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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARAGEN BIOSCIENCE, INC.
AND
TRANSPOSAGEN BIOPHARMACEUTICALS, INC.,
Petitioner,

v.

KYOWA HAKKO KIRIN CO., LTD.,
Patent Owner.

Case IPR2017-01262
Patent 7,425,446 B2

Before JAMES T. MOORE, ERICA A. FRANKLIN, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

MOORE, *Administrative Patent Judge*.

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

I. INTRODUCTION

Aragen Bioscience, Inc. and Transposagen Biopharmaceuticals, Inc. (collectively "Petitioner")[1] filed a Petition requesting an *inter partes* review of claims 1–6 of U.S. Patent No. 7,425,446 B2 (Ex. 1001, "the '446 Patent"). Paper 1 ("Pet."). Kyowa Hakko Kirin Co., Ltd. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp.").

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition and the Preliminary Response, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. Accordingly, we decline to institute an *inter partes* review of the '446 Patent.

A. Related Proceedings

Petitioner has submitted additional Petitions challenging claims of U.S. Patent 8,067,232 B2 (IPR2017-01254), and U.S. Patent 6,946,292 B2 (IPR2017-01252), which have similar specifications.

According to the parties, the '446 Patent is also at issue in *Kyowa Hakko Kirin Co. v. Aragen Bioscience, Inc.*, Case No. 3-16-cv-05993-JD (N.D. Cal.) ("the copending district court litigation"). Pet. 59.

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[1] Petitioner further identifies GVK Biosciences, Private Limited and GVK Davix Technologies Private Limited as real parties-in-interest. Pet. 59.

B. The '446 Patent

The '446 Patent, titled "Antibody Composition-Producing Cell" relates to a cell for the production of an antibody molecule such as an antibody useful for various diseases having high antibody-dependent cell-mediated cytotoxic activity ("ADCC"), a fragment of the antibody and a fusion protein including a region of the antibody. The Patent also relates to a method for producing an antibody composition using the cell, the antibody composition itself, and the use thereof. Ex. 1001, Abstract.

The antibody molecule is produced in part by altering the fucosyltransferase 8 (FUT8) gene of a host cell involved in the production of α1,6-fucosyltransferase which disrupts its expression and changes the antibody by limiting fucose attachment. Ex. 1001, claim 1.

ADCC is an inflammatory response mediated by natural killer ("NK") cells that can result in the killing of tumor cells. *See* Pet. 3–4 (citing Ex. 1026[2] ¶¶ 22–25). In ADCC, the fragment crystallizable ("Fc") portions of immunoglobulin G ("IgG") -type antibodies decorating a target cell (e.g., a tumor cell) are recognized by Fc receptors (e.g., FcγRIII or CD16[3]) on the NK cell surface. *Id.* The interaction between target cell-specific antibodies and Fc receptors activates the NK cell, which then kills the target cell. *Id.* 24.

According to the instant Specification, the hinge region and the second domain of the constant region ("Cγ2 domain") of the antibody are

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[2] Declaration of Dr. Royston Jefferis. At this time we find that, based upon his credentials and experience, Dr. Jefferis is qualified to testify to this subject matter. Ex. 1026, ¶¶ 4–6 and Exhibit B thereto.

[3] A class of low-affinity Fc receptors found on the surface of NK cells.

important to this binding, and thus ADCC activity expression. The same is said for the sugar chain binding to the Cγ2 domain. Ex. 1001, 1:64–2:10. The '446 Patent states that, despite efforts to investigate the effects of altering the antibody, "it cannot be said that an actual important structure for the effector [f]unction was identified" *Id*. 2:36–37.

Also according to the Specification, high ADCC activity is found when the ratio of antibodies having fucose that is not bound to N-acetylglucosamine in the reducing end of the sugar chain is raised relative to antibodies having fucose bound there. *Id.* 20:46:59. This is the alteration of the antibody caused by manipulation of the FUT8 gene.

The Specification discloses the design and testing of a mammalian host cell line for producing antibodies where the FUT8 gene—the gene encoding α1,6-fucosyltransferase—was enhanced (Example 11) and disrupted (Examples 12, 13), thereby either over-expressing or reducing (or eliminating) α1,6-fucosyltransferase activity and thus the binding of fucose into the sugar chain. *Id*. 89:10–111:47. In short, a deletion in the α1,6-fucosyltransferase gene of mammalian cells produced more potent cells. Specifically, the "ADCC activity of produced antibodies can be improved by disrupting the FUT8 allele in host cells," *Id.* 111:45–46.

C. Representative Claim

Claim 1, the sole dependent claim, recites,

> 1. An isolated mammalian host cell which has decreased or no α1,6-fucosyltransferase activity for adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked sugar chains by deleting a gene encoding α1,6-fucosyltransferase or by adding a mutation to said gene to reduce or eliminate the α1,6-fucosyltransferase activity, wherein said mammalian host cell produces an antibody molecule.

Ex. 1001, 183:30–37.

Depending from claim 1, claims 2–5 are each limited to a host cell types CHO (Chinese hamster ovary), NSO (a mouse myeloma cell), SP 2/0 (another mouse myeloma cell), and YB 2/0 (a rat myeloma cell), respectively. *Id.*, 183:37–38 and 184:29-34. Also depending from claim 1, claim 6 recites that the antibody molecule is an IgG antibody. *Id.*, 184:34-36.

D. The Asserted Prior art and Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 17):

Ground	**Reference(s)**	**Basis**	**Claims**
1	Rothman,[4] Umaña,[5] knowledge of a person of ordinary skill in the art ("POSA")	§ 103	1–6
2	Harris,[6] Umaña, knowledge of POSA	§ 103	1–6
3	Rothman, Umaña, Malý,[7] knowledge of POSA	§ 103	1–6
4	Harris, Umaña, Malý, knowledge of POSA	§ 103	1–6

[4] Rothman et al., *Antibody-dependent cytotoxicity mediated by natural killer cells is enhanced by castonspermine-induced alterations of IgG glycosylation*, 26(12) MOLEC. IMMUNOL. 1113–23 (1989). Ex. 1002.
[5] WO 99/54342, published Oct. 28, 1999. Ex. 1004.
[6] Harris et al., *Refined structure of an intact IgG2a monoclonal antibody*, 36 Biochemistry 1581–97 (1997). Ex. 1003.
[7] Malý et al., *The α(1,3)fucosyltransferase Fuc-TVII controls leukocyte trafficking through an essential role in L-, E-, and P-selectin ligand biosynthesis*, 86 CELL 643–53 (1996). Ex. 1005.

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