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Paper No. 13
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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 IPR2017-01252
Patent 6,946,292 B2

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

POLLOCK, *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. ("Petitioner")[1] filed a Petition requesting an *inter partes* review of claims 1–12 of U.S. Patent No. 6,946,292 B2 (Ex. 1001, "the '292 Patent"). Paper 1 ("Pet."). Kyowa Hakko Kirin Co., Ltd. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 10 ("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 '292 Patent.

A. Related Applications and Proceedings

The '292 Patent shares substantially the same specification with U.S. Patent Nos. 8,067,232 B2 ("the '232 Patent), 7,425,446 B2 ("the '446 Patent"), and 7,737,325 B2 ("the '325 Patent"), which are related as follows. The '232 Patent issued from Application No. 12/048,348 ("the '348 Application"), which is a continuation of Application No. 11/131,212 (now the '325 Patent), which is a divisional of Application No. 09/971,773 (now the '292 Patent). This chain of continuations and divisionals was first filed

[1] Petitioner further identifies GVK Biosciences, Private Limited and GVK Davix Technologies Private Limited as real parties-in-interest. Pet. 55.

on October 9, 2001, and each patent in the family claims benefit of provisional Application No. 60/268,916, filed February 16, 2001, as well as foreign applications PCT/JP01/08804 and JP 2000-308526, filed October 5, 2001, and October 6, 2000, respectively.

In addition to the instant Petition challenging claims 1–12 of the '292 Patent, Petitioner has submitted Petitions challenging claims of the '446 Patent (IPR2017-01262), and the '232 Patent (IPR2017-01254). Petitioner does not presently challenge the '325 Patent.

According to the parties, the '292 Patent is 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. 56; Paper 5.

B. The '292 Patent and Relevant Background

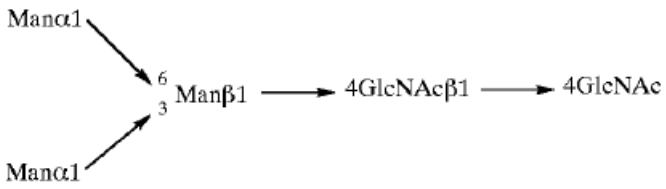
The '292 Patent relates to the development of host cells for the production of antibody molecules that enhance antibody-dependent cytotoxicity (ADCC). *See* Ex. 1001, 5:35–43, Title. As explained by Petitioner, ADCC is an inflammatory response mediated by NK (natural killer) cells that can result in the killing of tumor cells. *See* Pet. 3–4 (citing Ex. 1026[2] ¶¶ 21–24).

In ADCC, the Fc portions of IgG-type antibodies decorating a target cell (e.g., a tumor cell) are recognized by Fc receptors (e.g., FcγRIII or CD16) 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.* at 4. According to the Specification, the Fc region of IgG-type antibodies contains two complex-type, N-glycoside-linked ("N-

[2] Declaration of Dr. Royston Jefferis.

linked") oligosaccharide (sugar) chains, which are known to greatly influence ADCC activity. *See generally* Ex. 1001, 1:40–5:32. Despite prior art attempts to explore this structure-function relationship, the inventors of the '292 Patent assert that, "a truly important sugar chain structure has not been specified yet." *Id*. at 2:9–37, 5:18–32; *see also, id.* at 2:34–37 (stating that, whereas "structures of sugar chains [on IgG-type antibodies] are various and complex, and it cannot be said that an actual important structure for the effector function was identified").

N-linked oligosaccharide chains comprise a common core structure illustrated in formula (I) of the '292 Patent, reproduced below.



Id. at 2:50–55. Formula (I) shows the common core structure of N-linked oligosaccharide chains comprising a branched arrangement of mannose sugars (Man) and two N-acetyl glucosamine moieties (GlcNAc). The mannose end of the core is referred to as the "non-reducing end," and the terminal GlcNAc end the "reducing end." At the non-reducing end, enzymatic attachment and modification of additional sugars moieties result high mannose-, hybrid-, or complex-type sugar chains, depending on the number and type of residues added. *See generally*, *id.* at 2:38–3:2; *see also* Prelim. Resp., 5–6 (illustrating hig mannose-, hybrid, and complex-type sugar chains). At the reducing end, the terminal GlcNAc is linked to the amino acid asparagine ("N" or "Asn") of a polypeptide chain. *Id.* In the Fc region of an antibody, a terminal GlcNAc at the reducing end of a complex-type oligosaccharide chain is attached to each of the two antibody heavy

chains; the 6 position of the terminal GlcNAc may bear a fucose moiety added by α1,6-fucosyltransferase. *See id.* at 3:2–4:6, 20:37–46, 23:22–26, 23:34–24:11.

According to the Specification, reducing or eliminating the addition of fucose at the reducing end of N-linked oligosaccharide chains of the Fc region significantly improves the ADCC response. *See generally*, Ex. 1001, 5:35–67, 7:6–8:13. The Specification also 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 disrupted, thereby reducing or eliminating α1,6-fucosyltransferase activity. *Id.*; *see generally*, Ex. 1001, 7:15–43, 98:25–111:46; *see*, *e.g.*, 111:43–45 ("ADCC activity of produced antibodies can be improved by disrupting the FUT8 allele in host cells"); Ex. 1037[3], 89:16–22.

In particular, Example 12 of the Specification details the cloning of exon 2 of a mammalian FUT 8 gene using a Fut8 cDNA probe.[4] Ex. 1001, 98:25–99:37. In Example 13, the genomic DNA was then used to "knock out" or create a deletion in the α1,6-fucosyltransferase gene of mammalian cells. *Id.* at 99:38–111:45. Antibodies produced in cells bearing the disrupted α1,6-fucosyltransferase gene "showed a significantly more potent ADCC activity than the antibody produced by the strain . . . before gene disruption." *Id.* at 111:31–42, Fig. 42.

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[3] Transcript of Dr. Brian Van Ness Deposition taken in the copending district court litigation.

[4] According to the Specification, the process involved designing PCR primers based on "a mouse FUT8 cDNA sequence (GenBank, AB025198)." *Id.* at 98:34–38.

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