Trials@uspto.gov
571.272.7822

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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*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

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), and Patent Owner filed a Surreply (Paper 13). On February 15, 2018, we instituted an *inter partes* review of claims 1–17 on two obviousness grounds. Paper 14 ("Dec. Inst."), 20.

Patent Owner filed a response to the Petition. Paper 37 ("PO Resp."). Petitioner filed a Reply. Paper 65("Reply"). With our authorization, Patent Owner filed a Surreply (Paper 78, "Surreply"), and Petitioner filed a Sur-Surreply (Paper 85, "Sur-surreply").

The parties also filed motions to exclude certain evidence. Paper 75 (Patent Owner's motion); Paper 80 (Petitioner's motion). The parties filed responsive papers to those motions. Paper 84 (Petitioner's opposition); Paper 88 (Patent Owner's reply); Paper 83 (Patent Owner's opposition); Paper 87 (Petitioner's reply).

An oral hearing was held on November 14, 2018, a transcript of which has been entered in the record. Paper 94 ("Tr.").

We have authority under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine Petitioner has shown by a preponderance of the evidence that claims 1–17 of the '487 patent are unpatentable as obvious.

A. Related Proceedings

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

Petitioner also filed a petition for *inter partes* review of the ’487 patent on different grounds in IPR2017-01879. Pet. 4; Paper 7, 2. We instituted trial and enter a Final Written Decision in that proceeding concurrently with this decision.

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 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, including 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 claim. 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 Ground of Unpatentability

We instituted trial on the following grounds:

References	**Basis**	**Claims challenged**
Hart[1] and Schering-Plough[2]	§ 103(a)[3]	1–17
Hart, Schering-Plough, and Hoogenboom[4]	§ 103(a)	1–17

[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] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, which was enacted on September 16, 2011, made amendments to 35 U.S.C. § 103. AIA § 3(b). Those amendments became effective eighteen months later on March 16, 2013. *Id.* § 3(n). Because the application from which the '487 patent issued was filed before March 16, 2013, any citations to 35 U.S.C. § 103 in this Decision are to the pre-AIA version of the statute.
[4] Hoogenboom, et al. US 5,565,332, issued Oct. 15, 1996 ("Hoogenboom," Ex. 1402).

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 or partially human antibodies." *Id.* (citing Ex. 1400 ¶ 27).

In its Preliminary Response, Patent Owner proposed a slightly different definition of the level of ordinary skill in the art. Prelim. Resp. 38 (citing Ex. 2101 ¶ 14). In our Decision on Institution, however, we noted that we did not discern a substantive difference between the parties' respective definitions. Dec. Inst. 5. In any event, Patent Owner does not address the level of ordinary skill in the art in its Patent Owner Response.

We agree with and adopt Petitioner's definition of the level of ordinary skill in the art. We further note that the prior art itself corroborates this finding and 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. § 42.100(b) (2016);[5] *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 in the specification with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

The parties dispute the meaning of "human antibody," which appears in each challenged claim. According to Petitioner, the term should be construed to encompass both partially human and fully human antibodies. Pet. 20–21. Patent Owner, on the other hand, argues the term should be limited to fully human antibodies, as would have been understood by a person of ordinary skill in the art. PO Resp. 7–31. In our Institution Decision, we preliminarily construed the term to include both partially and fully human antibodies. Dec. Inst. 6–8. Now, having considered the arguments and evidence presented during trial, we maintain our prior

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[5] A recent amendment to this rule does not apply here, because the Petition was filed before November 13, 2018. *See* "Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board," 83 Fed. Reg. 51,340 (Oct. 11, 2018) (to be codified at 37 C.F.R. pt. 42).

construction and determine the broadest reasonable interpretation of "human antibody" that is consistent with the specification includes partially human antibodies.

The specification of the '487 patent repeatedly teaches that the antibodies of the invention include both "partially human" and "fully human" monoclonal antibodies. *See, e.g.*, Ex. 1001, 20:57–59 ("Antibodies of the invention include, but are not limited to, partially human (preferably fully human) monoclonal antibodies . . . ."); *see also id.* at 21:1–2 ("The desired antibodies are at least partially human, and preferably fully human.").

The specification also states:

> A method for producing an antibody comprises immunizing a non-human animal, such as a transgenic mouse, with an IL-4R polypeptide, whereby antibodies directed against the IL-4R polypeptide are generated in said animal. Procedures have been developed for generating *human antibodies* in non-human animals. The antibodies may be partially human, or preferably completely human.

Ex. 1001, 19:38–44 (emphasis added). Thus, the specification teaches that the "human antibodies" generated can be "partially human" or "completely human." *Id.* Stated somewhat differently, the specification expressly indicates that the phrase "human antibodies" broadly encompasses both "partially human" and "completely human" antibodies. *Id.*

Patent Owner contends that we misunderstand the specification. PO Resp. 10–11. Specifically, Patent Owner contends that by referring to "[t]he antibodies" rather than to "human antibodies" in the last sentence quoted above, the antecedent basis for "the antibodies" is "antibodies directed against the IL-4R polypeptide." *Id.* at 11 (citing Ex. 2141 ¶¶ 29–30; Ex. 2185 ¶ 20). In effect, Patent Owner asks us to ignore the second

sentence of the passage to interpret the specification that way. We decline to do so, as we read the specification as a whole.

Moreover, we are not persuaded that a person of ordinary skill in the art reading the specification would interpret "human antibodies" to be limited to fully human antibodies. If that were the case, the specification would not need to repeatedly clarify that some "human antibodies" are fully human. For example, the specification states:

> Examples of antibodies produced by immunizing such transgenic mice are the *human monoclonal antibodies* designated 6-2 (described in example 6); 12B5 (described in example 8); and MAbs 63, 1B7, 5A1, and 27A1 (all described in example 9). Monoclonal antibodies 6-2, 12B5, 63, 1B7, 5A1, and 27A1 are *fully human antibodies*, and are capable of inhibiting activity of both IL-4 and IL-13.

Id. at 21:6–13 (emphases added). Here, the specification describes MAbs 6-2, 12B5, 63, 1B7, 5A1, and 72A1 as "human monoclonal antibodies." *Id.* Thus, if a person of ordinary skill in the art necessarily equated "human monoclonal antibodies" with fully human antibodies, the specification would not need to state—in the very next sentence—that those same antibodies are "fully human antibodies." *See id.* The only rational reason for clarifying that these "human" antibodies are "fully human" antibodies is because a person of ordinary skill in the art reading the specification as a whole would understand that "human" monoclonal antibodies are broad enough to also embrace partially human antibodies. We find that interpretation to be reasonable given the specification expressly states that "[a]ntibodies of the invention include, but are not limited to, partially human (preferably fully human) monoclonal antibodies." *See* Ex. 1001, 20:57–59; *see also id.* at 21:1–2 ("The desired antibodies are at least partially human, and preferably fully human.").

Taken as a whole, we have found nothing in the specification that clearly limits the term "human antibodies" to fully human antibodies, alone. On the contrary, as explained above, the specification supports construing the term more broadly to include partially human antibodies.

We find the Federal Circuit's decision in *Nobel Biocare* to be instructive. *Nobel Biocare Servs. AG v. Instradent USA, Inc.*, 903 F.3d 1365, 1380–82 (Fed. Cir. 2018). In that case, the patent owner argued that its claim to a dental implant with a "coronal region having a frustoconical shape" should be construed to mean "the coronal region as a whole has a frustoconical shape." *Id.* at 1380. The patent owner argued that the Board erred by construing the term to include both partly and wholly frustoconical coronal regions. *Id.* The Federal Circuit affirmed the Board's broader construction where the specification taught embodiments with both wholly and partly frustoconical regions. *Id.* The Federal Circuit noted that "there is a strong presumption against a claim construction that excludes a disclosed embodiment." *Id.* at 1381 (quoting *In re Katz Interactive Call Processing Patent Litig.*, 639 F.3d 1303, 1324 (Fed. Cir. 2011)). The court held that the patent owner had not overcome the presumption "[b]ecause the claim language does not require the exclusion of those embodiments, and there is no basis in the intrinsic record for excluding them." *Id.*

Likewise, here, Patent Owner has not identified anything in the intrinsic record that overcomes the presumption. Patent Owner cites an amendment to the claims made during prosecution where, in response to an anticipation rejection, the applicant amended claim 1 to recite "an isolated human antibody" and canceled dependent claim 11, which recited a "human, partially human, humanized, or chimeric antibody." Ex. 1002, 68, 69, 245. Patent Owner asserts that this demonstrates that "human" antibodies are

distinct from "partially human, humanized, or chimeric" antibodies. PO Resp. 20.

Patent Owner's position is unpersuasive because canceled claim 11 does not identify distinct classes of antibodies. As we noted in our Decision on Institution, Patent Owner admitted that "humanized antibodies are only partially human antibodies." Dec. Inst. 7 (quoting Prelim. Resp. 41). Applying that same logic, chimeric antibodies are partially human antibodies, as well. Moreover, the specification of the '487 patent equates chimeric and humanized antibodies, stating "[a]dditional embodiments include chimeric antibodies, e.g., humanized versions of murine monoclonal antibodies. Such *humanized antibodies* may be prepared by known techniques." Ex. 1001, 19:21–23 (emphasis added). Thus, according to the specification, partially human, humanized, and chimeric antibodies overlap and may describe the same antibody. In light of the ambiguity and overlap between the various claim terms, it is reasonable to interpret "human" and "partially human" as similarly overlapping, particularly given the interchangeable use of the terms. *See* Ex. 1001, 19:41–44 ("Procedures have been developed for generating human antibodies in non-human animals. The antibodies may be partially human, or preferably completely human.").

We also note that the applicants inserted the word "human" in claim 1 to traverse an inherent anticipation rejection. Ex. 1002, 73. In doing so, the applicants argued that the prior art taught making antibodies "against murine *or* human IL-4R, so the skilled artisan is not *necessarily* led to make an anti-human IL-4R antibody." *Id.* at 74; *see also id.* at 76 (noting the examiner unfairly characterized the prior art abstract as teaching human antibodies where the abstract refers to "[*m*]*ammalian* antibodies" that are immunoreactive with "*mammalian* IL-4 receptors"). Thus, the applicant

traversed the anticipation rejection by distinguishing the amended claim reciting "human antibodies" from prior art that was directed to murine antibodies. Given the circumstances of the amendment, nothing indicates the applicants added "human" to claim 1 to limit the scope of the claims to fully human antibodies.

Consistent with that reading, after Patent Owner's amendment to claim 1, the examiner continued to characterize the remaining claims 1–10 and 12–16 as being "drawn to an isolated human antibody that competes with a reference antibody for binding to human IL-4 receptor . . . said isolated antibody *that is a human antibody, . . . wherein the antibody is humanized*, is full length or fragment thereof." Ex. 1002, 46 (emphasis added); *see also id.* at 49. In other words, even after the applicant amended claim 1 to recite "an isolated human antibody," the examiner continued to understand the scope of the claims to include both fully and partially human antibodies. That reading, on the examiner's part, aligns with the rationale for the amendment, whereby "human" was added to claim 1 to distinguish the subject matter from the prior art's disclosure of murine antibodies without regard to whether the antibodies were fully or partially human. Like the examiner, we read "a human antibody" broadly to include an antibody that "is humanized." Ex. 1002, 46.

We are required to consider the prosecution history when determining the broadest reasonable interpretation of the claims. *See Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015). But, to apply prosecution history disclaimer, the party seeking to invoke the disclaimer "bears the burden of proving the existence of a 'clear and unmistakable' disclaimer that would have been evident to one skilled in the art." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1064 (Fed. Cir. 2016).

Under the facts and circumstances presented here, we find the cited prosecution history to be equivocal, at best. We are not inclined—as Patent Owner suggests—to speculate and attribute the examiner's statements to a "copy and paste" error. Surreply 5–6 (citing Ex. 1002, 46, 85, 119, 120–121). Even if the examiner had simply copied and pasted the language from one Office Action to the next, the examiner consistently summarized the claims as being drawn to "an isolated antibody . . . said isolated antibody *that is a human antibody* . . . wherein the antibody is *humanized*." *See* Ex. 1002, 46, 85, 119, 120–121. That is, the examiner clearly included humanized antibodies in his interpretation of a "human antibody," and, as Petitioner notes, Patent Owner never corrected the examiner's interpretation. Sur-surreply 3.

We therefore will not narrow the meaning of "human antibody" where Patent Owner has not shown a "clear and unmistakable" disclaimer that the term "human antibody," as interpreted in the claims, should be limited to fully human antibodies. *See Trivascular*, 812 F.3d at 1064 (finding no error in PTAB's conclusion that Petitioner failed to meet its burden of demonstrating a "clear and unmistakable" disclaimer during prosecution).

As further support for its narrow construction, Patent Owner relies heavily on extrinsic evidence and the testimony of its experts, Dr. Wayne Marasco and Dr. Fred Finkelman.[6] Ex. 2101 ¶¶ 15–21; Ex. 2141 ¶¶ 24–30;

[6] Patent Owner also submits the testimony of Stephen Kunin, said to be "an expert on US patent practice and procedure." PO Resp. 21; Ex. 2183. Whether the testimony is admissible or not (*see* 37 C.F.R. 42.65(a)), we give Mr. Kunin's testimony little weight, as he does not address certain portions of the specification and prosecution history relied upon in this Decision. *See, e.g.*, Ex 1002, 46, 49.

Ex. 2185 ¶¶ 16–21. Citing various papers, Drs. Marasco and Finkelman assert that the "convention in the field had long been to refer to antibodies by their species of origin." Ex. 2101 ¶ 17 (citing Ex. 1402, 13:5–28; Ex. 2103, 128); *id.* ¶ 21 (citing Ex. 2104, 65); Ex. 2141 ¶ 27 (citing Ex. 2171; Ex. 2172; Ex. 1206; Ex. 1409, 7-8; Ex. 1206); Ex. 2185 ¶ 18 (citing Ex. 1402; Ex. 2103; Ex. 2171; Ex. 2172; Ex. 1206; Ex. 1409; Ex. 2140). That evidence, however, is not inconsistent with the disclosure of the specification, which refers to "fully human" antibodies when identifying antibodies that contain no non-human fragments. Ex. 1001, 21:6–13. Moreover, we note that Riechmann,[7] cited in the specification of the '487 patent (Ex. 1001, 19:34–35), refers to humanized antibodies (i.e., partially human antibodies) as "human" antibodies. Ex. 1415, 325; *see also* Ex. 1477 ¶¶ 9–10.

The specification is "the single best guide to the meaning of a disputed term," and "[u]sually, it is dispositive" as claims must be construed "in view of the specification, of which they are a part." *Hamilton Beach Brands, Inc. v. f'real Foods, LLC*, 908 F.3d 1328, 1339 (Fed. Cir. 2018) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc)) (finding PTAB did not err in its construction that "follows the claim's plain language read in line with the specification"). And the specification in this case expressly identifies "human" antibodies as embracing both "fully human" and "partially human" antibodies. Ex. 1001, 19:41–44.

Patent Owner also notes the district court judge in the parallel district court proceeding construed the term "human antibody" to mean a "fully

[7] Riechmann et al., *Reshaping Human Antibodies for Therapy*, 332 Nature 323–27 (1988) ("Riechmann," Ex. 1415).

human" antibody. Surreply 6 (citing Ex. 2300, 18–21). After considering the evidence as outlined above, we reach a different conclusion than the district court based on the broader applicable case law here.

Accordingly, having considered the arguments and evidence presented during trial, we determine the broadest reasonable interpretation of "human antibody" includes both fully human and partially human antibodies.

C. 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. PO Resp. 31–66; Surreply 7–15. Having considered the arguments and evidence presented at trial, we determine that Petitioner has established by a preponderance of the evidence that 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. 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 the 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).

One way a patent's subject matter can be proved obvious is by "noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *KSR*, 550 U.S. at 420. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *Id.* at 421.

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 supplies the missing limitation through its description of techniques for humanizing murine anti-hIL-4R blocking antibodies so they can be employed "for long term treatment of allergic disorders." *Id.* (quoting Ex. 1007, 2:18–22, 5:1–23, 6:30–34).

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.* at 36 (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).

Based on the arguments and evidence presented at trial, we agree with Petitioner and its expert, Dr. Zurawski, that the combination of Hart and Schering-Plough teaches each limitation of claim 1. *See* Ex. 1400 ¶¶ 133–150. We have considered the arguments and evidence regarding claims 2–17, including Dr. Zurawksi's persuasive supporting testimony. *See* Ex. 1400 ¶¶ 151–209. Based on Petitioner's contentions and supporting evidence, we find that the combination of Hart and Schering-Plough teaches each limitation of those claims, as well. *See id.* We further note that Patent Owner has not argued the specific limitations of the dependent claims.

We are also persuaded that Petitioner has shown 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. Petitioner's expert, Dr. Zurawski, explains that a person of ordinary skill in the art would have had a reason to graft the CDRs and other binding-determinant amino acid residues from MAb230 into a human framework according to the teachings of Schering-Plough to "derive a less immunogenic version of MAb230 that could be used as a potential therapeutic." Ex. 1400 ¶ 132.

Dr. Zurawski further 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). Moreover, we credit the testimony of Dr. Zurawski that techniques for preparing a humanized antibody that retains MAb230's specificity and affinity for hIL-4R were well known and within the ability of a person of ordinary skill in the art. *Id.* ¶ 138. Dr. Zurawski also states that, as of 1995, over 100 examples of humanized antibodies have been successfully achieved. *Id.* (quoting Ex. 1409, 33).

In response, Patent Owner argues we should reject this ground because the proper construction of "human antibody" does not include humanized antibodies (i.e., partially human antibodies). PO Resp. 37–47. As explained above, however, we have construed "human antibody" to include partially human antibodies and, therefore, reject Patent Owner's argument.

Patent Owner also argues that Petitioner's arguments rely on impermissible hindsight to arrive at the claimed invention. PO Resp. 33 (citing Ex. 2141 ¶¶ 31–33; Ex. 2185 ¶¶ 22–56; Ex. 2101 ¶¶ 22–35). Patent Owner criticizes Petitioner's immediate focus on MAb230 rather than considering the full scope and content of the prior art. *Id.* at 33. According to Patent Owner, Petitioner (1) presents an oversimplified view of the art and ignores the numerous other immune-cell signaling molecules involved in allergic disorders that a person of ordinary skill in the art would have considered in developing candidate therapeutic targets; (2) ignores the wide range of strategies in the prior art for altering IL-4R signaling; and

(3) ignores the fact that MAb230 was one of at least twelve anti-IL-4R antibodies in the prior art and was not and never has been recognized in the art as a candidate for modification to create a therapeutic. *See id.* at 34–46; Ex. 2141 ¶¶ 31–33, 41; Ex. 2185 ¶¶ 22–56; Ex. 2101 ¶¶ 22–35.

We agree with Petitioner, however, that the motivation to humanize murine antibodies specific for IL-4R for use in treating allergic disorders is taught in Schering-Plough. *See* Reply 8. Schering-Plough expressly states that "[n]on-human monoclonal antibodies [specific for IL-4R] could advantageously be humanized and thus be used for long term treatment of allergic disorders." Ex. 1007, 2:1–23 (citation omitted). That other strategies may have existed for inhibiting IL-4R signaling does not change our analysis. The law "does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach away." *PAR Pharm.*, 773 F.3d at 1197–98 (rejecting argument that there were better methods available to address the prior art concerns).

Here, although others in the art (including Petitioner) may have been pursuing different avenues for inhibiting IL-4 activity, that activity is inapposite to our analysis. Patent Owner has not identified any persuasive evidence in the record that teaches away from humanizing MAb230. *See Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1348, 1350 (Fed. Cir. 2015) (rejecting argument that claims were not obvious where prior art references teaching high concentrations did not teach away from use of lower concentrations, as claimed).

Patent Owner and its expert Dr. Finkelman argue that a person of ordinary skill in the art would not have chosen to humanize MAb230 because of the risk of unacceptable side effects from blocking both IL-4 and IL-13 activity, such as parasitic infection, inflammatory disease, and cancer.

PO Resp. 54 (citing Ex. 2185 ¶¶ 43–49). According to Patent Owner, because IL-4 and IL-13 were known to have protective effects, a person of ordinary skill in the art "would not have had a reason to modify an antibody that blocked both IL-4 and IL-13 activity and would not have had a reasonable expectation of success in doing so." *Id.* at 54–59.

We are not persuaded that the potential risk of side effects would have deterred a person of ordinary skill in the art from developing a way to block both IL-4 and IL-13 signaling. *See* Ex. 1477 ¶¶ 44–49. First, we note the literature cited by Patent Owner's expert Dr. Finkelman characterizes the side effects as theoretical. Dr. Finkelman's own paper states that although studies "*suggest* that T_H2 cytokine antagonists *may* increase the risk and severity of [side effects,] such therapy should be relatively safe" if certain "commonsense precautions" are taken. Ex. 2159, 772 (emphasis added); *see* Ex. 1477 ¶ 46; *see also* Ex. 2185 ¶ 47 (noting both "IL-4 and IL-13 exert antitumoral properties *in vitro* and ***possibly*** *in vivo*" (emphasis added)). Thus, we credit the testimony of Petitioner's expert, Dr. Zurawski, who supports his opinion with several references touting the benefits of inhibiting both IL-4 and IL-13 signaling. Ex. 1477 ¶¶ 45 (citing Ex. 1407, 14 ("Several researchers say that perhaps a more promising drug target than either cytokine is the portion of the receptor molecule on immune system cells that is shared by both IL-4 and IL-13. . . . Several companies are already seeking an effective way to block the receptor's signaling."); Ex. 1011, 412 (stating therapies directed at IL-4R are "especially interesting" because such agents "may be expected to inhibit the signaling induced by the binding of both IL-4 and IL-13 because of shared receptor subunits")).

Patent Owner also argues that even if a person of ordinary skill in the art would have chosen to develop anti-IL-4R antibodies as a therapeutic strategy, Petitioner has failed to show why a person of ordinary skill in the art would have selected MAb230 from the known murine anti-IL-4R antibodies. PO Resp. 46, 59–61 (citing Ex. 2101 ¶¶ 32–35; Ex. 2141 ¶¶ 31–33; Ex. 2185 ¶¶ 39–41, 50–53). Patent Owner argues that MAb230 is manufactured for "RESEARCH USE ONLY," and that the literature in the art consistently describes MAb230 as a research tool. PO Resp. 47–49. Moreover, Patent Owner argues that Petitioner has not identified any prior art that suggests modifying MAb230 to make a therapeutic antibody, even though it had been commercially available as a research tool for 20 years. *Id.* at 47 (citing Ex. 2101 ¶ 34; Ex. 2141 ¶¶ 31–33; Ex. 2185 ¶¶ 39–41); *see also id.* at 48–53.

The problem with Patent Owner's argument is that the law does not require the prior art to explicitly suggest humanizing MAb230. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 964 (Fed. Cir. 2014) ("A motivation to combine may be implicit in the prior art—silence does not imply teaching away."). Rather, we look to the prior art as a whole and determine what it would have taught a person of ordinary skill in the art. *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (stating prior art "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole").

Moreover, as explained above, Petitioner need not show that MAb230 was the only option or even the best option for a person of ordinary skill in the art. On the contrary, Petitioner may show that MAb230 was a "suitable option from which the prior art did not teach away." *PAR Pharm.*, 773 F.3d at 1197–98. Here, Schering-Plough expressly teaches a person of ordinary

skill in the art that humanizing a non-human IL-4R antibody could be used for long term treatment of allergic disorders. Ex. 1007, 2:1–23. Schering-Plough identifies nine different murine anti-IL-4R antibodies, three of which inhibit IL-4R binding. *Id.* at 2:32–33, 14 (Table III); *see also* Ex. 1477 ¶¶ 23–24. Tony[8] discloses a murine antibody X2/45, which also blocks IL-4 activity. Ex. 1019, Abstract.

Dr. Zurawski credibly testifies that a person of ordinary skill in the art would have understood that MAb230 was a potent anti-hIL-4R blocking antibody (Ex. 1400 ¶ 148), and even more potent than the antibodies reported in Schering-Plough and Tony (Ex. 1477 ¶ 24). Accordingly, Dr. Zurawski concludes, "MAb230's reported ND_{50}/IC_{50} for inhibiting IL-4 activity sets it apart from any pre-May 1, 2001 anti-hIL-4R blocking antibody of which I am aware and makes MAb230 a natural choice for therapeutic development. It is a matter of common sense to select the most potent anti-hIL-4Rα blocking available for humanization." Ex. 1477 ¶ 24; *see also id.* ¶¶ 39–43 (considering literature cited by Patent Owner's expert and opining that none teaches against humanizing MAb230).

Patent Owner and Dr. Finkelman argue, however, that affinity alone does not indicate whether an antibody would make a good therapeutic because it depends on what the antibody does when bound to the antigen. PO Resp. 62; Ex. 2185 ¶¶ 54–56. Patent Owner asserts that a person of ordinary skill in the art would have been concerned that a high-affinity antibody would amplify the toxicities that would result from blocking IL-4

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[8] Tony et al., *Design of Human Interleukin-4 Antagonists Inhibiting Interleukin-4-Dependent and Interleukin-13-Dependent Responses in T-Cells and B-Cells with High Efficiency,* 225 EUR. J. BIOCHEM. 659–65 (1994) (Ex. 1019, "Tony").

and IL-13 activity. *Id.* As explained above, however, we are not persuaded that persons of ordinary skill in the art would have been deterred by the potential for theoretical side effects. Moreover, citing literature in support, Dr. Zurawski credibly explains that a person of ordinary skill in the art would have understood that high binding affinity/potency indicated that MAb230 was a promising candidate for therapeutic development. Ex. 1477 ¶¶ 52–53 (citing Ex. 1406, 2:14–20; Ex. 1410, 141; Ex. 1475, 499).

Patent Owner also argues that Petitioner has failed to show that a person of ordinary skill in the art would have had a reasonable expectation of success in modifying MAb230 to generate a therapeutic antibody. PO Resp. 63–66; Surreply 13–14. According to Patent Owner, Petitioner has only argued that a person of ordinary skill in the art could have successfully humanized MAb230. PO Resp. at 64 (citing Pet. 45). Regardless, Patent Owner argues that by May 1, 2001, "the prior art had not demonstrated the feasibility of targeting IL-4 or IL-13, either individually or in combination, to treat allergic disorders." *Id.* at 65. And given the risk of "potentially serious side-effects," Patent Owner argues that a person of ordinary skill in the art would not have had a reasonable expectation of success in developing a therapeutic by humanizing MAb230. *Id.* at 66 (citing Ex. 2185 ¶¶ 43–49).

In response, Petitioner notes that the claims do not require therapeutic efficacy. Reply 21; Sur-surreply 14. We agree with Petitioner that the pertinent question is not whether there is a reasonable expectation that the antibodies will actually be therapeutically effective. Rather, the question is whether a person of ordinary skill in the art would have reasonably expected to arrive at the claimed invention. *See Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) ("[T]he person of ordinary skill need only have a reasonable expectation of success of developing the claimed

invention."). Moreover, a reasonable expectation of success does not require "an absolute certainty for success." *PAR Pharm.*, 773 F.3d at 1198. Here, Dr. Zurawski testifies—and Patent Owner does not contest—that preparing a humanized antibody that retains MAb230's specificity and approximate affinity for hIL-4R using CDR-grafting was within the ability of a person of ordinary skill in the art. Ex. 1400 ¶ 138. Thus, we are persuaded that the record supports a reasonable expectation of success in humanizing Hart's MAb230 with the CDR grafting technique of Schering-Plough.

Even if we were to require some showing of a reasonable expectation of therapeutic efficacy, we note that Patent Owner's statements to the Office during prosecution of a related patent application tend to support that showing. In response to an enablement rejection where the examiner found the prior art taught inhibiting IL-4 is not effective in treating asthma, Patent Owner stated, "There is no reasonable basis for concluding that antibodies that bind to 'the perfect target' and inhibit 'an important regulator' would be therapeutically ineffective." Ex. 1407, 7. This is consistent with the art of record that teaches those of ordinary skill in the art believed a blocking antibody like MAb230 may have therapeutic potential. Ex. 1007, 2:1–22 ("Non-human monoclonal antibodies could advantageously be humanized and thus be used for long term treatment of allergic disorders." (citation omitted)); Ex. 1011, 410, 412 (stating "IL-4 receptor antagonism offers another potential therapeutic approach to IL-4 inhibition in allergic rhinitis" and that monoclonal antibodies to IL-4R are "especially interesting").

We note that Patent Owner has not separately presented evidence of secondary considerations of nonobviousness, such as unexpected results, long-felt but unmet need, or failure of others. To the extent Patent Owner contends that the evidence discussed above constitutes such evidence, we

have considered it in conjunction with Petitioner's evidence of obviousness and found it not to be persuasive. *In re Cyclobenzaprine, Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012) (stating "objective evidence [must] be considered before making an obviousness determination").

Accordingly, having considered the arguments and evidence presented at trial, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–17 are unpatentable as obvious over Hart and Schering-Plough.

D. 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. For the reasons discussed above, however, we have already determined that claims 1–17 are unpatentable as obvious over Hart and Schering-Plough. In light of that determination, we need not address whether the same claims are also unpatentable as obvious over the combination of Hart, Schering-Plough, and Hoogenboom.

III. MOTIONS TO EXCLUDE

The party moving to exclude evidence bears the burden of proving that it is entitled to the relief requested—namely, that the material sought to be excluded is inadmissible under the Federal Rules of Evidence ("FRE"). *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

A. Petitioner's Motion to Exclude

Petitioner filed a Motion to Exclude the testimony of Stephen G. Kunin. Paper 80. Patent Owner relies on the testimony of Mr. Kunin as an expert in U.S. patent practice and procedure and offered his opinion

regarding claim construction. Ex. 2183. We considered but do not rely on Mr. Kunin's testimony in rendering this Decision. Accordingly, we dismiss Petitioner's Motion to Exclude as moot.

B. Patent Owner's Motion to Exclude

1. Portions of Exhibits 1400 and 1477

Patent Owner filed a Motion to Exclude portions of testimony from Exhibits 1400 (Zurawski Decl.) and 1477 (Zurawski Rebuttal Decl.) that are not cited in the Petition or Reply. Paper 75, 1–3. We do not rely on any of the cited testimony and, therefore, dismiss as moot Patent Owner's motion related to that testimony.

Patent Owner also argues paragraphs 24 and 38 of Dr. Zurawski's Rebuttal Declaration (Ex. 1477) should be excluded because the paragraphs rely on inadmissible hearsay evidence relating to Exhibit 1455, the MAb230 data sheet. Even if Exhibit 1455 were inadmissible hearsay, we agree with Petitioner that Dr. Zurawski is entitled to rely on the datasheet under FRE 703 as information that an expert in his field would reasonably rely on. *See* Paper 84, 2–3; FRE 703 ("An expert may base an opinion on facts or data in the case that the expert has been made aware of or personally observed. If experts in the particular field would reasonably rely on those kinds of facts or data in forming an opinion on the subject, they need not be admissible for the opinion to be admitted."). Patent Owner argues Petitioner has failed to show an expert would rely on Exhibit 1455 because it does not include the necessary experimental detail underlying the experiments. Paper 88, 2. We are not persuaded, however, that an expert would require such experimental detail for a commercial datasheet that is provided when a customer purchases MAb230. Accordingly, we find Dr. Zurawski is entitled to rely

on Exhibit 1455 and we deny Patent Owner's motion as to paragraphs 24 and 38 of Exhibit 1477.

2. Exhibit 1407

Patent Owner also moves to exclude Exhibit 1407 as inadmissible hearsay. Paper 75, 3–4. Exhibits 1407 is an excerpt from the prosecution history of related U.S. Patent Application No. 10/324,493. Patent Owner argues that the Petition relies on Exhibit 1407 for the truth of the matter asserted when alleging that "hIL-4R was known in the prior art as 'the perfect target' for therapeutic agents because it is an 'important regulator' of allergic disorders." *Id.* at 3–4 (citing Paper 1, 23). Patent Owner also argues that Petitioner's Reply similarly relied on Exhibit 1407 for the statement that "[s]everal companies [were] already seeking an effective way to block the [IL-4] receptor's signaling" and "IL-4 and IL-13-induced signaling by blocking IL-4R was a preferred strategy for treating allergic diseases." *Id.* at 4.

Petitioner notes that the Petition relies on Exhibit 1407 and Patent Owner failed to timely object. Paper 84, 4–5. We agree with Petitioner that Patent Owner failed to timely object to the evidence within ten days of instituting trial. *See* Paper 18 (objections filed March 2, 2018); 37 C.F.R. § 42.64(b)(1) (stating objections to evidence submitted during a preliminary proceeding must be filed within ten days of the institution of trial). Patent Owner's objection to those portions of Exhibit 1407 cited in the Petition is therefore waived.

Patent Owner asserts it is entitled to object to inadmissible evidence in the Reply. But the evidence objected to in the Reply (i.e., Ex. 1407, pages 7 and 14) was also cited in the Petition. *See* Reply 9, 11–15, 19, 21, 24 (citing pages 7 and/or 14 of Exhibit 1407). Patent Owner cannot rehabilitate its

waived objection when the same evidence is relied upon in the Reply. We, therefore, find Patent Owner's objection to pages 7 and 14 of Exhibit 1407 to be waived and deny Patent Owner's motion as to Exhibit 1407.

3. Exhibits 1432 and 1455

Patent Owner also moves to exclude the entirety of Exhibits 1432 (Defendant's Invalidity Contentions) and 1455 (MAB 230 Data Sheet). Paper 75, 4–8. We do not rely directly on either exhibit for purposes of rendering this Decision. Accordingly, we dismiss Patent Owner's Motion to Exclude as moot as to Exhibits 1432 and 1455.

4. Exhibits 2133 and 2304

Patent Owner moves to exclude portions of Exhibits 2133 and 2304, which are transcripts from the cross-examination of Dr. Zurawski. Paper 75, 8–10. We do not rely on the objected-to testimony for purposes of rendering this Decision. Accordingly, we dismiss Patent Owner's Motion to Exclude as moot as to those portions of Exhibits 2133 and 2304.

IV. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has established by a preponderance of the evidence that claims 1–17 of the '487 patent are unpatentable as obvious over Hart and Schering-Plough.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–17 of the ’487 patent are held unpatentable as obvious;

FURTHER ORDERED that Petitioner’s Motion to Exclude is *dismissed as moot*;

FURTHER ORDERED that Patent Owner’s Motion to Exclude is *dismissed as moot-in-part and denied-in-part*; and

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirement of 37 C.F.R. § 90.2.

For PETITIONER:

Lauren Fornarotto
John Garvish
John Campbell
Matthew Cameron
McKOOL SMITH P.C.
lfornarotto@mckoolsmith.com
jgarvish@mckoolsmith.com
jcampbell@mckoolsmith.com
mcameron@mckoolsmith.com

For PATENT OWNER:

Eldora Ellison
David Holman
David Roadcap
Jaime Canaves
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
eellison-PTAB@skgf.com
dholman-PTAB@skgf.com
droadcap-PTAB@skgf.com
jcanaves-PTAB@skgf.com