Paper No. 1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANOFI-AVENTIS U.S. LLC,

GENZYME CORP.

and

REGENERON PHARMACEUTICALS, INC.,

Petitioners,

v.

IMMUNEX CORPORATION,

Patent Owner.

***Inter Partes* Review No. IPR2017-01879**

Patent 8,679,487

PETITION FOR *INTER PARTES* REVIEW UNDER 35 U.S.C. 312

Table of Contents

Petitioners' Exhibit List

Exhibit	Description
1001	U.S. Patent No. 8,679,487 ("the '487 Patent").
1002	Excerpts from the File History of U.S. Patent No. 8,679,487 (U.S. Patent Application No. 12/829,231 ("'231 Application")).
1003	Excerpts from the File History of U.S. Patent Application No. 14/175,943, which is a continuation of U.S. Patent No. 8,679,487 ("'943 Application").
1005	*Curriculum Vitae* of Dr. Gerald Zurawski, Ph.D.
1006	U.S. Patent Publication No. 2008/0160035 ("Stevens" or "'035 Publication").
1007	European Patent Application No. EP 0604693 ("Schering-Plough").
1008	U.S. Patent Application No. 09/847,816 ("'816 Application").
1009	PCT International Publication No. WO 96/33735 ("Kucherlapati").
1010	Zurawski, *et al.*, *The Primary Binding Subunit of the Human Interleukin-4 Receptor is Also a Component of the Interleukin-13 Receptor*, Journal of Biological Chemistry (June 9, 1995) ("Zurawski").
1011	Agosti, et al., *Novel Therapeutic Approaches for Allergic Rhinitis*, 20 Immunology and Allergy Clinics of North America 401–423 (2000) ("Agosti").
1014	Thorsten Hage, et al., *Crystal Structure of the Interleukin-4/Receptor a Chain Complex Reveals a Mosaic Binding Interface*, 97 Cell 271–281 (1999) ("Hage").

1015	Whitty, et al., *Interaction Affinity Between Cytokine Receptor Components on the Cell surface*, 95 Proc. Natl. Acad. Sci. USA, 13165–13170 (October 1998) ("Whitty").
1016	United States Patent Application Pub. No. 2002/0002132 ("Pluenneke" or "'132 Publication").
1026	Perez de la Lastra, et al., *Epitope Mapping of 10 monoclonal antibodies against the pig analogue of human membrane cofactor protein (MCP)*, Immunology 1999, 96:663-670 ("Perez de la Lastra").
1028	U.S. Patent Application No. 10/324,493 ("'493 Application").
1029	U.S. Patent No. 7,186,809 ("the '809 Patent").
1031	U.S. Patent No. 7,465,450 ("the '450 Patent").
1032	U.S. Application No. 12/291,702 (the "'702 Application").
1039	U.S. Patent No. 9,587,026 ("'026 Patent").
1049	*Curriculum Vitae* of Mike McKool.
1051	*Curriculum Vitae* of John F. Garvish, II.
1200	Declaration of Dr. Gerald Zurawski, Ph.D.
1201	Amgen's November 23, 2016 Response to the Oppositions requested regarding European Patent No. 2 292 665 ("Immunex's EU Opposition Response").
1202	U.S. Patent Publication No. 2002/0076409 ("March").
1203	Comparison of '132 Publication disclosure to '487 Patent specification using Microsoft Word compare feature.

1204	Hart, et al., *Diminished responses to IL-13 by human monocytes differentiated in vitro,* 29 Eur. J. Immunol. 1999, 2087–2097 ("Hart").
1205	PCT International Publication No. WO 98/08957 ("Penn State").
1206	MAb 230 technical information from R & D System's webpage circa 1996 and 1997 with Affidavit ("R&D Systems Catalog").
1207	Hefta, et al., (1996) *Measuring antibody affinity using biosensors, Antibody Engineering*. A Practical Approach, (McCafferty et al., eds.), pp. 99-117, Oxford Univ. Press, Oxford.
1208	Parks, D., Herzenberg, L., and Herzenberg L. (1989) *Flow cytometry and fluorescence-activated cell sorting*, in Fundamental Immunology (Paul, W., ed.). Raven, New York.
1209	Zurawski, et al., *Receptors for interleukin-13 and interleukin-4 are complex and share a novel component that functions in signal transduction*, 12 EMBO J. 1993, 2663–2670.
1210	Medarex Form S-3 dated March 3, 2000.
1211	Excerpts from U.S. Patent Application No. 09/785,934 ("'934 Application").
1212	Affidavit of Mike McKool in Support of Motion for *Pro Hac Vice* Admission.
1213	Affidavit of John F. Garvish, II in Support of Motion for *Pro Hac Vice* Admission.

Pursuant to 35 U.S.C. § 312 and 37 C.F.R. § 42.100, Sanofi-Aventis U.S. LLC and Genzyme Corp. ("Sanofi"), and Regeneron Pharmaceuticals, Inc. ("Regeneron") (collectively, "Petitioners"), request *inter partes* review of U.S. Patent No. 8,679,487 (Ex. 1001), which issued March 25, 2014. As explained herein, there is a reasonable likelihood that Petitioners will prevail in establishing that the '487 Patent is unpatentable as anticipated.

I. INTRODUCTION

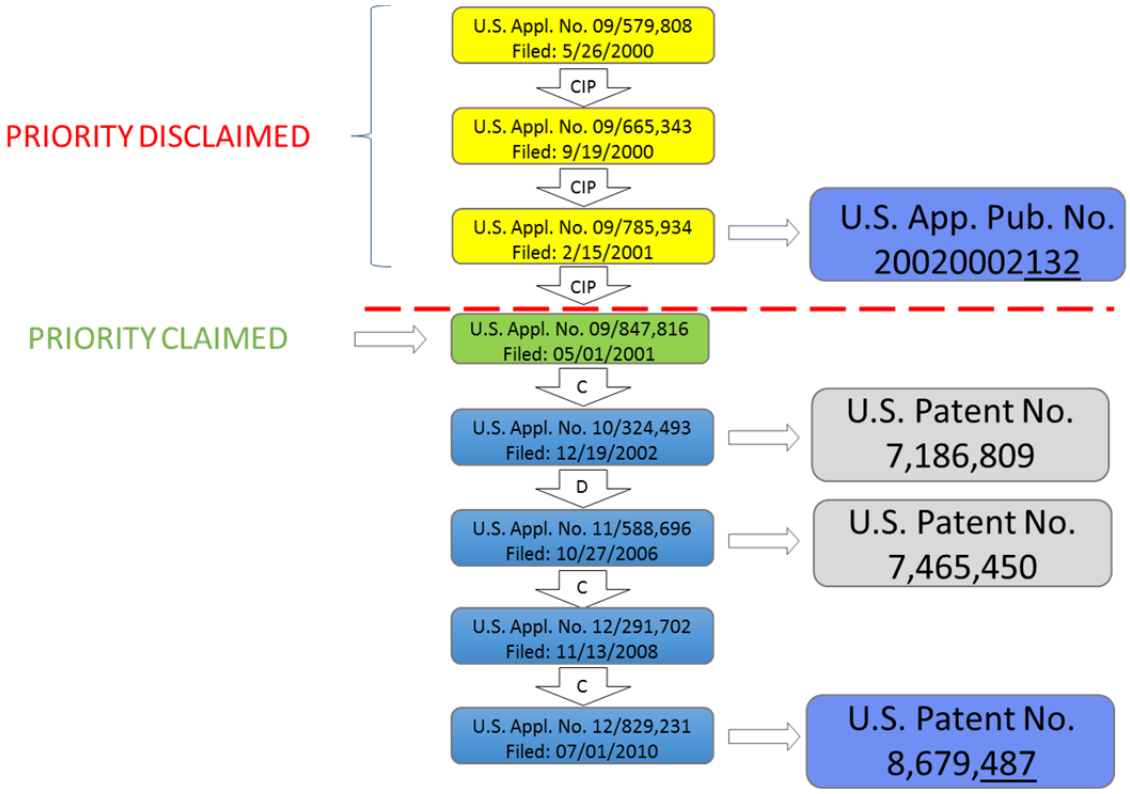
The '487 Patent is one member of an extended patent family sharing a specification that dates back to May 1, 2001. This original specification discloses six monoclonal antibodies ("mAbs") that interact with the human interleukin-4 ("IL-4") receptor ("IL-4R")—mAbs 12B5, 6-2, 27A1, 5A1, 63, and 1B7. The initial patents in this family claimed the various mAbs disclosed in the specification. But toward the end of 2008, Patent Owner changed tactics. Rather than claiming specific antibodies solely described in the original specification, Patent Owner began to file new continuing applications attempting to claim an expansive universe of antibodies by their functional relationship to a disclosed antibody—that is, attempting to claim any antibody that competes with one of the mAbs disclosed in the specification. Among the fundamental problems with this strategy is that Patent Owner did not invent this expansive universe of antibodies

or describe them in the original specification. More importantly, Patent Owner's broad claims ensnare the prior art, including Patent Owner's own prior art, disclosing a human antibody to IL-4R.

The '487 Patent is titled "Anti-Interleukin-4 Receptor Antibodies." It includes one independent claim and sixteen dependent claims directed to "isolated human antibod[ies] that compete[] with a reference antibody for binding to human [] interleukin-4 (IL-4) receptor." Ex. 1001, Claim 1. The cover of the '487 Patent indicates that the '487 Patent issued from the '231 Application, the fifth application in the claimed priority chain, filed July 1, 2010. The '487 Patent claims a 2001 priority date through a series of continuation and divisional applications beginning with the '816 Application, filed May 1, 2001. Ex. 1001, Cover.

Although not shown on the cover of the '487 Patent, three patent applications in the chain precede the filing of the '816 Application. These applications are U.S. Application Nos. 09/579,808 ("'808 Application"), filed on May 26, 2000; 09/665,343 ("'343 Application"), filed on September 19, 2000; and 09/785,934 ('934 Application"), filed on February 15, 2001. The '934 Application published on January 3, 2002 as the '132 Publication. These applications and the '132 Publication each disclose Patent Owner's prior art human antibody specific for human IL-4R, referred to as mAb 6-2. During prosecution of the '487 Patent,

Patent Owner *expressly disclaimed priority* to the '132 Publication and to the three earliest applications. Instead, Patent Owner confirmed priority for the '487 Patent beginning with the '816 Application, filed later on May 1, 2001. Ex. 1002 at 0145. The relationship between these applications, the '132 Publication, and the '487 Patent is shown below:



In the initial '487 Patent family prosecutions, Patent Owner sought claims directed to the antibodies it developed and disclosed in the specification that accompanied the '816 Application. The first patent to issue—the '809 Patent—includes claims directed to mAb 12B5. Ex. 1029, Claim 1. The claims generally

cover combinations of antibodies and antibody derivatives comprising a light chain variable region sequence of SEQ ID NO:10 and/or heavy chain variable region sequence of SEQ ID NO:12, which correspond to the variable regions of mAb 12B5. The second patent to issue—the '450 Patent—also relates to mAb 12B5 and generally covers methods of treating septic arthritis with an antibody comprising the variable regions found in mAb 12B5. Ex. 1031, Claim 1. The application for the '809 Patent, as originally filed, additionally claimed antibodies comprising light and/or heavy chain sequences corresponding to the five other disclosed mAbs. Ex. 1028, Claims 1-3, 7-17.

But following these early applications, in November of 2008, Patent Owner changed prosecution tactics. This tactical change occurred after Petitioners' publication of their discoveries and advances in this field. Rather than attempting to draft claims that reflect its own purported research and clinical development efforts, Patent Owner's later applications in the '487 Patent family make a run at claiming Petitioners' new advances as its own.

Petitioners are pioneers in antibody discovery and development, and have also filed applications and been awarded patents directed to antibodies to human IL-4R ("hIL-4R"). One such application—Petitioner Regeneron's Stevens application—published on July 3, 2008 ("Stevens"). Ex. 1006. Stevens is directed

to high-affinity antibodies to hIL-4R, and includes claims to antibodies having specific heavy chain and light chain variable sequences. *Id.*, Claims 3-13. Stevens also includes data demonstrating that at least certain of its antibodies compete for binding to IL-4R with Patent Owner's mAb 12B5 (referred to in Stevens as the "control antibody"), inhibit IL-4 binding to IL-4R, inhibit the biological effects of IL-4 and interleukin-13 ("IL-13") in cells, and have binding affinity constants higher than 1×10^{10}. *Id.*, Figs. 1A-1C, Claim 1, Examples 2-5, Tables 1, 3-5.

On November 13, 2008—four months after Petitioner's Stevens application published—Patent Owner filed the '702 Application, which attempted to cover antibodies disclosed in Stevens by functionally claiming, *inter alia*, any "isolated antibody that competes for binding to human IL-4 receptor with a fully human control antibody comprising the light chain variable region sequence (SEQ ID NO: 10) and the heavy chain variable region sequence (SEQ ID NO: 12) of antibody 12B5." Ex. 1032 at 0069. Not surprisingly, the amino acid sequences for Petitioner's antibodies disclosed in Stevens and which Petitioner invented using its own transgenic mice technology, are different from Patent Owner's 12B5 antibodies claimed in the '809 and '450 Patents. *Compare* Ex. 1006 *with* Ex. 1029 *and* Ex. 1031. As a result, using functional claims that capture the disclosure in

Stevens, Patent Owner's '702 Application sought to cover a genus of antibodies significantly broader than 12B5.

Ultimately, Patent Owner abandoned the claims of the '702 Application. But before doing so, Patent Owner filed the '231 Application—which ultimately issued as the '487 Patent—continuing its strategy of pursing broad claims intended to cover antibodies beyond its own disclosed antibodies using language that tracks Stevens' disclosure. Ex. 1002 at 0180-0255. The '231 Application included claims similar to the '702 Application, including the claim that issued as independent Claim 1 of the '487 Patent. That claim seeks to cover all isolated human antibodies that compete with a reference antibody containing SEQ ID NOS: 10 and 12 (such as mAb 12B5) for binding to hIL-4R. Ex. 1001, Claim 1.

By seeking broad, functionally-defined claims covering antibodies that Patent Owner did not invent or describe, but that others invented, Patent Owner consequently obtained claims that are anticipated by the prior art. Indeed, Patent Owner's broad claiming strategy in the '487 Patent ensnares its own prior art patent publication—the '132 Publication—which discloses mAb 6-2, an isolated human antibody that competes with mAb 12B5 for binding to human IL-4R. Ex. 1016, Example 6 (¶¶ [0246]–[0247]). The '132 Publication shares much of the same specification with the '487 Patent specification and specifically discloses

mAb 6-2—one of the six human IL-4R antibodies disclosed in the ’487 Patent specification—and the method for making mAb 6-2. Ex. 1016 at ¶ [0246]. But the ’132 Publication has an earlier effective filing date, and a different inventive entity—John Pluenneke. And, importantly, the ’487 Patent *explicitly disclaimed priority* to the ’132 Publication. Ex. 1002 at 0145. As a result, the ’132 Publication is invalidating prior art to the broad claims of the ’487 Patent.

On March 23, 2017, Petitioners filed IPR2017-01129 against the ’487 Patent. In that IPR, Petitioners assert that all the claims of the ’487 Patent are invalid in light of Stevens. Although Stevens was published after the asserted priority date of the ’487 Patent, Stevens is prior art because the applications to which the ’487 Patent claim priority do not provide written description and enablement support for the full scope of the ’487 Patent claims as required by 35 U.S.C. § 120. Thus, the ’487 Patent is not entitled to any priority date before its actual filing date of July 1, 2010. But should the Board disagree and determine that the ’487 Patent is entitled to its claimed May 1, 2001 priority date, the claims of the ’487 Patent are nevertheless invalid in light of Patent Owner’s ’132 Publication and its disclosure of the 6-2 antibody.

The Board has the opportunity to make things right by confirming for the reasons described in IPR2017-01129 that the broad, functionally-defined claims of

the ’487 Patent—which cover competing antibodies that the Patent Owner did not invent—are invalid in light Stevens, or alternatively, for the reasons described here, are invalid in light of Patent Owner’s disclaimed ’132 Publication.

II. MANDATORY NOTICES

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

Sanofi-Aventis U.S. LLC, Genzyme Corp., and Regeneron Pharmaceuticals, Inc. are the real parties-in-interest for Petitioners. Additionally, Patent Owner asserted infringement of the challenged patent against Sanofi, Sanofi-Aventis U.S. LLC, Genzyme Corp., Aventisub LLC, and Regeneron Pharmaceuticals, Inc. in a lawsuit styled: *Immunex Corporation v. Sanofi, et al.* (Case No. 17-cv-02613), pending in the United States District Court for the Central District of California. As a result, Petitioners further identify Sanofi and Aventisub LLC as real parties-in-interest, although neither Sanofi nor Aventisub LLC controls or funds this IPR.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

On March 20, 2017, Petitioners filed a complaint against Amgen Inc. and Immunex Corporation in the United States District Court for the District of Massachusetts, Case No. 17-cv-10465, seeking a declaration that Petitioners’ development, manufacturing, sale, promotion and related activities for their product Dupixent® (dupilumab) do not directly or indirectly infringe the ’487

Patent. Petitioners voluntarily dismissed this action, without prejudice, on May 1, 2017.

On April 5, 2017, Patent Owner filed a complaint against Sanofi, Sanofi-Aventis U.S. LLC, Genzyme Corporation, and Aventisub LLC in the United States District Court for the District of Central California, Case No. 2:17-cv-02613, alleging infringement of the '487 Patent.

On March 23, 2017, Petitioners filed IPR2017-01129 which challenges the '487 Patent on a different ground than the ground in this Petition and Patent Owner filed its preliminary response on July 6, 2017.

On June 28, 2017, Sanofi, Sanofi-Aventis U.S. LLC, Genzyme Corporation, and Aventisub LLC filed an answer and counterclaims against Immunex Corp. and Amgen Inc. in the United States District Court for the District of Central California, Case No. 2:17-cv-02613.

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

Lead counsel: John B. Campbell (Reg. No. 54,665) of McKool Smith P.C.

Back-up counsel: Mike McKool (*pro hac vice* pending) and John F. Garvish (*pro hac vice* pending), of McKool Smith P.C.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Email: RS-IPR@McKoolSmith.com

Post: John B. Campbell, McKool Smith P.C., 300 W. 6th Street, Suite 1700, Austin, Texas 78701.

Telephone: (512) 692-8700

Fax: (512) 692-8744

Petitioners consent to electronic service.

III. GROUNDS FOR STANDING

Petitioners certify that the '487 Patent is available for *inter partes* review, and that Petitioners are not barred or estopped from requesting an *inter partes* review challenging the claims on the grounds identified in this Petition.

IV. STATEMENT OF PRECISE RELIEF REQUESTED FOR EACH CLAIM CHALLENGED

A. Claims for Which Review Is Requested (37 C.F.R. § 42.104(b)(1))

Petitioners request the review and cancellation of claims 1–14 and 16–17 (the "Challenged Claims") of the '487 Patent.

B. Statutory Grounds of Challenge (37 C.F.R. § 42.104(b)(2))

The Challenged Claims should be canceled for the following reasons:

Ground 1: Claims 1–14 and 16–17 are invalid under 35 U.S.C. § 102(e) based on U.S. Patent Publication No. 2002/0002132 (the "'132 Publication"). Ex. 1016.

The '487 Patent's earliest claimed priority date is May 1, 2001. The '132 Publication (Ex. 1016) is a published patent application that was filed on February15, 2001, and thus qualifies as prior art under 35 U.S.C § 102(e). Although the '132 publication was referenced during prosecution of the '487 Patent, it was never expressly relied on by the Examiner for a grounds of rejection or otherwise.[1]

[1] The examiner cited March et al., U.S. Patent Publication No. 2002/0076409 (Ex. 1202 ("March")) as "art made of record and not relied upon." Ex. 1002 at 0051. Like the '132 Publication, March is prior art under 35 U.S.C. 102(e) and discloses mAb 6-2. Ex. 1202 at ¶¶ [0219]–[0220]. That the Examiner identified March as "art made of record" demonstrates the relevance of the disclosure regarding the mAb 6-2 antibody in March, which is similar to that disclosed in the '132 Publication. Despite citing March in the prosecution history, the examiner did not rely on March to formulate any rejection, presumably due to the absence of any

Ground 1 of this Petition is not cumulative with IPR2017-01129 in which Petitioners also challenge the validity of the '487 Patent. In IPR2017-01129, Petitioners assert that the Challenged Claims are anticipated by Stevens—a U.S. Patent Application filed by Petitioner Regeneron in 2007, which published in 2008, that teaches claimed antibodies of the '487 Patent—because the Challenged Claims are not entitled to the '487 Patent's purported May 1, 2001 priority date, making Stevens invalidating prior art. The anticipation ground presented in IPR2017-01129 is substantially different from the anticipation ground presented in this Petition. Specifically, this Petition relies on Patent Owner's own '132 Publication—which was filed February 15, 2001 and is prior art to the '487 Patent based on its purported May 1, 2001 priority date—the '132 Publication's disclosure of the fully human anti-hIL-4R antibody referred to specifically as mAb 6-2, and testing of mAb 6-2 to demonstrate that it inherently satisfies the challenged claims. Petitioners could not have filed this Petition sooner, because the testing of the prior art 6-2 antibody disclosed in the '132 Publication was only recently completed on July 19, 2017. Ex. 1200 ¶ 81.

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competition data regarding mAbs 6-2 and 12B5. Accordingly, the arguments presented in this Petition are not redundant in view of March.

V. FIELD OF TECHNOLOGY

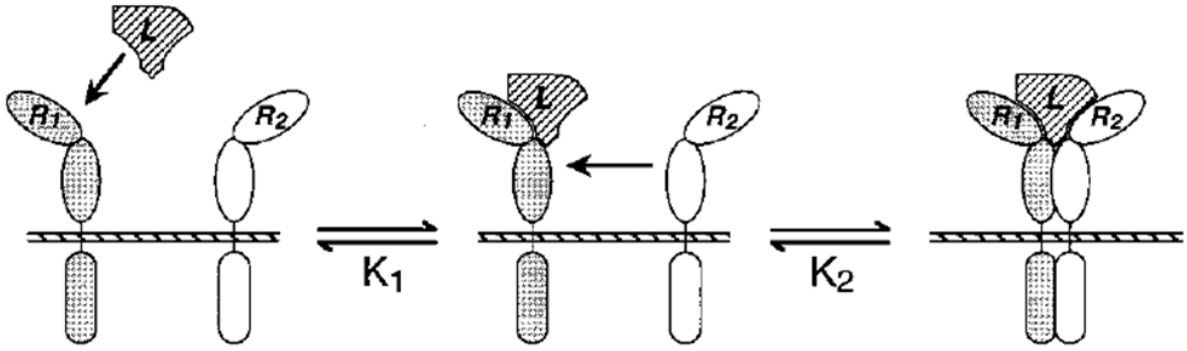
The '487 Patent is directed to antibodies that block hIL-4R and accordingly inhibit IL-4 and IL-13 induced signaling. Ex. 1001 at 0001 (Title, Abstract), 0016(18:32)-0017(19:5).

A. IL-4 and IL-13

IL-4 and IL-13 are small signaling proteins (called cytokines) that regulate the adaptive immune system. Ex. 1200 ¶¶ 27-29. Before May 1, 2001, IL-4 and IL-13 were understood to play a pivotal role in the development of several hyperactive allergic disorders (*e.g.*, eczema, hay fever, and some types of asthma). *Id.* In particular, it was known that IL-4 induced signaling mediates a wide variety of immunogenic responses, which ultimately culminate in the body releasing cytotoxic chemicals that cause many of the symptoms associated with allergies (*e.g.*, inflammation, flushing). Ex. 1200 ¶¶ 27-28; Ex. 1011 at 405-409; Ex. 1007 at 2:1-14. It was also known that IL-13 mediates many of the same immunogenic responses as IL-4. Ex. 1200 ¶¶ 28-29.

Prior to May 1, 2001, skilled artisans discovered that IL-4 and IL-13 induce overlapping physiological effects because they share a common receptor subunit, termed IL-4 receptor alpha ("IL-4Rα"). Ex. 1200 ¶ 29; Ex. 1010 at 13869. As illustrated below, IL-4 signaling through IL-4R occurs in a two-step process. First,

IL-4 ("L") binds to IL-4Rα ("R_1") to form an IL-4/IL-4Rα complex. Second, the IL-4/IL-4Rα complex associates with one of two other subunits ("R_2") to form a ternary (three-member) signaling complex. Ex. 1200 ¶ 31.



Ex. 1015 at 13166. The two potential subunits with which the IL-4/IL-4Rα complex may associate are called common gamma chain ("γc") and IL-13 receptor alpha 1 ("IL-13Rα1"). Ex. 1200 ¶¶ 30-33. When the IL-4/IL-4Rα complex associates with the γc subunit, it is termed a "Type 1" receptor complex, and when it associates with the IL-13Rα1 subunit, it is termed a "Type 2" receptor complex. Ex. 1200 ¶¶ 30-33.

IL-13 induced signaling utilizes the same receptor subunits that comprise the Type 2 receptor, but the interaction begins with IL-13Rα1. Ex. 1200 ¶¶ 32-33; Ex. 1014 at 271. First, IL-13 binds to IL-13Rα1. Second, the IL-13/IL-13Rα1 complex associates with IL-4Rα to form a ternary signaling complex. Ex. 1200

¶ 33. The binding site between IL-4Rα and the IL-13/IL-13Rα1 complex coincides with the binding site between IL-4Rα and IL-4 ("IL-4Rα's active site"). Ex. 1200 ¶¶ 29-33; Ex. 1014 at 279.

Because IL-4Rα's active site is integral to IL-4 and IL-13 induced signaling, skilled artisans understood that a therapeutic agent that blocks IL-4Rα's active site would simultaneously inhibit both IL-4 and IL-13 induced signaling. Ex. 1200 ¶ 34; Ex. 1011 at 412; Ex. 1014 at 279. Accordingly, IL-4Rα's active site became a target for therapeutics directed toward mitigating the effects of hyperactive allergic disorders well before May 1, 2001. Ex. 1200 ¶ 34; Ex. 1011 at 410-412; Ex. 1007 at 2:19-23. In particular, monoclonal antibodies that block the active site of IL-4Rα ("anti-hIL-4R blocking antibodies") were known as "especially interesting" therapeutics because "[s]uch agents may be expected to inhibit the signaling induced by the binding of both IL-4 and IL-13 because of shared receptor subunits [*i.e.*, IL-4Rα]." Ex. 1011 at 412; Ex. 1007 at 2:19-20; Ex. 1200 ¶ 34.

B. Monoclonal Antibodies

Many prior art anti-hIL-4R blocking antibodies were derived from mice. *E.g.*, Ex. 1007; Ex. 1200 ¶ 38. It was widely understood in the prior art that the first step for isolating anti-hIL-4R antibodies from mice is to isolate the extracellular domain of hIL-4Rα for use as the target antigen—a molecule that

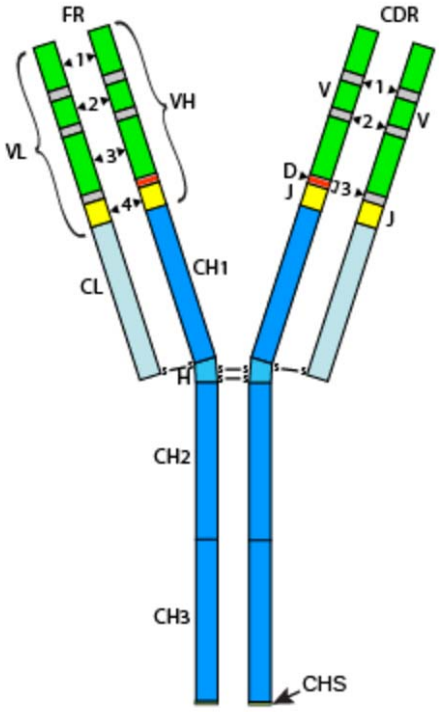
causes the immune system to produce antibodies against it. Ex. 1007 at 6:56-57 (teaching using as the antigen the "the extracellular domain of the human 130 kDa IL-4R," which is hIL-4Rα). Subsequently, the mice are immunized with hIL-4Rα once every few weeks until significant evidence of anti-hIL-4R antibody production is detected. Ex. 1007 at 4:9-41, 7:40-54. Next, the mice are sacrificed and the B-cells in their spleens (which produce antibodies) are harvested. Ex. 1007 at 4:9-11. The harvested B-cells are fused to cancerous B-cells, called myelomas, to form immortal B-cells, called hybridomas. Ex. 1007 at 3:57-4:14; Ex. 1200 ¶ 40.

Because each hybridoma expresses antibodies with identical structure, the hybridomas can be isolated and allowed to proliferate *in vitro* such that each isolated culture produces many copies of the same antibody—called monoclonal antibodies (mAbs). Subsequently, the mAbs can be screened by the appropriate functional assays for desirable features (*e.g.*, blocking IL-4R). Ex. 1007 at 4:14-21, Examples 2-4, 7. Each of these steps was described in the prior art.

As shown in the figure below,[2] antibodies are generally understood as "Y-shaped proteins." Ex. 1200 ¶ 35. They are composed of two identical heavy

[2] http://www.imgt.org/IMGTeducation/Tutorials/index.php?article=IGandBcells&chapter=Properties&lang=UK&nbr=3.

chains and two identical light chains, which are bound together by disulfide bonds. Ex. 1200 ¶ 35. These chains are further subdivided into variable regions (VH, VL) and constant regions (CH1-CH3, CL). Ex. 1200 ¶ 35. An antibody's binding characteristics (*e.g.*, specificity and affinity) are primarily determined by the sequence of amino acids within its variable regions, while the constant regions mediate how the immune system responds to an antibody/antigen complex. Ex. 1200 ¶¶ 36-37. The variable region for each heavy and light chain is subdivided into four framework regions (FRs) and three complementarity determining regions (CDRs). Ex. 1200 ¶ 36. The CDRs fold together to form the antibody's antigen binding site. Ex. 1200 ¶ 36. The specific part of an antigen to which the antibody binds is called the epitope. Ex. 1200 ¶ 36.



Antibody illustration showing variable regions with CDRs (green) and constant regions (blue)

C. Isolating Human Antibodies

Although "human" and "murine" (mouse) antibodies are composed of the same 20 amino acid building blocks, the amino acid sequences that compose an antibody correlate to the DNA of the host species from which the antibody was derived. Ex. 1200 ¶ 39. Thus, the sequence of amino acids in a "human" antibody can differ from a "murine" antibody, and the human immune system is capable of identifying and targeting characteristically murine antibodies as foreign invaders (*e.g.*, as it would for a pathogen). Ex. 1200 ¶ 39. Accordingly, humans who have

been systemically injected with fully murine antibodies often develop an undesirable human anti-mouse antibody ("HAMA") reaction. Ex. 1200 ¶ 39. To mitigate the risk of an HAMA reaction, by May 1, 2001, skilled artisans had devoted considerable research toward developing techniques for making antibodies with characteristically human amino acid sequences. *E.g.*, Ex. 1200 ¶ 39; Ex. 1007; Ex. 1009.

One such prior art technique for making human antibodies, described in the '132 Publication, involves the use of transgenic mice. Ex. 1016 at 1, ¶ [0010] ("Particular antibodies provided herein include human monoclonal antibodies generated by procedures involving immunization of transgenic mice."), at 11, ¶ [0155] ("Examples of techniques for production and use of [] transgenic animals are described in U.S. Patents 5,814,318, 5,569,825, and 5,545,806 . . . ."); Ex. 1200 ¶ 119-120. Transgenic mice are mice that have been genetically modified with foreign (*e.g.*, human) genes to express, for example, human antibodies instead of murine antibodies when exposed to a foreign antigen (such as hIL-4Rα). *See* Ex. 1016 at 18, ¶ [0235]; Ex. 1200 ¶¶ 118-119.

To make human antibodies to IL-4R using this technique, a transgenic mouse is "immuniz[ed] . . . with an IL-4R polypeptide" so that "antibodies directed against the IL-4R polypeptide are generated in said [mouse]." Ex. 1016 at 11,

¶ [0153]; Ex. 1200 ¶ 54. The antibodies are then isolated "by conventional procedures, e.g., by immortalizing spleen cells harvested from the transgenic [mouse] after completion of the immunization schedule" and fusing the spleen cells "with myeloma cells to produce hybridomas, by conventional procedures." Ex. 1016 at 11, ¶ [0157]; Ex. 1200 ¶ 54. The hybridomas in turn produce human IL-4R monoclonal antibodies, which can be "purified by conventional techniques." Ex. 1016 at 11, ¶ [0158]; Ex. 1200 ¶ 54. The hybridomas may be screened to "identify[] a hybridoma cell line that produces a monoclonal antibody that binds an IL-4R polypeptide." Ex. 1016 at 11, ¶ [0158]; Ex. 1200 ¶ 54. These hybridomas or mAbs may be further screened to identify mAbs with particular properties, such as "the ability to inhibit an IL-4-induced and an IL-13-induced biological activity." Ex. 1016 at 10, ¶ [0149]; Ex. 1200 ¶ 54.

D. Antibody Assays

After antibodies have been isolated, they may be tested to determine their characteristics. One such test is a competition assay to determine whether the antibodies compete with other antibodies for binding to an antigen. For example, antibody competition assays can generally assess the capability of two antibodies to bind to the same or overlapping epitopes on an antigen. Ex. 1200 ¶ 46. Prior to May 1, 2001, several competition assays were known in the art. Although the '487

Patent specification does not describe any antibody-antibody competition assay, Patent Owner has endorsed the flow cytometry assay described in Perez de la Lastra et al. (Ex. 1026 at 664), which was known before May 1, 2001, as being suitable for determining competition. Ex. 1201 [Immunex's EU Opposition Response] at 12-13 ("D24 [Perez de la Lastra] provides methods for determining competition between antibodies and competition was identified successfully using those methods. A skilled person could therefore use a method disclosed in D24 [Perez de la Lastra] to identify competition between a test antibody and a reference antibody of claim 1, which bind to human IL-4R.").

Another type of assay that may be performed to measure the functional characteristics of an antibody is a signaling inhibition assay. A signaling inhibition assay measures an antibody's ability to inhibit a biological activity of a cell. An example of one such assay that is particular to IL-4 and IL-13 activity is the CD23 assay described in Example 5 of the '487 Patent. Ex. 1016 at 19, ¶¶ [0242]–[0245]. Ex. 1200 ¶ 63. "CD23" is a cell surface receptor that binds to antibodies of the IgE isotype. Ex. 1200 ¶ 63. IL-4 and IL-13 induced signaling increases CD23 expression. Accordingly, an antibody that inhibits IL-4 and IL-13 signaling will reduce IL-4 and/or IL-13 induced CD23 expression. Ex. 1200 ¶ 63. Thus, a CD23 assay measures the ability of a particular test antibody to inhibit IL-4 or IL-13

induced expression of CD23. Ex. 1200 ¶ 63. As noted in the '487 Patent, a flow cytometry-based assay may be used to conduct a CD23 expression assay. Ex. 1001 at 40:64-64; *see also* Ex. 1016 at 19, ¶ [0244].

One may also measure the functional characteristics of antibodies with a binding affinity assay. A binding affinity assay measures the strength with which a particular antibody binds to its partner antigen. An antibody with a relatively higher binding affinity constant ("K_a") binds more strongly to its antigen than an antibody with a relatively lower binding affinity constant. Ex. 1200 ¶ 64. Although no binding affinity assay is described in the '487 Patent, one assay that was known in the art for assessing antibody binding affinity prior to May 1, 2001 is called a surface plasmon resonance assay. Ex. 1200 at ¶ 44; *see also, e.g.*, Ex. 1009 [Kucherlapati] at 32-35 (describing a surface plasmon resonance assay to measure antibody affinity).

VI. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSITA") relevant to the subject matter disclosed in the '487 Patent and the earlier applications in its family 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. Furthermore, a

POSITA 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. *See* Ex. 1200 ¶ 22. For purposes of this Petition, the 35 U.S.C. § 102 invalidity analysis is performed from the perspective of a POSITA as of the '487 Patent's claimed May 1, 2001 priority date. Ex. 1200 ¶¶ 21-22.

VII. THE '487 PATENT

A. Admitted Prior Art and Alleged Improvement

Patent Owner admits that anti-hIL-4R blocking antibodies were readily isolatable by skilled artisans before May 1, 2001. Ex. 1008 at 0026:6-7. ("Antibodies specific for IL-4 or IL-4R may be prepared by well known procedures."). Patent Owner also admits that human anti-hIL-4R blocking antibodies could be isolated from transgenic animals by "conventional procedures." Ex. 1008 at 0027:3-17.

Using the "conventional" methods for generating and isolating human anti-hIL-4R blocking antibodies from transgenic mice, Patent Owner obtained the amino acid sequences for the heavy and light chain variable regions of six human anti-hIL-4R blocking antibodies: mAbs 6-2, 12B5, 27A1, 5A1, 63, and 1B7 (the

"Six MAbs"). Ex. 1008 at 0028:10-0034:21.[3] However, the '487 Patent does not claim the sequence of any of the Six MAbs or their derivatives—earlier patents in the family claimed them. *Compare* Ex. 1001 *with* Ex. 1029 *and* Ex. 1031. The '487 Patent represents a radical extension beyond its original specification. Claim 1, the only independent claim, claims an "antibody" generically by purely functional terms: "[a]n isolated human antibody that competes with a reference antibody for binding to human IL-4 [] receptor." Ex. 1001. It further recites that the reference antibody—not the claimed antibody—"comprises" SEQ ID NOS: 10 and 12, which are the variable light and heavy chain amino acid sequences for mAb 12B5. *Id.* Notwithstanding that the claims hinge on antibody competition, the only disclosure in the original specification regarding competition with a claimed reference antibody does little more than mimic the claim. *See* Ex. 1008 at 0029:16-18 ("Particular monoclonal antibodies of the invention are selected from the group consisting of …**a MAb that competes with 12B5 for binding to** a cell that expresses **human IL-4R**.") (emphasis added).

[3] The encoding nucleotides and amino acid sequences for the Six MAbs are disclosed in SEQ ID NOS: 5-26. Ex. 1008 at 0051:13-30, 0053:11-0055:11.

The dependent claims do not meaningfully limit Claim 1. Ex. 1001. Claims 2–10 recite functional limitations linked with the "compet[ing]" function recited in Claim 1 (cross-blocking the reference antibody, inhibiting IL-4 and IL-13, and tightly binding to IL-4R). Claims 11–15 are directed to types of antibodies (full-length antibodies, specific antibody isotypes, antibody fragments, fusion proteins, and single chain antibodies) which were "conventional" in the prior art. Ex. 1001 at 0015(15:39-62), 0017(19:13-20), 0018(22:29-31), 0020(26:12-28). Claims 16–17 are directed to combining the claimed antibody with a pharmaceutically acceptable solvent or "kit." Ex. 1001, claims 16 and 17.

Individual claim elements in the '487 Patent claims also do not help distinguish them over the prior art. For example, as discussed further below, the BRI of "human" in the context of the claimed "isolated human antibodies" includes both "partially or fully human" antibodies. Ex. 1001 at 0017(20:57-60); 0018(21:1-2); 0017(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."). In addition, many of the '487 patent claims recite binding to "human IL-4 receptor." The '487 Patent, however, does not limit "human IL-4 receptor" to any particular form of the receptor, but instead states that "IL-4 receptor . . . encompass[es] this protein in various forms that are capable of

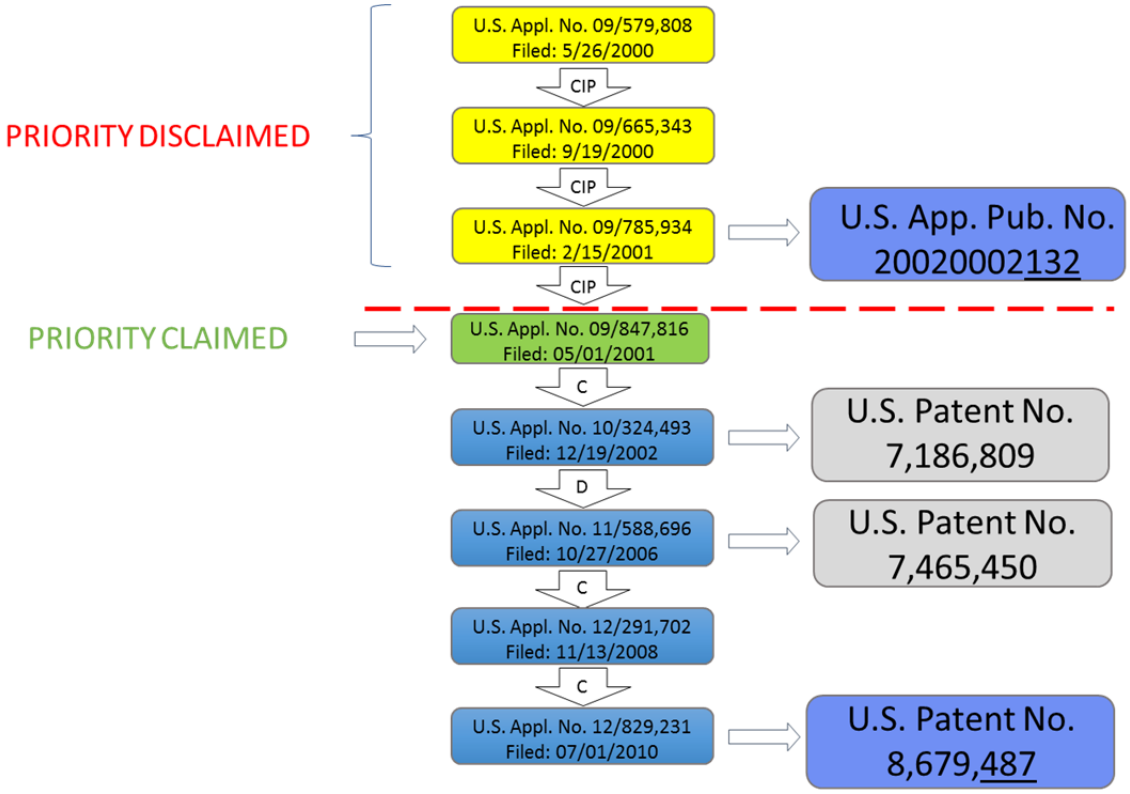
functioning as IL-4 antagonists, including but not limited to soluble fragments, fusion proteins, oligomers, and variants that are capable of binding IL-4." Ex. 1001 at col. 12:4-15. As a result, none of these claim elements, or others, meaningfully distinguish the claims over the prior art.

B. Prosecution History of the '487 Patent

Patent Owner filed the '231 Application on July 1, 2010. The '231 Application originally named Richard J. Armitage, Jose Carlos Escobar, Arvia E. Morris, and John D. Pluenneke as inventors. Ex. 1002 at 0164. On September 20, 2010, Patent Owner submitted declarations supporting the deletion of John D. Pluenneke as a named inventor. Ex. 1002 at 0144-0150. Patent Owner also expressly disclaimed priority to the three earliest applications in the family chain (shown below)—the '808 Application, '343 Application and '934 Application (which published as the '132 Publication)—and asserted that priority of the '231 Application was claimed only to the May 1, 2001 filing date of the '816 Application:

> As noted in the Specification of the present application, priority for the instant application begins with U.S. Pat App. No. 09/847,816, filed May 1, 2001 (3005-US-CIP3). **Priority is not claimed to any of U.S. Pat App. No. 09/579,808, filed May 26, 2000 (3005-US-NP), 09/665,343, filed September 19, 2000 (3005-US-CIP), or 09/785,934, filed February 15, 2001, published January 3, 2002 as U.S. Pub. No. 2002-0002132 (3005-US-CIP2).**

Ex. 1002 at 0145 (emphasis added). The relationship between the disclaimed U.S. Applications, the '132 Publication and the '487 Patent is shown below:



In addition, although the functionally-claimed genus of antibodies "that compete[]" is not described in the original specification, it was the central distinguishing factor that Patent Owner relied upon to overcome prior art asserted by the Examiner during prosecution of the '487 Patent. The Examiner first rejected the claims as anticipated by U.S. Patent No. 5,717,072 ("Mosley"), which teaches "an isolated human antibody that binds to human IL-4 receptor . . . and inhibits IL-4 mediated activities." Ex. 1002 at 0119-0120. Although Patent Owner

acknowledged that Mosley provides a "method for generating . . . anti-human IL-4 receptor antibodies," Patent Owner argued that the Examiner "only *assumes* that 'the antibody' of Mosley . . . competes for binding against the antibodies in the rejected claims" and that the Examiner's "assertion must be proved in order to support the rejection." Ex. 1002 at 0101 (emphasis in original).

In a series of subsequent rejections and responses, Patent Owner repeatedly argued that the Examiner had to *prove* that a prior art antibody competes with the '487 Patent's reference antibody to maintain the rejection. *See* Ex. 1002 at 0075-0076 (requesting "documentary evidence" that Mosley's antibodies compete because "it cannot be concluded that an antibody made according to Mosley would *necessarily* compete for binding with the reference antibody of the rejected claims") (emphasis in original), 0061 ("If it is a fact that any two antibodies that bind to the same 207 amino acid polypeptide [*i.e.*, extracellular portion of IL-4Rα] must *necessarily* compete for binding to the polypeptide, then let the evidence show it.") (emphasis in original), 0040. On November 11, 2011, Patent Owner filed a Response to a November 1, 2011 Advisory Action, further explaining its contention that Mosley does not inherently anticipate:

> Applicants' point is that the properties of Mosley's prophetic antibodies cannot simply be measured or tested because the antibodies do not actually exist. They must be inferred from Mosley's disclosure.

> So the relevant question is, if an antibody according to Mosley were made, would it necessarily have all of the properties recited in the rejected claims?

Ex. 1002 ['231 Application] at 0060. Ultimately, unable to produce evidence that prior art antibodies compete with the '487 Patent's reference antibody—evidence supplied by the Petitioners in this Petition—the Examiner relented, issued a notice of allowance, and the '487 Patent issued on March 25, 2014. Ex. 1002 ['231 Application] at 0001, 0021.

The '487 Patent prosecution history presents a prime example of the problem with defining an invention purely in terms of what it does instead of what it is. By claiming a genus of antibodies by an arbitrary function—"that ***competes*** with a reference antibody"—and demanding proof of a prior art antibody that performs that arbitrary function, Patent Owner was able to push amorphous, overly broad claims through prosecution. Yet, Patent Owner's own specification includes no proof of any specific antibody that competes with the claimed reference antibody.

The Examiner seemed to have subsequently appreciated this issue shortly after the Federal Circuit clarified the law on written description of functional antibody claims in *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014). In U.S. Application No. 14/175,943 ("the '943

Application"), a continuation application to the '487 Patent, Patent Owner again sought claims to "[a]n isolated human antibody that competes with a reference antibody." Ex. 1003 ['943 Application] at 0201. This time, the claimed "reference antibody" comprised the heavy and light chain variable region sequences of mAbs 27A1, 5A1, or 63. Ex. 1003 ['943 Application] at 0201; 0172:8-14 (27A1); 0173:8-14 (5A1); 0174:6-12 (63).

In rejecting the claims in the '943 Application—claims that are substantively identical to those in the '487 Patent—the Examiner noted that "[t]he instant claims encompass a genus of antibodies that are described only by their function of competing with a reference for binding to a specific target." Ex. 1003 ['943 Application] at 0081; 0085 (emphasis in original). However, the original specification shared by the '487 Patent and '943 Application "fails to disclose and there is no art-recognized correlation between the structure of the genus of yet to be discovered antibodies and the function of competing for binding to human IL-4 receptor with specific reference antibodies." Ex. 1003 ['943 Application] at 0096. Indeed, as noted above, the Examiner observed that the specification "does not disclose [any] antibodies that compete with the recited antibody." Ex. 1003 ['943 Application] at 0086. Accordingly, the Examiner rejected the claims under 35 U.S.C. § 112. Ex. 1003 ['943 Application] at 0084-0088. Afterwards, Patent

Owner abandoned its functional "antibody that competes" claims in favor of narrower claims limited to claimed antibodies (as opposed to reference antibodies) with the amino acid sequences from the CDRs of mAbs 27A1, 5A1, and 63. Ex. 1003 ['943 Application] at 0072-0074; 0077-0078. The Examiner issued a notice of allowance for these sequence-specific claims, which issued in U.S. Patent No. 9,587,026 on March 7, 2017. Ex. 1003 ['943 Application] at 0059; Ex. 1039.

C. Claim Construction

In an *inter partes* review, a claim is given its "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b). Petitioners submit that for the purpose of this Petition, as in their IPR2017-01129 Petition, the BRI of most of the terms recited in Claims 1-14 and 16-17 of the '487 Patent would be clear on their face to one of ordinary skill in the art. *See supra* Section VII.A. Petitioners therefore request that the claim terms be given their broadest reasonable interpretation (BRI), as understood by a POSITA and consistent with the specification.[4] With respect to terms that may

[4] District courts apply different standards of proof and claim interpretation. Any construction or application (implicit or explicit) of the claims in this Petition is specific to the BRI standard.

need to be defined or further clarified, Petitioners request that the Board adopt the following claim constructions.

1. *"human" (Claim 1)*

The BRI of "human" is "partially or fully human." As the Federal Circuit has explained, "[w]hen a patent thus describes the features of the 'present invention' as a whole, this description limits the scope of the invention." *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1308 (Fed. Cir. 2007). Like the patent in *Verizon*, the '487 Patent explains that "[a]ntibodies of **the invention include**, but are not limited to, **partially human** (preferably fully human) monoclonal antibodies that inhibit a biological activity of IL-4 and also inhibit a biological activity of IL-13." Ex. 1001 at 0017(20:57-60) (emphasis added). And the specification consistently describes "human antibodies" as including partially human antibodies. *See* Ex. 1001 at 0017(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.") (emphasis added), 0018(21:1-2). Because the '487 Patent defines the "[a]ntibodies of the invention" to include partially human antibodies, the BRI of "human" is "partially or fully human."

Petitioners anticipate that Patent Owner will assert that the term "human"

means "fully human" (or the like). Construing "human" in a way that excludes partially human antibodies would be inappropriate not only because it is contrary to Patent Owner's express definition of its "invention," but also because it would exclude disclosed embodiments. The '487 Patent explains that "embodiments include chimeric antibodies, e.g., humanized versions of murine monoclonal antibodies." Ex. 1001 at 0017(19:21-22). "Chimeric antibodies" are partially human antibodies. Ex. 1200 ¶ 77. As noted by this Board, and well established in the case law, "a general principle of claim construction counsels against interpreting claim terms in a way that excludes embodiments disclosed in the specification." *Nissan N. Am., Inc. v. Norman IP Holdings, LLC*, IPR2014-00564, Paper 36 at 7 (PTAB Aug. 26, 2015) (citing *Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276-77 (Fed. Cir. 2008)). Accordingly, any argument that "human" means "fully human" (or the like) should be rejected.

2. *"antibody" (Claim 1)*

The term "antibody" should be given its BRI meaning herein.[5] Despite not

[5] In IPR2017-01129, Patent Owner incorrectly argues that institution should be denied because in litigation Petitioners assert that "antibody" should be limited to the sequences of the Six MAbs or their equivalents. IPR2017-01129, Paper No. 14

providing its own express construction, Patent Owner states in related IPR2017-01129 that the term "antibody" requires construction, and attempts to take Petitioners to task for allegedly not providing any construction for the term. IPR2017-01129, Paper No. 14 at 15-16. To the contrary, Petitioners applied the '487 Patent's purported definition of "the term 'antibody'" as broadly "encompass[ing] whole antibodies and antigen binding fragments thereof." Ex. 1001 at 16:29–31. Dependent claims 11–15 further demonstrate that

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at 17. But the broadest reasonable interpretation applies here, and "may be the same as or broader than the construction of a term under the *Phillips* standard." *Facebook, Inc. v. Pragmatus AV, LLC*, 582 F. App'x 864, 869 (Fed. Cir. 2014); *see also Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2145-2146 (2016). Patent Owner "does not concede" that the term "antibody" should be limited to the Six MAbs (IPR2017-01129, Paper No. 14 at 17)—indeed, Patent Owner contends that it should *not* be limited by asserting in litigation that Petitioners' antibody infringes. Petitioners therefore demonstrate herein that under Patent Owner's own interpretation, the claims are anticipated by the '132 Publication. Moreover, even if "antibody" were limited to the Six MAbs, the claims are still anticipated by the '132 Publication's disclosure of mAb 6-2, which is one of the Six MAbs.

"antibody" includes full-length antibodies of any isotype, antibody fragments, fusion proteins, and/or single chain antibodies. Accordingly, Petitioners continue to use the term "antibody" consistent in breadth with the definition offered in the '487 Patent's specification and dictated by the dependent claims. *See supra* Section VII.A.

VIII. SCOPE AND CONTENT OF THE PRIOR ART

A. The '132 Publication

United States Patent Application No. 09/785,934, entitled "Use of Interleukin-4 Antagonists and Compositions Thereof" was filed on February 15, 2001 and published on January 3, 2002 as United States Patent Application Pub. No. 20020002132 (the "'132 Publication"). Ex. 1211 ['934 Application]; Ex. 1016 ['132 Publication]. The '132 Publication, which lists John D. Pluenneke as the inventor, is an application in the '487 Patent family continuation chain as illustrated above.

Despite being in the same patent family as the '487 Patent, the '132 Publication is § 102(e) prior art to the '487 Patent. Under 35 U.S.C. § 102(e), a U.S. patent application published *by another* having an earlier U.S. filing date can be relied on as prior art. 35 U.S.C. § 102(e)(1) ("A person shall be entitled to a patent unless … (e) the invention was described in —(1) an application for patent,

published under section 122(b), *by another filed in the United States before the invention by the applicant for patent*.") (emphasis added). The term, "by another," means a different inventive entity—*i.e.*, not all inventors are the same. *In re Kaplan*, 789 F.2d 1574, 1575 (Fed. Cir. 1986) ("It is a given . . . that a sole inventor and joint inventors including the sole inventor are separate 'legal entities,' a legal proposition from which certain legal consequences flow 'such as who must apply for patent.'") (citation omitted).

The '132 Publication is § 102(e) prior art to the '487 Patent because it is a published application filed "by another" before May 1, 2001. The '132 Publication lists John D. Pleunneke as the sole named inventor, and he is not an inventor on the '487 Patent. Rather, the '487 Patent identifies Richard J. Armitage, Jose Carlos Escobar, and Arvia E. Morris as the three named co-inventors. The '132 Publication was also "filed before the invention by the applicant for patent" because it was filed on February 15, 2001, before the '487 Patent's claimed May 1, 2001 priority date.

In addition, during prosecution Patent Owner expressly disclaimed priority to the '132 Publication. Ex. 1002 [Response to the Notice to File Missing Parts (9-20-2010)] at 0144-0145 ("Priority is not claimed to … 09/785,934, filed February 15, 2001, published January 3, 2002 as U.S. Pub. No. 2002-0002132 (3005-US-

CIP2).”). Because the ’132 Publication names different inventors from the ’487 Patent and was filed before the ’487 Patent’s claimed priority date, and Patent Owner expressly disclaimed priority to it, the ’132 Publication is § 102(e) prior art to the ’487 Patent.

Moreover, given that the ’132 Publication and the ’487 Patent are in the same family chain, the two include much of the same disclosure.[6] This includes the disclosure of mAb 6-2, one of the six antibodies discussed in the ’487 Patent specification. Ex. 1200 [Zurawski Declaration] at ¶ 118; Ex. 1203 (comparing ’132 Publication specification with ’487 Patent specification). Specifically, the ’132 Publication discloses that the “[p]articular antibodies provided herein include human monoclonal antibodies generated by procedures involving immunization of transgenic mice. Such human antibodies may be raised against human IL-4 receptor.” Ex. 1016 [’132 Publication], Abstract. The ’132 Publication also

[6] The disclosure and teachings in the ’132 Application are a subset of what is included in the ’487 Patent specification. At a high level, the specification of the ’487 Patent adds, *inter alia*, the disclosure starting at col. 20:57 to col. 27:8, as well as a portion of Example 6, all of Examples 8 and 9, and the disclosure of SEQ ID NOS. 4-26. *See* Ex. 1203.

includes a portion of Example 6 expressly disclosing mAb 6-2 as a fully human IL-4R blocking antibody that is an IL-4 and IL-13 antagonist and is of the IgG or IgM isotype:

> **One hybridoma cell line generated by procedures described above (see example 4) is designated 6-2**. **The anti-IL-4R monoclonal antibody secreted by this hybridoma is a blocking antibody**, **as determined in a conventional plate binding assay, and thus functions as an IL-4 antagonist. The monoclonal antibody produced by 6-2 also exhibits the ability to reduce an IL-13-induced biological activity**.
>
> One embodiment of the invention is directed to a hybridoma cell line produced as described above, wherein the hybridoma secretes an isotype IgM MAb directed against human IL-4R. Also provided herein are **IgG1 monoclonal antibodies derived from IgM monoclonal antibodies.**

Ex. 1016 [’132 Publication] at ¶¶ [0246]–[0247] (emphasis added).

In addition to disclosing the 6-2 antibody, the ’132 Publication also discloses how the 6-2 antibody was made, screened, and tested. This includes: (1) disclosure of the generation of transgenic mice in Example 3 (Ex. 1016 [’132 Publication] at ¶¶ [0232]–[0236]); (2) disclosure of how to generate and screen for anti-hIL-4R mAbs like mAb 6-2 from transgenic mice as shown in Examples 1 and 4 (Ex. 1016 [’132 Publication] at ¶¶ 0218–0220, [0237]–[0241]); and (3) disclosure of how to assay generated antibodies like mAb 6-2 for IL-4 and IL-13 blocking activity as described in Example 5 (Ex. 1016 [’132 Publication] at ¶¶ [0237]–[0241]). The

’132 Publication confirms that the mAb 6-2 was generated using the methodology described in Example 4. Ex. 1016 [’132 Publication] at ¶ [0246] (“One hybridoma cell line generated by procedures described above (see example 4) is designated 6-2.”).

The ’132 Publication’s disclosure of how mAb 6-2 was isolated mirrors the disclosure in the ’487 Patent’s original specification of how mAbs 6-2, 12B5, 27A1, 5A1, 63, and 1B7 were isolated. Accordingly, the ’132 Publication provides at least as much 35 U.S.C. § 112 support for mAb 6-2 as the ’487 Patent’s original specification provides for its claimed genus of “isolated human antibod[ies] that compete[] with a reference antibody.” Thus, to the extent that the Board determines that the claims of the ’487 Patent are entitled to 35 U.S.C. § 120 priority based on the filing of the ’816 Application (which is disputed by Petitioners in IPR2017-01129), then the ’132 Publication, and the substantially identical ’934 Application from which the ’132 Publication published, provide an enabling disclosure of all the elements of claims 1-14 and 16-17 of the ’487 Patent, and hence invalidate each of these claims. Ex. 1211 [’934 Application] at 0082-0144; Ex. 1016 [’132 Publication].

IX. REASONS FOR THE RELIEF REQUESTED UNDER 37 C.F.R. §§ 42.22(A)(2) AND 42.104(B)(4)

A. Ground 1 – The Challenged Claims Are Unpatentable as Anticipated by the '132 Publication

Claim 1 of the '487 Patent claims "[a]n 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 ['487 Patent], claim 1. For the reasons explained in detail herein, Claim 1 is unpatentable as anticipated by Patent Owner's own '132 Publication.

1. **Claim Element 1[a]:** *"[a]n isolated human antibody"*

The '132 Publication discloses an isolated human antibody, specifically, mAb 6-2, which is described as a human anti-IL-4R antibody that blocks human IL-4 and IL-13 signaling:

> One hybridoma cell line generated by procedures described above **(see example 4**) is **designated 6-2. The anti-IL-4R monoclonal antibody** secreted by this hybridoma is a **blocking antibody**, as determined in a conventional plate binding assay, and thus functions as **an IL-4 antagonist**. The monoclonal antibody produced **by 6-2 also exhibits the ability to reduce an IL-13-induced biological activity**.

Ex. 1016 ['132 Publication] at ¶ [0246] (emphasis added). While Example 6 does

not specifically state that mAb 6-2 is a human antibody, Example 4, entitled "Generation of Human Anti-IL-4R Monoclonal Antibodies," describes the procedures used to make and screen mAb 6-2 and indicates that the resulting antibodies are "human antibodies against the IL-4R". Ex. 1016 ['132 Publication] at ¶¶ [0240], [0246]. In addition, the '132 Publication discloses in Example 5 that anti-hIL-4R antibodies like mAb 6-2 were tested as a "purified protein." Ex. 1016 ['132 Publication] at ¶ [0243].

To the extent that the Board determines that the term "human" antibodies in the Challenged Claims does not encompass both "partially and fully human" antibodies as Petitioners propose, and is limited to only "fully human" antibodies, the '132 Publication describes the generation of fully human antibodies—such as mAb 6-2—by immunizing a particular strain of transgenic mouse with hIL-4R. *See* Ex. 1016 ['132 Publication] at ¶ [0237] ("Transgenic mice Strain ((CMD)++; (JKD)++; (HCo7)11952+/++; (KCo5)9272+/++ which is homozygous for disruptions of the endogenous heavy chain (CMD) and kappa light chain (JKD) loci (see example 3), was used to generate IL-4R-reactive monoclonal antibodies."); Ex. 1200 [Zurawski Declaration] at ¶¶ 119-120. The mouse from which mAb 6-2 was isolated is commonly referred to as the Medarex "HuMAb" mouse, which was commercially available from Medarex prior to 2001. Ex. 1200

[Zurawski Declaration] at ¶ 120; Ex. 1210 at 0039 (37). As explained in the '132 Application, the Medarex HuMAb mouse possess DNA encoding portions of the human heavy and kappa light chain immunoglobulin repertoire and accordingly produces fully human antibodies when immunized with human protein, such as hIL-4R. Ex. 1016 ['132 Publication] at ¶ [0235]; Ex. 1200 [Zurawski Declaration] at ¶ 120; Ex. 1210 at 0039 (37).

The '132 Publication and the '487 Patent share much of the same disclosure, including the disclosure of Example 3, which is directed to the "Generation of Transgenic Mice," and Example 4, which is directed to the "Generation of Human Anti-IL-4R Monoclonal Antibodies" by immunizing Example 3's transgenic mice with hIL-4R. Ex. 1016 at ¶¶ [0232]–[0241]; Ex. 1001 ['487 Patent] at 38:15-40:31. As noted above, Example 4 is the method by which mAb 6-2 in the '132 Publication was made and screened. Ex. 1016 ['132 Publication] at ¶ [0246]. Thus, to the extent that the specification of the '487 Patent provides an enabling disclosure of mAb 6-2 as a "fully human" antibody, so does the '132 Publication.

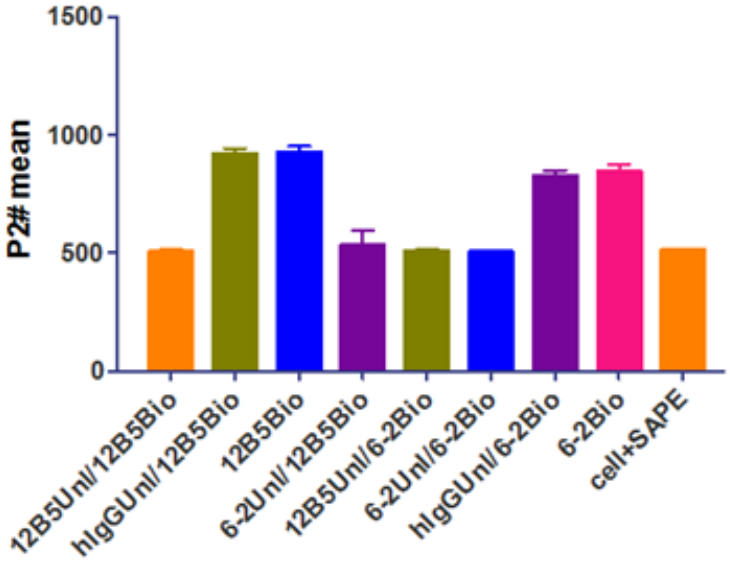
The '132 Publication thus describes an "isolated human antibody"—mAb 6-2, which was isolated and screened using its teachings in Examples 4-6.

2. **Claim Element 1[b]:** "*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.*"

The mAb 6-2 antibody described in the '132 Publication meets this limitation. As noted above, although the '132 Publication does not expressly describe that mAb 6-2 competes with the 12B5 reference antibody, competition with a reference antibody "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" is an inherent property of mAb 6-2. Ex. 1200 at ¶¶ 128-129; *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) ("[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.").

The inherent ability of the 6-2 antibody to compete with the claimed reference antibody was confirmed experimentally by Dr. Gerard Zurawski. Ex. 1200 at ¶ 128. Dr. Zurawski had both mAb 6-2 and a claimed reference antibody (mAb 12B5) prepared and tested for competition. Ex. 1200 at ¶¶ 79-106.

Although the ’487 Patent does not specify the competition assay or assay conditions to be employed for assessing competition, as noted above, Patent Owner previously endorsed an assay described in Perez de la Lastra (referred to as “D24”) in connection with a related European Patent—EP 2292665B1. Ex. 1201 [Immunex’s EU Opposition Response] at 12-13 (“D24 [Perez de la Lastra] provides methods for determining competition between antibodies and competition was identified successfully using those methods. A skilled person could therefore use a method disclosed in D24 [Perez de la Lastra] to identify competition between a test antibody and a reference antibody of claim 1, which bind to human IL-4R.”). Using an assay similar to that described in Perez de la Lastra, Dr. Zurawski confirmed that mAb 6-2 necessarily competes with the claimed reference antibody. Ex. 1200 at ¶¶ 128-129. This is reflected, for example, in the figure shown below from Dr. Zurawski’s declaration, which shows in column 4 the assay results where mAb 6-2 was pre-bound to IL-4R as the “first antibody” and the biotinylated reference antibody was introduced to the mAb 6-2/IL-4R complex as the “second antibody.” This is further reflected in column 5 of the figure below, which shows the competition assay results where a mAb 12B5 was pre-bound to IL-4R as the “first antibody” and a biotinylated mAb 6-2 antibody was introduced to the mAb 12B5/IL-4R complex as the “second antibody.”



Dr. Zurawski found that both of these assays showed little to no increase in fluorescent intensity when the biotinylated, second antibody was added to the suspension of Daudi B-cells expressing IL-4R, which demonstrates that mAb 6-2 strongly blocks binding of the reference antibody to human IL-4R and that the reference antibody likewise strongly blocks the binding of mAb 6-2 to human IL-4R. Ex. 1200 at ¶¶ 103-105. As specified in Perez de la Lastra, inhibition of at least 50% of antibody binding is considered competition. Ex. 1026 [Perez de la Lastra] at 667. Because mAb 6-2 was found to inhibit the binding of a 12B5 reference antibody by ~94% and mAb 12B5 was found to inhibit binding of mAb 6-2 by ~100%—both inhibition values well above Perez de la Lastra's 50% threshold—they compete for binding to human IL-4R. Ex. 1200 at ¶¶ 104-106, Table III. Dr. Zurawski's testing thus confirms that mAb 6-2 as disclosed in the

’132 Publication inherently competes with the ’487 Patent’s reference antibody (*e.g.*, mAb 12B5) for binding to human IL-4R. Ex. 1200 at ¶¶ 128-129; *In re Crish*, 393 F.3d 1253, 1258 (Fed. Cir. 2004) (“A long line of cases confirms that one cannot establish novelty by claiming a known material by its properties”).

Petitioner’s reliance on Dr. Zurawski’s experimental evidence to demonstrate inherency is proper because inherency can be established by experimental evidence, even if that experimental evidence is not contemporaneous with the disclosure of the prior art reference. For example, in *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373 (Fed. Cir. 2003), a previously unknown metabolite of a drug compound disclosed in the prior art was found to inherently anticipate claims to the metabolite itself even though the anticipating reference made no mention of metabolites, much less the specific metabolite that was claimed. *Id.* at 1376 (“[T]he ’233 patent does not expressly disclose DCL and does not refer to metabolites of loratadine”). Clinical studies performed by the alleged infringer after the critical date were found to be probative on the question of whether the metabolite was formed following administration of the drug. *Id.* at 1382; *see also* M.P.E.P. § 2112(II) (collecting cases). For the same reasons, Dr. Zurawski’s experiments are probative of an inherent property of mAb 6-2—*i.e.*,

that it necessarily competes with the claimed reference antibody for binding to human IL-4R.

In addition, to the extent that Patent Owner asserts that this element is not met because the 12B5 antibody had not been isolated at the time of the '132 Publication and hence one of skill in the art would not have understood mAb 6-2 to compete with the claimed reference antibody, such an assertion is immaterial under the law of inherent anticipation. Indeed, the law is well-settled that "inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure." *Schering*, 339 F.3d at 137; *see also Atlas Powder Co. v. Ireco,* Inc., 190 F.3d 1342, 1348-49 (Fed. Cir. 1999) ("Because 'sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention . . . . An inherent structure, composition, or function is not necessarily known."). Here, mAb 6-2 inherently possessed the property of competing with the reference antibody for binding to human IL-4R by the time it was isolated and disclosed in the '132 Publication. Under the law of inherency, one of skill in the art need not have appreciated, tested, or even been able to test for this property at the time. *SmithKline,* 403 F.3d, 1348 ("[O]ne of the principles underlying the doctrine of inherent anticipation is to ensure that the public remains free to make, use or sell

prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate.") (internal citations omitted); *In re Crish*, 393 F.3d at 1258 (explaining that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel").

That the '132 Publication anticipates the '487 Patent is a problem entirely of Patent Owner's own making. By broadly defining the invention of the '487 Patent solely by a function—*i.e.*, competing with a reference antibody—the claims of the '487 Patent encompass Patent Owner's prior art disclosure in the '132 Publication of mAb 6-2. Patent Owner could have claimed by sequence any of mAbs 12B5, 27A1, 5A1, 63, or 1B7—antibodies that Patent Owner appears to have isolated after filing the '132 Publication—without running afoul of the '132 Publication.[7] But instead of claiming the antibodies it actually invented, Patent Owner chose to pursue far more expansive claims in the '487 Patent. Because mAb 6-2 inherently

[7] Indeed, prior to the '487 Patent, Patent Owner obtained two patents that are narrowly drawn to MAb 12B5. *See* Ex. 1029 and Ex. 1031.

falls under the ambit of the '487 Patent's broadly claimed genus of antibodies,'487 Patent claim 1 is invalid.

3. ***Claim 2:*** *"[t]he isolated human antibody of claim 1, wherein when said reference antibody is bound to human IL-4 receptor, binding of said isolated antibody to said human IL-4 receptor is inhibited."*

As shown in Dr. Zurawski's declaration, the binding of mAb 6-2, disclosed in the '132 Publication, to human IL-4 receptor is necessarily inhibited when a 12B5 reference antibody is bound to IL-4R. Ex. 1200 at ¶¶ 79-106; 131. As discussed above in Section IX.A.2, this was confirmed by Dr. Zurawski, who had both mAb 6-2 and mAb 12B5, a claimed reference antibody, prepared and tested for cross-competition. Ex. 1200 at ¶¶ 79-106; 131. When using the assay specified in Perez de la Lastra, Dr. Zurawski found that when the tested reference antibody was bound to human IL-4R on Daudi B-Cells, binding of the 6-2 antibody was completely inhibited (*i.e.*, by ~100%). Ex. 1200 at ¶ 131; *see* bar graph in Section IX.A.2. Dr. Zurawski's testing thus confirms that mAb 6-2 inherently has the ability to be inhibited from binding to human IL-4 receptor by mAb 12B5 when 12B5 is bound to hIL-4R. Ex. 1200 at ¶ 131.

4. ***Claim 3:*** *"[t]he isolated human antibody of claim 1, wherein when said isolated human antibody is bound to human IL-4 receptor, binding of said reference antibody to said human IL-4 receptor is inhibited."*

As shown in Dr. Zurawski's declaration, MAb 6-2, disclosed in the '132 Publication, necessarily inhibits the binding of a 12B5 reference antibody to human IL-4R when mAb 6-2 is bound to hIL-4R. Ex. 1200 at ¶¶ 79-106, 134. As discussed above in Section IX.A.2, this was confirmed by Dr. Zurawski, who had both mAb 6-2 and mAb 12B5, a claimed reference antibody, prepared and tested for cross-competition. Ex. 1200 at ¶¶ 79-106, 134. Using the assay specified in Perez de la Lastra, Dr. Zurawski found that when mAb 6-2 was bound to human IL-4R on Daudi B-Cells, binding of the '487 Patent's reference antibody was significantly inhibited (*i.e.*, by ~94%). Ex. 1200 at ¶ 134. Dr. Zurawski's testing thus confirms that mAb 6-2 inherently has the ability to inhibit binding of mAb 12B5 to human IL-4 receptor when mAb 6-2 is bound to hIL-4R. Ex. 1200 at ¶ 134.

5. ***Claim 4:*** *"[t]he isolated human antibody of claim 1, wherein said isolated human antibody inhibits the binding of human IL-4 to human IL-4 receptor."*

The '132 Publication describes mAb 6-2 as a blocking antibody that inhibits the binding of human IL-4 to human IL-4R and "thus functions as an IL-4

antagonist." Ex. 1016 ['132 Publication] at ¶ [0246] ("The anti-IL-4R monoclonal antibody secreted by this hybridoma **[6-2] is a blocking antibody**, as determined in a conventional plate binding assay, **and thus functions as an IL-4 antagonist**.")**)** (emphasis added). Antibodies that block IL-4 binding and serve as IL-4 antagonists inhibit the binding of human IL-4 to human IL-4 receptor. Ex. 1200 at ¶ 137; *see also* Ex. 1016 ['132 Publication] at ¶¶ 0016-0017 ("IL-4 antagonists that may be employed include those compounds that inhibit biological activity of IL-4. … Suitable antagonists include … antibodies that bind IL-4, antibodies that bind IL-4R …").

6. ***Claim 5:*** *"[t]he isolated human antibody of claim 1, wherein said isolated human antibody inhibits the binding of human IL-13 interleukin-13 (IL-13) to human IL-4 receptor."*

To the extent that any antibody can block IL-13 from binding to IL-4R, the '132 Publication teaches that mAb 6-2 inhibits the binding of IL-13 to human IL-4 receptor. Although the '132 Publication never explicitly states that mAb 6-2 inhibits IL-13 binding to human IL-4 receptor, it indicates that antibodies that inhibit the binding of IL-13 to IL-4R can be identified by their ability to inhibit IL-13-induced biological activity. Specifically, the '132 Publication describes that "**[a]ntibodies** that bind to IL-4R and inhibit IL-4 binding ***may be screened in various conventional assays to identify those antibodies that also interfere with***

the binding of IL-13." Ex. 1016 ['132 Publication] at ¶ [0149] (emphasis added). The '132 Publication further describes that such "[a]ntibodies may be screened in binding assays or **tested for the ability to inhibit** … an **IL-13-induced biological activity."** Ex. 1016 ['132 Publication] at ¶ [0149] (emphasis added). As an example of a suitable assay for testing the ability of an antibody to inhibit IL-13 induced biological activity, the '132 Publication identifies Example 5—a CD23 assay. Ex. 1016 ['132 Publication] at ¶ [0149].

The '132 Publication specifically teaches that mAb 6-2 "reduce[s] IL-13-induced biological activity." Ex. 1016 ['132 Publication] at ¶ [0246]. In particular, the '132 Publication states that "**[t]he monoclonal antibody** produced by **6-2 also exhibits the ability to reduce an IL-13-induced biological activity**." *Id.* (emphasis added). Thus, the description in the '132 Publication that equates the inhibition of IL-13-induced biological activity with the inhibition of IL-13 binding, combined with the foregoing statement that mAb "6-2 also exhibits the ability to reduce an IL-13-induced biological activity," together teaches that mAb 6-2 inhibits IL-13 binding to human IL-4R. Ex. 1200 at ¶¶ 141-142.

The ability of mAb 6-2 to inhibit IL-13 signaling was confirmed by Dr. Zurawski, who found that mAb 6-2 inhibits IL-13-induced biological activity using a CD23 assay like that described in Example 5. Ex. 1200 at ¶ 153-154; *see*

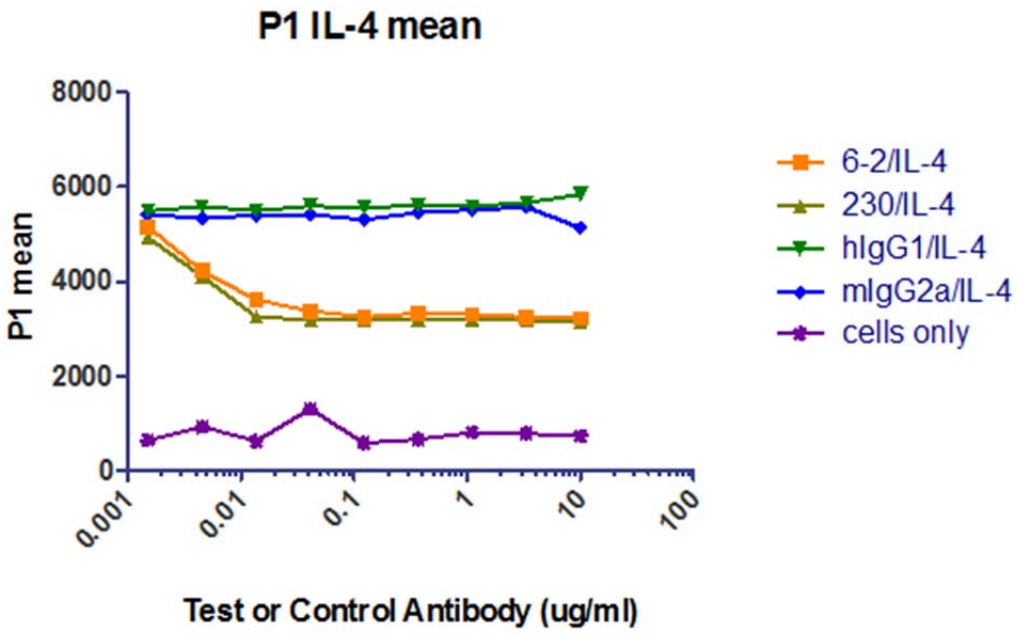
also Ex. 1016 [’132 Publication] at ¶¶ [0242]–[0245] (describing the Ex. 5 CD23 assays). Dr. Zurawski found that mAb 6-2 inhibited IL-13 induced CD23 expression in a transformed human monocytic cell line called U937.[8] This confirms the statements in the ’132 Publication that mAb 6-2 inhibits IL-13 induced biological activity.

7. ***Claim 6:*** *“[t]he isolated human antibody of claim 1, wherein said isolated human antibody inhibits human IL-4 signaling through human IL-4 receptor.”*

The ’132 Publication teaches that mAb 6-2 inhibits IL-4 signaling through human IL-4 receptor. Specifically, the ’132 Publication describes the mAb 6-2 antibody “as an IL-4 antagonist.” Ex. 1016 [’132 Publication] at ¶ [0246] (“The anti-IL-4R monoclonal antibody secreted by this hybridoma **[6-2]** is a blocking antibody … and thus **functions as an IL-4 antagonist**.”**)** (emphasis added). The ’132 Publication further states that “**IL-4 antagonists** … in accordance with the present invention include compounds that **inhibit a biological activity of IL-4.**” Ex. 1016 [’132 Publication] at ¶ [0016].

[8] U937 is a standard cell line that expresses CD23 is the presence of IL-4 or IL-13. One skilled in the art can thus use the U937 cell line to measure IL-4 and IL-13 signaling inhibition. Ex. 1200 at ¶ 107.

The ability of mAb 6-2 to inhibit IL-4 induced biological activity (*i.e.*, signaling) was confirmed by Dr. Zurawski using a CD23 assay like that in Example 5 of the '132 Publication and the '487 Patent. Ex. 1200 at ¶¶ 107-112; 146-148. The figure below shows the results of an assay to test the ability of mAb 6-2 to inhibit IL-4 induced CD23 expression:



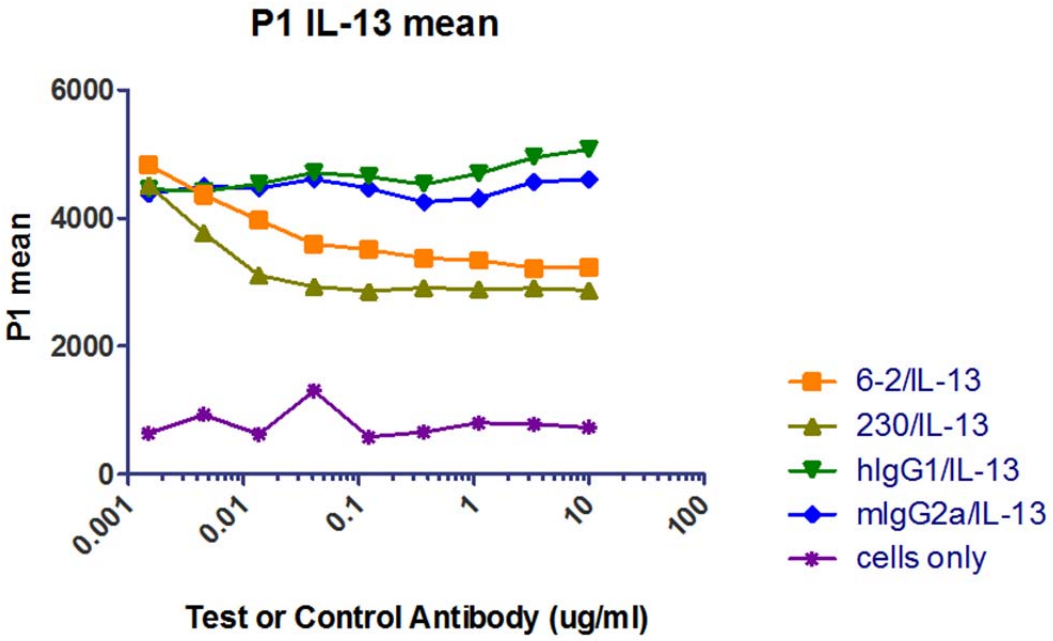
Ex. 1200 at ¶ 146. Dr. Zurawski found that mAb 6-2 (data shown as orange squares) inhibits CD23 expression induced by IL-4 at increasing concentrations relative to the negative control hIgG1 antibody (data shown as upside down dark green triangles). Ex. 1200 at ¶ 147. Dr. Zurawski further found the concentration dependent inhibition by mAb 6-2 of CD23 expression induced by IL-4 to be similar to that observed with the positive control antibody, MAB230 (data shown

as light green triangles). Ex. 1200 at ¶ 147. As a result, Dr. Zurawski concluded that mAb 6-2 inhibits IL-4 induced CD23 expression in the human monocytic cell line, U937, and confirmed that mAb 6-2 inhibits IL-4 signaling through human IL-4 receptor. Ex. 1200 at ¶ 147. This confirms that the ability of mAb 6-2 to inhibit human IL-4 signaling through human IL-4 receptor is an inherent biological and biochemical property possessed by mAb 6-2. Ex. 1200 at ¶ 148.

8. ***Claim 7:*** *"[t]he isolated human antibody of claim 1, wherein said isolated human antibody inhibits human IL-13 signaling through human IL-4 receptor."*

The '132 Publication teaches that mAb 6-2 "reduce[s] IL-13-induced biological activity." Ex. 1016 ['132 Publication] at ¶ [0246] ("**The monoclonal antibody** produced by **6-2 also exhibits the ability to reduce an IL-13-induced biological activity**.") (emphasis added).

As noted above, the ability of mAb 6-2 to inhibit IL-13 signaling was confirmed by Dr. Zurawski. Ex. 1200 at ¶¶ 107-112; 152-154. The figure below shows the results of an assay to test the ability of mAb 6-2 to inhibit IL-13 induced CD23 expression:



Ex. 1200 at ¶ 152. Dr. Zurawski found that mAb 6-2 (data shown as orange squares in the above figure) inhibits CD23 expression induced by IL-13 at increasing concentrations relative to the negative control hIgG1 antibody (data shown as upside down dark green triangles in the above figure). Ex. 1200 at ¶ 153. Dr. Zurawski further found that the concentration dependent inhibition by mAb 6-2 of CD23 expression induced by IL-13 to be similar to that observed with the positive control antibody, MAB230 (data shown as light green triangles in the figure above). As a result, Dr. Zurawski concluded that mAb 6-2 inhibits IL-13 induced CD23 expression in the human monocytic cell line, U937, and confirmed that mAb 6-2 inhibits IL-13 signaling through human IL-4 receptor. Ex. 1200 at ¶ 153. This confirms that the ability of mAb 6-2 to inhibit human IL-13 signaling

through human IL-4 receptor is an inherent biological and biochemical property possessed by mAb 6-2. Ex. 1200 at ¶ 154.

9. ***Claims 8-10:*** *"[t]he isolated human antibody of claim 1, wherein* ***said*** *isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least 1×10^8 [1×10^9] [1×10^{10}]."*

As shown in Dr. Zurawski's declaration, the 6-2 antibody, disclosed in the '132 Publication, inherently possesses a binding affinity that meets the requirements of claims 8-10. Ex. 1200 at ¶ 160. Using a surface plasmon resonance-based affinity assay, Dr. Zurawski determined that the K_a (association constant) of mAb 6-2 for binding to human IL-4R is $3.44x10^{10}$ 1/M. Ex. 1200 at ¶¶ 113-114; 159. This K_a value is at least 1×10^8, at least 1×10^9, and at least 1×10^{10}.

10. ***Claim 11:*** *"[t]he isolated human antibody of claim 1, wherein said isolated human antibody is a full-length antibody."*

The '132 Publication describes that mAb 6-2 can be a full length IgM or IgG1 antibody:

> [T]he **[6-2] hybridoma** secretes an isotype **IgM MAb** directed against human IL-4R. Also provided herein are **IgG1 monoclonal antibodies** derived from **IgM monoclonal antibodies**.

Ex. 1016 ['132 Publication] at ¶¶ [0246]–[0247] (emphasis added). "IgM MAb" and "IgG1 monoclonal antibodies" refer to full-length antibodies. Ex. 1200 at ¶ 163.

11. ***Claim 12:*** *"[t]he isolated human antibody of claim 1, wherein said isolated human antibody is an IgA antibody, an IgD antibody, an IgE antibody, IgG antibody, an IgG1 antibody, an IgG2 antibody, an IgG3, antibody, an IgG4 antibody, or an IgM antibody."*

As noted above, the '132 Publication describes that mAb 6-2 can be an IgM or IgG1 antibody. Ex. 1016 ['132 Publication] at ¶¶ [0246]–[0247] (emphasis added). These are two of the antibody isotypes specified in claim 12. Ex. 1200 at ¶ 166.

12. ***Claim 13:*** *"[t]he isolated human antibody of claim 1, wherein said isolated human antibody is a fragment of an antibody."*

The '132 Publication describes mAb 6-2 in one embodiment as an antibody fragment. Ex. 1200 at ¶ 169. As discussed above, the '132 Publication states that mAb 6-2 is an IL-4 antagonist. Ex. 1016 ['132 Publication] at ¶ [0246]. The '132 Publication further describes that "[a]**ntibodies that function as IL-4 antagonists may be employed** in the methods of the present invention" and that such "**antibodies preferably are** monoclonal antibodies or **antigen binding fragments**

thereof." Ex. 1016 ['132 Publication] at ¶ [0145] (emphasis added); Ex. 1200 at ¶ 169.

13. ***Claim 14:*** *"[t]he isolated human antibody of claim 1, wherein said isolated human antibody is a fusion protein."*

The '132 Publication teaches that immunoglobulins such as the mAb 6-2 antibody can be used to prepare fusion proteins:

> As one alternative, **an oligomer is prepared using polypeptides derived from immunoglobulins. Preparation of fusion proteins comprising certain heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described,** e.g., by Ashkenazi et al. (PNAS USA 88110535, 1991); Byrn et al. (Nature 344:677, 1990); and Hollenbaugh and Aruffo ("Construction of Immunoglobulin Fusion Proteins", in Current Protocols in Immunology, Suppl. 4, pages 10.19.1 - 10.19.11, 1992).

Ex. 1016 ['132 Publication] at ¶ [0131] (emphasis added); *see also* Ex. 1016 ('132 Publication, 2001) at ¶¶ 0145; 0151. As attested to by Dr. Zurawski, a skilled artisan would understand that a fusion protein is the result of fusing genes that encode different proteins together and expressing the resultant protein. Ex. 1200 ¶ 172; Ex. 1205 at 0008, 6:30–0009, 7:5. Accordingly, a POSITA would understand the '132 Application's disclosure of "heterologous polypeptides fused to various portions of antibody-derived polypeptides" to teach a 6-2 antibody made as a fusion protein. Ex. 1200 at ¶ 172.

14. ***Claim 16:*** *"[a] composition comprising said isolated human antibody of claim 1 and a pharmaceutically acceptable diluent, buffer, or excipient."*

The '132 Publication describes that antibodies—like mAb 6-2—can be included in various pharmaceutical compositions. Ex. 1200 at ¶ 175. Specifically, as noted above, the '132 Publication teaches that mAb 6-2 is an IL-4 antagonist. Ex. 1016 ['132 Publication] at ¶ [0246]. The '132 Publication further teaches compositions of IL-4 antagonists, like mAb 6-2, with a pharmaceutically acceptable diluent, buffer, or excipient. *See* Ex. 1016 ['132 Publication] at ¶ [0180] (teaching "a composition comprising at least one **IL-4 antagonist and one** or more additional components such as a **physiologically acceptable carrier, excipient or diluent**.") (emphasis added).

15. ***Claim 17:*** *"[a] kit comprising said isolated human antibody of claim 1."*

The '132 Publication describes that antibodies, such as mAb 6-2, can be included in kits. Ex. 1200 at ¶ 178. As noted above, the '132 Publication teaches that mAb 6-2 is an IL-4 antagonist. Ex. 1016 ['132 Publication] ¶ [0246]. The '132 Publication further teaches that IL-4 antagonists, like mAb 6-2, can be supplied in kits for use by medical practitioners. Ex. 1016 ['132 Publication] at

¶ [0183] ("**Kits for use by medical practitioners include an IL-4 antagonist**…") (emphasis added).

X. CONCLUSION

For the reasons set forth above, claims 1-14 and 16-17 of the '487 Patent are unpatentable. Petitioners therefore requests that an *inter partes* review of these claims be instituted and that claims 1-14 and 16-17 be canceled.

Dated: July 28, 2017

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition for *Inter Partes* Review complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). According to the word count feature of the word-processing system used to prepare this Petition, the Petition contains 11,786 words, excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: July 28, 2017

/John B. Campbell/
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e) and 37 C.F.R. § 42.105(a), the undersigned certifies that on July 28, 2017, a complete copy of this Petition for *Inter Partes* Review and all exhibits were served on Patent Owner at the correspondence address of record listed below by FedEx®:

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