Paper No. 12

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.

Case IPR2017-01884
Patent 8,679,487

PETITIONERS' REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE

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1018	Keegan, Interleukin 4 Receptor (1998) ("Keegan")

1019	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*, Eur. J. Biochem. 1994, 225:659-665 ("Tony")
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1405	Queen, et al., *A humanized antibody that binds to the interleukin 2 receptor*, 86 Proc. Natl. Acad. Sci, USA 10029–10033 (1989) ("Queen 1989 Paper")
1406	U.S. Patent No. 5,530,101
1407	Excerpts from the File History of U.S. Patent Application No. 10/324,493
1408	Harlow & Lane, *Antibodies, A Laboratory Manual* 567–592 (1988)
1409	David King, *Applications and Engineering of Monoclonal Antibodies* (1998) ("King")
1410	Winter et al., *Humanized Antibodies*, TiPS 1993, 14(5):139–43
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1420	Dr. Lara Marks, *The life story of a biotechnology drug: Alemtuzumab, available at* http://www.whatisbiotechnology.org/exhibitions/campath/introduction
1421	Corren, et al., *A Randomized, Controlled, Phase 2 Study of AMG 317, an IL-4Ra Antagonist, in Patients with Asthma*, Am. J. Respir. Crit. Care Med., 2010, 181:788–796.
1422	Junghans, et al., *Anti-Tac-H, a Humanized Antibody to the Interleukin 2 Receptor with New Features for Immunotherapy in Malignant and Immune Disorders*, Cancer Research, 1990, 50:1495–1502
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1425	Bullens, et al., *Effects of anti-IL-4 receptor monoclonal antibody in in vitro T cell cytokine levels: IL-4 production by T cells from non-atopic donors*, Clin. Exp. Immunol., 1998, 113:320–326

1426	Wang, et al., *IL-4 Function Can Be Transferred to the IL-2 Receptor by Tyrosine Containing Sequences Found in the IL-4 Receptor α Chain*, Immunity, 1996, 4:113–121
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As authorized by the Board, Petitioners submit this Reply to address three issues raised in Patent Owner's ("PO") Preliminary Response ("POPR"): (1) new evidence that contradicts PO's assertion that there is no motivation to combine the cited references; (2) the Board's discretion under 35 U.S.C. § 325(d); and (3) the Board's discretion under 35 U.S.C. § 314(a). For the reasons discussed herein and in the Petition, the Board should institute trial on all grounds.

I. New Evidence Undercuts Patent Owner's Obviousness Arguments.

PO's own actions belie its assertion that a person of ordinary skill in the art ("POSITA") would not have been motivated to derive a human therapeutic from the MAb230 antibody ("MAb230") disclosed in Hart. PO argues that a "lack of evidence that ***anyone*** has ever considered MAb230 a clinical candidate in the [past] 20 years" establishes that a POSITA would never choose to derive a therapeutic from MAb230 out of the "sea of options." POPR at 47-48 (emphasis added). In fact, as Petitioners learned after their filing and as revealed in PO's brief filed in related litigation on September 25, 2017, ***the named '487 Patent inventors*** used MAb230 for this very purpose. Ex. 1434 at 7. As PO concedes, the '487 Patent inventors "devised a plan to isolate . . . a human antibody that binds to the ***same epitope*** as MAb230 with the objective of isolating an antibody that . . . is able to simultaneously disrupt IL-4 and IL-13 induced signaling." *Id.* (quoting Amended Answer ¶ 21) (emphasis added). And, as explained in the Petition, this is

precisely why a POSITA ***would*** have been motivated to derive a human antibody from MAb230. *See* Pet. at 42 ("[A] POSITA would have been motivated to derive a humanized antibody that likewise binds to MAb230's therapeutically relevant epitope."). Thus, PO's own use of MAb230 makes clear that skilled artisans would have been—and indeed, were—motivated to derive a human therapeutic that replicates MAb230's binding characteristics. *See National Steel Car, Ltd. v. Canadian Pacific Ry., Ltd.*, 357 F.3d 1319, 1337-39 (Fed. Cir. 2004).

Moreover, PO's argument that Petitioners failed to identify "properties [that] would have led a [POSITA] to consider MAb230 a good candidate for developing a therapeutic," POPR at 55, rings hollow given that Petitioners identified the very property—disruption of IL-4 and IL-13 induced signaling—that PO avows motivated the '487 Patent inventors. *Compare* Ex. 1434 at 7 *with* Pet. at 42-44, 47, 57. Petitioners' expert, Dr. Zurawski, concluded that a POSITA would have been motivated to derive a therapeutic from MAb230 at the time of the alleged invention because Mab230 was known in the prior art to potently inhibit IL-4 and IL-13. Ex. 1400 at ¶¶ 141, 148. Tellingly, Dr. Zurawski provided these opinions ***before*** Petitioners learned that the '487 Patent's named inventors came to the same conclusion, for the same reason, and before the priority date. Ex. 1434 at 7. Thus, PO's subsequent statements in the litigation not only corroborate Dr. Zurawski's

testimony that a POSITA would have been motivated to derive a human antibody based on MAb230, but also contradict PO's position in the POPR.

PO does not (because it cannot) deny that it used MAb230 in attempting to derive a human therapeutic. Instead, PO argues that its use of MAb230 is not evidence of a motivation to combine because it is "simply . . . what the inventors did" and the inventors are "genius[es]." Ex. 1433 at 19:14-24. But whether the named '487 Patent Inventors are "genius[es]" is irrelevant here because their actions simply corroborate Petitioners' assertion that a POSITA would have been motivated to derive a therapeutic from MAb230 based on the teachings of the prior art. Pet. at 43-44. Even if the '487 Patent Inventors were "genius[es]," the '487 Patent is—for the reasons articulated in the Petition and further confirmed by PO's own actions—"the product not of innovation but of ordinary skill and common sense." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007). By PO's own argument, any "hindsight obviousness arguments are undone by [PO's] own contemporaneous decisions" to follow the teaching of the prior art and use MAb230 to develop the '487 Patent antibodies. POPR at 55-56.

II. The Board Should Not Exercise Its Discretion Under § 325(d).

The '487 Patent claims antibodies "that compete with a reference antibody for binding to [IL-4R]." Ex. 1001 at Claim 1. To overcome rejections during prosecution, PO demanded that the Examiner provide evidence that prior art anti-

IL-4R antibodies practice the "competes" limitation, and because the Examiner lacked such evidence, she was ultimately persuaded to grant the '487 Patent. Ex. 1002 at 0028-30. The Petition now presents the very evidence that PO demanded and that the Office lacked when it granted the '487 Patent—evidence that Hart's MAb230 practices the '487 Patent's "competes" limitation. Thus, PO's argument that the Petition asserts substantially the same obviousness arguments presented during prosecution is refuted by the intrinsic record. Because the Petition presents prior art and arguments that have not been previously considered by the USPTO, there are no "competing interests" under § 325(d). *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00739, Paper 16, at 18. Accordingly, § 325(d) is inapplicable to the Petition.

III. The Board Should Not Exercise Its Discretion Under § 314(a).

The *General Plastic* factors weigh in favor of institution because Petitioners' reason for delaying filing was not a tactical decision but the result of diligent testing that could not be completed prior to the filing of the first petition. *Xactware Solutions, Inc. v. Eagle View Techs., Inc.*, IPR2017-00021, Paper 9, at 10 ("Weighed against the factors . . . are any non-strategic reasons Petitioner offers for the delay in filing its [subsequent] Petition or any other justification for allowing its [subsequent] Petition to go forward.").

Contrary to PO's assertion, Petitioners could not complete testing before

July 19, 2017. The ’487 Patent does not specify how the “competes” limitation could be assessed experimentally, and PO never indicated which experiments could be used until November 23, 2016, when in a European Patent Office proceeding for a related patent, PO endorsed two types of competition assays disclosed in the Perez reference as methods for determining competition between antibodies. Ex. 1201 at 12-13. With this first insight into how PO believed competition could be evaluated in the context of the ’487 Patent, Petitioners immediately identified and retained experts, prepared the relevant antibodies and conducted the relevant experiments. Petitioners were diligent in filing this Petition only eight business days after the experiments were completed (and only three days after IPR2017-01879 Petition was filed). Ex. 1400 at ¶99.

The remaining *General Plastic* factors also weigh in favor of Petitioners. Petitioners were not aware that a combination of the three references would render the Challenged Claims obvious until the experimental testing was complete on July 19, 2017. No Board decision was issued prior to the filing of this Petition and while the POPR had been filed in the first petition, it largely responded to 35 U.S.C. § 120 and 35 U.S.C. §112 arguments that are not at issue in this Petition. Finally, because the initial petition was denied, factors six and seven are irrelevant. For the above reasons, the Board should institute the Petition on all grounds.

Dated: December 18, 2017

Respectfully submitted,

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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 December 18, 2017, a complete copy of Petition's Reply to Patent Owner's Preliminary Response was served via electronic mail to the following:

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