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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

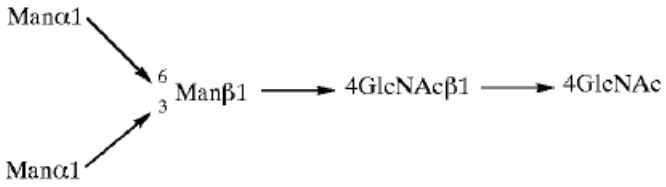
The '292 Patent relates to the development of host cells for the production of antibody molecules that enhance antibody-dependent cytotoxicity (ADCC). *See* Ex. 1001, 5:35–43, Title. As explained by Petitioner, ADCC is an inflammatory response mediated by NK (natural killer) cells that can result in 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.

C. Representative Claims

Petitioner challenges claims 1–12, of which claims 1 and 7 are independent:

> 1. An isolated fucosyltransferase knock-out host cell wherein when a gene encoding an antibody molecule is introduced in to said host cell, said host cell produces an antibody composition comprising the antibody molecule,
>
> said host cell being a mammalian cell,
>
> said antibody molecule comprising a Fc region comprising complex N-glycoside-linked sugar chains bound to the Fc region,
>
> said sugar chain comprising a reducing end which contains an N-acetylglucosamine, wherein the sugar chains do not contain fucose bound to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains.

Ex. 1001, 183:26–39.

> 7. An isolated fucosyltransferase knock-out host cell comprising a gene encoding an antibody molecule, wherein said host cell produces an antibody composition comprising the antibody molecule,
>
> said host cell being a mammalian cell,
>
> said antibody molecule comprising a Fc region comprising complex N-glycoside-linked sugar chains bound to the Fc region,
>
> said sugar chain comprising a reducing end which contains an N-acetylglucosamine, wherein the sugar chains do not contain fucose bound to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains.

Ex. 1001, 184:25–37.

Dependent claims 2–5 and 8–11 limit the host cell types of the independent claims (Ex. 1001, 183:40–47, 184:38–45); dependent claims 6

and 12 specify that the antibody molecule is an IgG antibody (Ex. 1001, 183:48–49, 184:46–47).

D. The Asserted Prior art and Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 17–18):

Ground	**Reference(s)**	**Basis**	**Claims**
1	Rothman,[5] Umaña,[6] knowledge of POSA	§ 103	1–12
2	Harris,[7] Umaña, knowledge of POSA	§ 103	1–12
3	Rothman, Umaña, Malý,[8] knowledge of POSA	§ 103	1–12
4	Harris, Umaña, Malý, knowledge of POSA	§ 103	1–12
5	Rothman, Umaña, Gao,[9] knowledge of POSA	§ 103	5 and 11
6	Harris, Umaña, Gao, knowledge of POSA	§ 103	5 and 11

[5] Rothman et al., *Antibody-dependent cytotoxicity mediated by natural killer cells is enhanced by castanospermine-induced alterations of IgG glycosylation,* 26(12) MOLEC. IMMUNOL. 1113–23 (1989). Ex. 1002.
[6] WO 99/54342, published Oct. 28, 1999. Ex. 1004.
[7] Harris et al., *Refined structure of an intact IgG2a monoclonal antibody*, 36 Biochemistry 1581–97 (1997). Ex. 1003.
[8] 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.
[9] Gao et al., *Characterization of YB2/0 cell line by counterflow centrifugation elutriation*, 44 Exp. Toxic. Pathol. 435–38 (1992). Ex. 1006.

Petitioner also relies on the Declarations of Dr. Brian G. Van Ness (Ex. 1007) and Dr. Royston Jefferis (Ex. 1026). Petitioner further relies on the June 22, 2017, transcript of the deposition testimony of Dr. Brian Van Ness taken in the copending district court litigation (Exhibit 1037), and a supplemental paper relating to that testimony (Paper 11), both of which were entered in this case subject to the Board's Order of August 9, 2017 (Paper 9).

E. Overview of the Asserted References

i. Rothman (Ex. 1002)

Rothman describes the functional analysis of monoclonal IgG antibodies ("mAbs") produced in culture in the presence of various glycosylation inhibitors. *See, eg.*, Ex. 1002, Abstract, 1121.[10] Rothman reports that, although oligosaccharide modification did not significantly influence antigen binding to target cells, "a correlation was observed between the efficiency of promoting ADCC and the glycosylation phenotype of the mAb." *Id.* at 1121. In particular, ADCC was enhanced when the IgG oligosaccharides were metabolically modified by exposure to castanospermine (Cs) and certain other inhibitors. *See, e.g., id* at Abstract, 1121. Rothman suggests that "absence of core fucosylation itself would appear to be a likely candidate as a structural feature necessary for enhancement of NK cell-mediated ADCC." *Id.* at 1122; *see also id.* ("[I]t is tempting to speculate that polyclonal variability in the expression of core fucosylation may confer a functional advantage to host defense by diversifying the effector activity of IgG.").

[10] Where possible, we refer to the native page numbers of the exhibits.

ii. Harris (Ex. 1003)

Harris describes the crystal structure (including oligosaccharide components) of an IgG-type monoclonal antibody directed against a canine lymphoma. *See* Ex. 1003, Abstract; 1591–92. In comparing the Fc region of the canine antibody against that of a human antibody, Harris states that,

> the principal differences lie in the orientation and placement of Fuc2 and of the branch ends Gal7 and Nag9 (Figure 10).[11] The fucose residue may be of particular interest. In both this antibody and the human Fc it interacts with Tyr313 [of the IgG heavy chain], but the interactions are quite different in the two cases. This fucose is also near the Fcγ receptor binding site and could influence binding by the receptor.

Id. at 1592. With respect to effector function, Harris further states:

> No direct evidence, that we know of, suggests that the oligosaccharides form part of any effector binding site. Degradation or modification of the carbohydrate has, however, been clearly shown to eliminate or reduce effector functions such as . . . binding to Fc receptors . . . .

Id. at 1593–94.

iii. Umaña (Ex. 1004)

Umaña is directed to the production of antibodies and other proteins having altered glycosylation patterns that provide improved therapeutic properties. Ex. 1004, Abstract, 2. In particular, Umaña states that,

> the present invention is directed to a method for producing altered glycoforms of proteins having improved therapeutic values, e.g., an antibody which has an enhanced antibody dependent cellular cytotoxicity (ADCC), in a host cell. The invention provides host cells which harbor a nucleic acid

[11] We understand Fuc2, Gal7, and Nag9 to refer to specifically numbered sugar moieties (fucose, galactose, and N-acetyl glucosamine, respectively) of the IgG oligosaccharide chains.

> encoding the protein of interest, e.g., an antibody, and at least one nucleic acid encoding a glycoprotein-modifying glycosyl transferase.

Id. at 3:6–11. Among the techniques taught by Umaña, are "the use of gene knockout technologies . . . to tailor the host cell's glycosyl transferase and/or glycosidase expression levels." *Id.* at 15:20–22.

iv. Malý (Ex. 1005)

According to Malý, five genes (Fuc-TVII, Fuc-TIII, V, VI, and TIV) encode α(1,3)fucosyltransferases in humans. Ex. 1005, 649; *see id*. at 643. Malý discloses the targeted disruption of the mouse homolog of Fuc-TVII, and the generation of mice homozygous for the knockout of this gene. Ex. 1005, 644.

According to Malý, "mice deficient in α(1,3)fucosyltransferase Fuc-TVII exhibit a leukocyte adhesion deficiency characterized by absent leukocyte E- and P-selectin ligand activity and deficient HEV[12] L-selectin ligand activity." *Id.*, Abstract. Malý indicates that "Fuc-TVII decorates the oligosaccharide components of these glycoproteins with α(1,3) fucose residues essential to effective E- and P-selectin ligand activity." *Id.* at 649.

v. Gao (Ex. 1006)

Gao describes the separation of YB2/0 cells into cell fractions according to cell cycle stages using counterflow centrifugal elutriation. Ex. 1006, 435. According to Gao, "[t]he YB2/0 plasmacytoma cell line is a highly efficient partner for the production of hybridomas." *Id.* at 437.

[12] Short for high endothelial venules, cells which express specific adhesion molecules such as this ligand.

II. ANALYSIS

a. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved based on underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, if present. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Although the *KSR* test is flexible, we "must still be careful not to allow hindsight reconstruction of references . . . without any explanation as to *how* or *why* the references would be combined to produce the claimed invention." *TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1066 (Fed. Cir. 2016) (citation omitted).

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review). "To satisfy its burden of proving obviousness, a

petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) (citing *KSR*, 550 U.S. at 418).

We analyze the challenges presented in the Petition in accordance with the above-stated principles.

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) (citation omitted).

Petitioner proposes that we construe "knock-out" as used in independent claims 1 and 7 as "any gene deletion that results in reduced or removed gene expression." Pet. 17 (citing Ex. 1007, ¶¶ 54–57; Ex. 1026 ¶¶ 48–52; Ex. 1036-B, Aug. 12, 2004 Amendment at 32–35). Patent Owner contends that construction of this term is unnecessary at this stage, but opposes Petitioner's definition to the extent it "requires 'gene deletion' as the only means to knock-out the FUT8 gene." Prelim. Resp. 23. For the purpose of this Decision, we agree with Patent Owner that it is unnecessary

to determine the scope of genetic techniques that may be used to create the claimed "knock-out host cell." *See* Ex. 1001, 7:28–38.

We also agree with Patent Owner's position that the "fucosyltransferase knock-out" of the instant claims, refers to a disruption of FUT8, the gene encoding α1,6-fucosyltransferase. *See* Prelim. Resp. 29; *see id.* at 2, fn.3. As indicated by the Specification, α1,6-fucosyltransferase is responsible for adding fucose at the 6 position of N-acetylglucosamine in the reducing ends of an antibody's sugar chains, whereas disruption of the gene encoding this enzyme results in antibodies with more potent ADCC function. *See id.* at 3:60–4:1, 23:22–26, 111:31–45.

Although Petitioner's proposed construction does not expressly refer to α1,6-fucosyltransferase or the FUT 8 gene encoding it, Petitioner's obviousness arguments are in accord with our interpretation of "fucosyltransferase knock-out." In particular, Petitioner asserts that one of ordinary skill in the art would be motivated to obtain the host cells of the challenged claims "by 'knocking-out' the gene for the enzyme that adds the fucose to the sugar chain—α(1,6)fucosyltransferase." *See* Pet. 19, 25, 32, 39 (citations omitted); *see also* Ex. 1026 ¶ 45 ("The standard approach would have been to import the antibody genes into a host cell to express the antibody, and to genetically 'knock out' the enzyme that added α-1,6-fucose to the sugar chain (i.e., the α-1,6-fucosyltransferase enzyme)."). Further crystallizing this interpretation, Petitioner's expert, Dr. Van Ness testified that, "the independent claims of the '292 are directed to creating mammalian host cells—including those that are transfected with antibody genes—that have the cells' α1,6-fucosyltransferase genes knocked out, in order to

express afucosylated antibodies with enhanced effector (ADCC) function." Ex. 1007 ¶ 45.

In view of the above, we construe a "fucosyltransferase knock-out host cell" as a host cell in which FUT8, the gene encoding α1,6-fucosyltransferase, is disrupted.

At this stage of the proceeding, we find that no explicit construction of any other claim term is necessary to determine whether to institute a trial in this case. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999)).

B. Person of Ordinary Skill in the Art.

According to Petitioner, one of ordinary skill in the art as of the earliest possible filing date of the invention would have had A) "knowledge of the scientific literature . . . concerning the means and methods for creating cells in which the gene for the fucose-adding enzyme fucosyltransferase was knocked out, resulting in a modified sugar chain giving improved antibodies" and, B) "a doctorate in molecular immunology or biochemistry of glycoproteins including antibodies, knowledge of routine genetic procedures including gene 'knock-outs,' and a few years' practical experience working on the genetics of antibodies." Pet. 15–16 (citing Ex. 1026 ¶¶ 11–13; Ex. 1007 ¶¶ 18–20). Petitioner further directs us to the level of skill in the art indicated by Applicants during prosecution. *Id*. (citing Ex. 1036-B, Aug. 12, 2004 Amendment at 32–35) (indicating, for example, that the state of the art with respect to genetic manipulation techniques was "quite advanced").

Patent Owner does not propose an alternative definition. *See* Prelim. Resp. 19–22. Patent Owner argues, however, that the cited references fail to disclose "the FUT8 gene or any method of knocking out the FUT8 gene to create the claimed fucosyltransferase knock-out host cell," such that part A) of Petitioner's proposed definition is merely an attempt to "make up for the missing elements and the missing motivation to combine in the prior art references they cite" (*id.* at 2–3, 8–9, 20–22). In light of our construction of "fucosyltransferase knock-out," we agree with Patent Owner to the extent that part A) of Petitioner's proposed definition avoids the salient issue, discussed in section II(C)(iii), below, of whether Petitioner has established that the prior art discloses a mammalian α1,6-fucosyltransferase gene, or any method of deleting or adding a mutation to the genomic α1,6-fucosyltransferase gene, as required by the challenged claims.

Accordingly, on this record, we adopt part B) of Petitioner's definition of the level of ordinary skill in the art. Specifically – a person of ordinary skill in the art would have had a doctorate level degree in a field concerned with molecular immunology or biochemistry of glycoproteins including antibodies, knowledge of routine generic genetic procedures including gene knock-outs, and a few years practical experience working on the genetics of antibodies.

We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton*

Indus. Prods., Inc. v. Solid State Sys. Corp., 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Asserted Grounds

We next turn to the six grounds of invalidity asserted in the Petition: whether the subject matter of claims 1–12 of the ’292 Patent would have been obvious to a person of ordinary skill in the art at the time of the invention over Rothman or Harris in view of Umaña (Grounds 1 and 2); Umaña and Malý (Grounds 3 and 4) or, in the case of claims 5 and 11 only, Umaña and Gao (Grounds 5 and 6). Pet. 17–18.

Briefly, Petitioner contends that Rothman and Harris each suggest a link between removal of fucose and improved ADCC—and thus motivation to obtain “fucosyltransferase knock-out” host cells producing antibodies that “do not contain fucose bound to the 6 position of N-acetylglucosamine at the reducing end of the sugar chains,” as required by the independent claims. *See* Pet. 18–19, 31–32. Asserting that one of ordinary skill in the art “would achieve this result by ‘knocking out’ the gene for the enzyme that adds the fucose to the sugar chain— α(1,6)fucosyltransferase,” Petitioner relies on Umaña, as “teach[ing] the creation of mammalian host cells with modified sugar-adding genes (including ‘knock-outs’) to create sugar-modified antibodies with more efficient ADCC” properties.” *See e.g.,* Pet. 18–19. Petitioner further asserts that “[t]he necessary steps for creating such a host cell . . . were in the common knowledge.” *See, e.g., id.* at 19 (citing Ex. 1007 ¶¶ 32–34, 39–42, 70–77). With respect to Grounds 3 and 4, Petitioner further argues that one of ordinary skill in the art would have been “emboldened . . . to pursue ‘knock-out’ of α1,6-fucosyltransferase” by

Malý's "knockout of the gene for α(1,3)-fucosyltransferase in mouse embryos." *Id.* at 32, 39.[13]

Patent Owner responds that the challenged claims are not obvious because 1) neither Rothman nor Harris suggests a link between removal of fucose and improved ADCC and, 2) the Petition fails to provide a reasoned explanation of how one of ordinary skill in the art would have combined the asserted references to generate the "fucosyltransferase knock-out" having the claimed properties, "especially given that none of the references mention the gene encoding α1,6-fucosyltransferase (FUT8), let alone knocking out the FUT8 gene to create a fucosyltransferase knock-out host cell." Prelim. Resp. 23–56.

We address these issues below.

i. Grounds 1, 3, and 5 (based on Rothman)

Petitioner relies on Rothman's teachings regarding "a possible involvement of core fucosylation of IgG in NK cell-mediated ADCC," and the reference's conclusion that the "absence of core fucosylation itself would appear to be a likely candidate as a structural feature necessary for enhancement of NK cell-mediated ADCC," as providing motivation to target the α1,6-fucosyltransferase gene for genetic knockout. *See, e.g.*, Pet. 18–20. Patent Owner contends that Petitioner's expert, Dr. Jefferis, fails to credit Rothman (or Harris) with discovering a correlation between defucosylation and enhanced ADCC in several review articles. Prelim. Resp. 54–56. Patent Owner further argues that one of ordinary skill in the art would not

[13] Petitioner further references Gao, in Grounds 5 and 6, merely to highlight the applicability of cell line YB2/0 for production of hybridomas. *Id.* at 45–48.

have read Rothman the way Petitioner urges based on a review article by Wright and Morrison (Ex. 2004) published before the earliest possible filing date of the '292 Patent, which potentially contradicts a portion of Rothman's analysis. *See id.* at 51–53.

We do not find Patent Owner's position persuasive on the current record. Dr. Jefferis's failure to mention Rothman in two review articles is insufficient to overcome Rothman's express teaching that the "absence of core fucosylation itself would appear to be a likely candidate as a structural feature necessary for enhancement of NK cell-mediated ADCC." *See* Ex. 1002, 1122. And although we do not find Patent Owner's arguments based on Wright and Morrison unreasonable, Patent Owner's explanation of how one of ordinary skill in the art would interpret Rothman in view of this reference rests on attorney argument, which is entitled to little probative value. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997). Accordingly, on the present record, Petitioner has shown sufficiently that Rothman provides a link between removal of fucose and improved ADCC and, thus, motivation to generate IgG-type antibodies in cells lacking α1,6-fucosyltransferase activity. This determination does not, however, end our inquiry with respect to Petitioner's assertion of obviousness.

ii. Grounds 2, 4, and 6 (based on Harris)

With respect to Grounds 2, 4, and 6, Petitioner relies on Harris to establish motivation to generate IgG-type antibodies in cells lacking α1,6-fucosyltransferase activity. In particular, Petitioner points to Harris's teaching that the fucose residue of an IgG-type antibody "may be of particular interest" because it is "near the Fcγ receptor binding site and could influence binding by the receptor." *See, e.g.*, Pet. 25–31 (quoting Ex. 1003,

1592) (emphasis removed); *see also* Ex. 1026 ¶¶ 80, 124 (asserting that Harris "describes the correlation between sugar chain modification—including the removal of fucose, particularly—and improved ADCC"); Ex. 1007 ¶¶ 87, 111 (same).

We do not find Petitioner's arguments persuasive. Although Harris draws attention to the proximity of the fucose moiety and the Fcγ receptor binding site, it merely hypothesizes that the fucose "could," therefore, "influence" Fcγ binding. *See* Ex. 1003, 1592. We do not read Harris as suggesting that any such potential influence would have a positive effect on ADCC. To the contrary, Harris's teaching that "[d]egradation or modification of the carbohydrate has . . . been clearly shown to eliminate or reduce effector functions such as . . . binding to Fc receptors," suggests that any potential influence would more likely reduce, rather than enhance, ADCC. Ex. 1003, 1593–94. Moreover, as Patent Owner points out, "Harris does not mention removing fucose or improved ADCC, much less any causal relationship between the two. Rather, Harris suggests that the ***presence*** of fucose is required for receptor binding since fucose ***interacts*** with Tyr313 on the Fc region." Prelim. Resp. 13–14.

For at least these reasons, the Petition fails to show sufficiently that the subject matter of claims 1–12 would have been obvious over Harris, in view of Umaña, Malý, and/or Gao. Accordingly, for at least these reasons, we decline to institute trial with respect to Grounds 2, 4, and 6.

iii. A gene encoding α1,6-fucosyltransferase

Every challenged claim is directed to an isolated fucosyltransferase knock-out host cell. In section II(A), above, we construe a "fucosyltransferase knock-out host cell" as a host cell in which FUT8, the

gene encoding α1,6-fucosyltransferase, is disrupted. As we understand the challenged claims in light of the Specification, the disruption of this particular fucosyltransferase makes possible the production of antibodies having "complex N-glycoside-linked sugar chains . . . [that] do not contain fucose bound to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains." Consistent with our reading, Petitioner's expert, Dr. Van Ness testified that, the challenged claims "are directed to creating mammalian host cells. . . that have the cells' α1,6-fucosyltransferase genes knocked out, in order to express afucosylated antibodies with enhanced effector (ADCC) function." Ex. 1007 ¶ 45. Accordingly, we agree with Patent Owner that creating the fucosyltransferase knock-out host cells of the challenged claims "requires knocking out the gene encoding α1,6-fucosyltransferase." *See* Prelim. Resp. 2.

Patent Owner further argues that,

> none of the references mention the gene encoding α1,6-fucosyltransferase (FUT8), let alone knocking out the FUT8 gene to create a fucosyltransferase knock-out host cell that, upon having a gene encoding an antibody introduced into it, produces antibody molecules with complex sugar chains that do not contain fucose bound to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains, or explain how a POSA would have overcome these obstacles.

Id. at 25–26; *see also id.* at 1–2 (arguing that the Petition fails to render obvious "an α1,6-fucosyltransferase knock-out host cell" having the claimed properties). We find Patent Owner's arguments persuasive.

Citing paragraphs 39–41 of Dr. Van Ness's Declaration, Petitioner asserts that "*[t]he* human fucosyltransferase gene sequence was cloned in 1994." Pet. 7 (emphasis added). Elaborating on Petitioner's assertion, Dr. Van Ness testifies that "*[t]he* human fucosyltransferase gene sequence

had been cloned in 1994 by Sasaki et al. (269(20) J. BIOL. CHEM. 14730–37 (1994)).” Ex. 1007 ¶ 40 (referencing Ex. 2009) (emphasis added); *see also id*. at ¶ 77 (referencing “the known genetic sequence of α1,6-fucosyltransferase”). We do not find these statements supported by the present record.

First, in addition to the α1,6-fucosyltransferase recited in independent claim 1, Malý discloses that there are *five* human fucosyltransferase genes encoding α1,3-fucosyltransferases alone. Ex. 1005, 649. Moreover, Sasaki nowhere mentions α1,6-fucosyltransferase, but instead discloses the cloning of Fuc-TVII, a member of “a unique class of the α1,3-fucosyltransferase family.” Ex. 2009, 14730.

Petitioner presents no evidence suggesting that the nucleotide sequence of any α1,3-fucosyltransferase is related to that of the α1,6-fucosyltransferase recited in claim 1. Nor does Petitioner establish that any of the α1,3-fucosyltransferases are involved in the fucosylation of antibodies, or are otherwise capable of adding fucose to the 6 position of N-acetylglucosamine in the reducing end of sugar chains. *See* Ex. 1037 98:17–20 (Dr. Van Ness admitting that he is “not aware” whether α1,3-fucosyltransferases are involved in adding fucose to the complex sugar chain in antibodies); Prelim. Resp. 46–47.

Petitioner further contends that during prosecution, Patent Owner admitted “that the gene sequence for α(1,6)-fucosyltransferase had already been published.” Pet. 7 (citing Ex. 1036, Aug. 12, 2004 Amendment at 33–34). Agreeing that the genetic sequence of α1,6-fucosyltransferase was “known,” Petitioner’s expert, Dr. Van Ness, further testifies that “a POSA could have determined [the sequence of α1,6-fucosyltransferase]

independently and routinely." Ex. 1007 ¶¶ 41, 77. Dr. Van Ness's sole support for this positon is that "during prosecution of the '292 patent, the patentee cited specific prior-art articles that confirm that sufficient information of the gene sequence for α1,6-fucosyltransferase had already been published." *Id.* ¶ 40 (citing Ex. 1036, Aug. 12, 2004 Amendment at 33–34)). These assertions are not supported in the record before us.

According to the Specification, the inventors of the '292 Patent cloned Exon 2 of the FUT 8 genomic sequence using a cDNA probe, and used that DNA to create a genomic knockout of α1,6-fucosyltransferase in mammalian cells. *See* Ex. 1001, 98:25–111:46. In responding to a lack of enablement rejection under § 112, first paragraph, Applicants argued that "one of ordinary skill in the art would have been able to prepare a cell in which the enzyme activity of α1,6-fucosyltransferase . . . is deleted or decreased without limitation to the exon 2." Ex. 1036, Aug. 12, 2004 Amendment at 32–33. Applicants asserted that, "[o]ne of ordinary skill in the art would appreciate the intron and exon structures of . . . α1,6-fucosyltransferase[] by using a method similar to the method described in Example 12 of the present specification, *if the cDNA of the target gene is known*." *Id*. at 39–40 (emphasis added).

Thus, contrary to Petitioner's argument, Applicants did not admit that the genetic sequence of α1,6-fucosyltransferase was known, but that the intron/exon structure of the gene could be determined based upon knowledge of the FUT8 cDNA disclosed in Example 12 of their Specification. On the present record, Petitioner fails to establish that DNA encoding any portion of the FUT8 DNA sequence was in the prior art. Because knowledge of at least some portion of this sequence is necessary to

create the "fucosyltransferase knock-out host cell" of the challenged claims, we find unsupported Petitioner's blanket assertions that "all limitations of claims 1 and 7 are taught by *Rothman* and *Umaña*," and other combinations of asserted prior art. *See* Pet. 19, 32, and 39–40.

With respect to his contention that the Applicants "cited specific prior-art articles that confirm that sufficient information of the gene sequence for α1,6-fucosyltransferase had already been published," Dr. Van Ness relies on Applicants' statement that:

> In reference (i), the structure motif which is important to the activity of the fucosyltransferase was expected from fucosyltransferases derived from various species (see Figs. 2, 3, 4 and 6). In the reference (ii), the structure which is important to the activity of the fucosyltransferase was similarly expected (Fig. 3).

Ex. 1007 ¶ 40 (quoting Ex. 1036, Aug. 12, 2004 Amendment at 34). As we understand his testimony, Dr. Van Ness does not suggest that "reference (i)" or "reference (ii)" disclose any portion of the FUT8 DNA sequence, but that Applicants allegedly admitted that FUT8 DNA sequence could be derived from information about other fucosyltransferases contained in those references.

As an initial matter, we note that Applicants predicated the above statements regarding structures and structural motifs on the knowledge of cDNA for α1,6-fucosyltransferase, which Petitioner does not establish as prior art. *See* Ex. 1036, Aug. 12, 2004 Amendment at 34 (stating "that the relevant structures can be determined based on the cDNA"). *Id.* Moreover, the "structures" Applicants reference in the prosecution history are not DNA sequences but protein-based motifs; Dr. Van Ness does not establish that one of ordinary skill in the art could have derived any portion of the gene

sequence for α1,6-fucosyltransferase from protein-based "structures," irrespective of whether they were important to the activity of fucosyltransferases generally. Because Dr. Van Ness cites no other evidence for the proposition that one of ordinary skill in the art would have "independently and routinely" determined the DNA sequence of α1,6-fucosyltransferase, we accord his opinion little weight. *See* Ex. 1007 ¶ 41.

In sum, Petitioner argues that "[k]nowing [the DNA sequence of α1,6-fucosyltransferase] . . . would have allowed a POSA to target [this gene] and disable it by using well known 'knock-out' techniques." Pet. 7; Ex. 1007 ¶ 41 (same); *see also* Pet. 7–9, 13 (arguing that techniques for knocking out targeted genes were routine). But Petitioner fails to establish adequately that DNA encoding a mammalian α1,6-fucosyltransferase was either available, or could be routinely obtained by those of ordinary skill in the art. Lacking sufficient evidence of access to that starting material, we agree with Patent Owner that the cited prior art fails to disclose or render obvious DNA sequence encoding α1,6-fucosyltransferase (FUT8), or means for

> knocking out the FUT8 gene to create a fucosyltransferase knock-out host cell that, upon having a gene encoding an antibody introduced into it, produces antibody molecules with complex sugar chains that do not contain fucose bound to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains.

See Prelim Resp. 25–26.

Thus, on the record before us, the Petition fails to show sufficiently that the subject matter of any challenged claim would have been obvious over the combined disclosures of Rothman, Harris, Umaña, Malý, and/or Gao.

Accordingly, we deny the Petition.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has not shown there is a reasonable likelihood that it would prevail in proving the unpatentability of claims 1–12 of the '292 Patent.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner's request for *inter partes* review of claims 1–12 of the '292 Patent is denied and no *inter partes* review is instituted.

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