapeutic candidate." Prelim. Resp. 47 (citing Ex. 2101 ¶¶ 22–35). Patent Owner also criticizes Petitioner's failure to consider the wide range of other therapeutic strategies and targets discussed as potential treatments for allergic disorders in the prior art. *Id.* at 48 (citing Ex. 2101 ¶¶ 24–26). According to Patent Owner, Petitioner has not shown that the prior art provides any reason to generate a humanized version of MAb230 as a potential therapeutic for allergic diseases. Patent Owner also asserts that Petitioner has not demonstrated that a person of ordinary skill in the art would have had a reasonable expectation of success in producing a therapeutically effective modified MAb230. *Id.* at 58–59.

At this stage of the proceeding, we are persuaded that Petitioner has made a sufficient showing that a person of ordinary skill in the art would have had a reason to humanize Hart's MAb230 using Schering-Plough's humanization technique to create a potential therapeutic for allergic diseases with a reasonable expectation of success. For example, Petitioner's declarant, Dr. Zurawski, testified that "MAb230 was known to block both

IL-4 and IL-13 activity and to exhibit an IC_{50} value for IL-4 inhibition in the range of 20–40 pM, which would have indicated to the skilled artisan that MAb230 is a promising candidate from which to derive an effective therapeutic." Ex. 1400 ¶ 136 (citing Ex. 1204, Fig. 8; Ex. 1206). Dr. Zurawski further testified that humanization of murine antibodies is "relatively routine and many antibodies have been successfully humanized." *Id.* ¶ 138 (quoting Ex. 1409, 33).

We note that Patent Owner's arguments rely on new testimonial evidence from its declarant, Dr. Marasco. Ex. 2101. To the extent Dr. Marasco's testimony raises a genuine issue of material fact with respect to Petitioner's alleged hindsight bias and assertions of reasonable expectation of success, we view the facts in the light most favorable to Petitioner for purposes of making this Decision. *See* 37 C.F.R. § 42.108(c). We will be able to review the parties' respective arguments more thoroughly once the record is developed further at trial.

Accordingly, having considered the arguments and evidence, we are persuaded that Petitioner has shown a reasonable likelihood that it would prevail in its assertion that claims 1–17 are unpatentable as obvious over Hart and Schering-Plough.

E. Obviousness over Hart, Schering-Plough, and Hoogenboom

Petitioner asserts claims 1–17 of the '487 patent are also unpatentable as obvious over Hart, Schering-Plough, and Hoogenboom. Pet. 56–61. Patent Owner opposes Petitioner's assertion for many of the same reasons stated above. Prelim. Resp. 47–59. On this record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the challenged claims are unpatentable as obvious over Hart, Schering-Plough, and Hoogenboom.

We incorporate here our findings and discussion of the disclosures of Hart and Schering-Plough.

1. Hoogenboom (Ex. 1402)

Hoogenboom relates to the production of antibodies with increased human characteristics over a parent antibody specific for the same antigen. Ex. 1402, 1:5–7. Hoogenboom teaches epitope imprinted selection ("EIS") for rebuilding a mouse antibody into a human antibody with the same specificity. *Id.* at 29:52–54. According to Hoogenboom, "[h]umanised antibodies which may be obtained using the present invention are likely to be better than conventional CDR-grafted humanized antibodies, in the sense that they will be less likely to involve an anti-idiotypic response." *Id.* at 13:41–45. Moreover, Hoogenboom states that the EIS approach may humanize antibodies more rapidly than by CDR-grafting. *Id.* at 30:1–2.

2. Analysis

Petitioner argues that as an alternative to CDR grafting, which results in a partially human antibody, a person of ordinary skill in the art would have also found it obvious to convert Hart's MAb230 into a fully human antibody using Hoogenboom's EIS approach. Pet. 56. According to Petitioner, a person of ordinary skill in the art would have combined Hoogenboom's teaching of EIS with the teachings of Hart and Schering-Plough because a fully human antibody would be less likely to invoke a human anti-mouse antibody ("HAMA") response. Pet. 57–58 (citing Ex. 1400 ¶¶ 214, 217). Petitioner further asserts that a person of ordinary skill in the art would have had a reasonable expectation of success in doing so because Hoogenboom "provides detailed disclosure of the successful isolation of a fully human anti-TNF antibody that exhibited the same binding characteristics as the murine antibody upon which it was based." *Id.* at 58–

59 (citing Ex. 1402, 26:20–29; Ex. 1400 ¶ 219). Petitioner then explains that the analysis with respect to the remaining claims is largely the same as the prior ground. *Id.* at 59–60 (citing Ex. 1400 ¶¶ 217, 218, 221).

In response, Patent Owner makes the same arguments alleging Petitioner improperly relied on hindsight bias and failed to demonstrate a reasonable expectation of success in combining the cited references. Prelim. Resp. 49–59. For the same reasons stated above, we find Petitioner has made a sufficient showing that each of the limitations of the challenged claims is taught by the combination of Hart, Schering-Plough, and Hoogenboom. We further find that Petitioner has shown sufficiently that a person of ordinary skill in the art would have had a reason to combine the cited references to produce a fully human equivalent of MAb230 with a reasonable expectation of success. Pet. 57–60 (citing Ex. 1400 ¶ 219). In light of competing testimonial evidence from Patent Owner's declarant, Dr. Marasco, we view these issues in the light most favorable to Petitioner solely for purposes of this decision. *See* 37 C.F.R. § 42.108(c). We will have the opportunity to consider the issues fully once the record has been developed at trial.

Accordingly, having considered the arguments and evidence, we are persuaded that Petitioner has shown a reasonable likelihood that it would prevail in its assertion that claims 1–17 are unpatentable as obvious over Hart, Schering-Plough, and Hoogenboom.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has established a reasonable likelihood of prevailing on its assertion that claims 1–17 of the '487 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted on the following ground:

Claims 1–17 as unpatentable as obvious over Hart and Schering-Plough; and

Claims 1–17 as unpatentable as obvious over Hart, Schering-Plough, and Hoogenboom.

FURTHER ORDERED that no other proposed grounds of unpatentability are authorized.

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

PETITIONER:

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