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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.

[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

[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.

Ground	Reference(s)	Basis	Claims
5	Rothman, Umaña, Gao,[8] knowledge of POSA	§ 103	5
6	Harris, Umaña, Gao, knowledge of POSA	§ 103	5

Petitioner also relies on the Declarations of Dr. Brian G. Van Ness (Ex. 1007)[9] 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 1038), 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 10).

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, e.g.*, 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

[8] Gao et al., *Characterization of YB2/0 cell line by counterflow centrifugation elutriation*, 44 Exp. Toxic. Pathol. 435–38 (1992). Ex. 1006.
[9] We find Dr. Van Ness to be qualified to testify to the subject matter of this proceedings by virtue of his education and experience. Ex. 1007 ¶¶ 4–12 and Exhibit B thereto.
[10] Where possible, we refer to the native page numbers of the exhibits.

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. Further "it 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." *Id*. We are not provided with evidence or argument that Rothman itself describes a gene encoding mammalian α1,6-fucosyltransferase.

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, 1590–92. 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. 1592.

With respect to effector function, Harris further states:

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[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.

> 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. Again, we are not provided evidence or argument that Harris itself describes a gene encoding mammalian α1,6-fucosyltransferase.

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:

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

Id. 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.* 15:20–22. As above, we are not provided evidence or argument that Umaña itself describes a gene encoding mammalian α1,6-fucosyltransferase.

iv. Malý (Ex. 1005)

According to Malý, five genes Fucosyltransferase VII ("Fuc-TVII"), Fucosyltransferase III ("Fuc-TIII"), Fucosyltransferase V ("Fuc-TV"), Fucosyltransferase VI ("Fuc-TVI"), and Fucosyltransferase IV ("Fuc-TIV") encode α(1,3)fucosyltransferases in humans. Ex. 1005, 649; *see id*. 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 (Footnote added). 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. As with the other references, we are not provided evidence or argument that Malý itself describes a gene encoding mammalian α1,6-fucosyltransferase.

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.* 437. We are not provided evidence or argument that Gao itself describes a gene encoding mammalian α1,6-fucosyltransferase.

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

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

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 the term "which has decreased or no α-1,6-fucosyltransferase activity for adding fucose" of the challenged claims should mean "which has zero or no α-1,6-fucosyltransferase activity for adding fucose." Pet. 17. Petitioner also proposes that the term "deleting a gene encoding α-1,6-fucosyltransferase or by adding a mutation to said gene to reduce or eliminate the α-1,6-fucosyltranferase activity" should be interpreted to mean "deleting a gene encoding α-1,6-fucosyltransferase or by adding a mutation to said gene to remove or eliminate the α-1,6-fucosyltranferase activity." *Id.*

The rationale behind this interpretation is that the claim is not enabled for a mere decrease in activity as the 'knock out' of the gene eliminates the

activity entirely. *Id*, 17–20. Petitioner relies upon prosecution history of the grandparent application wherein the Examiner rejected claims as lacking enablement as support for this position.

We are not persuaded by this position. Whatever the scope of the claims might be, we will not intentionally read them in a manner contrary to their express language in order to exclude subject matter which might not have been enabled in a previous application.

Patent Owner asserts that no construction is required at this time. Prelim. Resp. 20. At this stage of the proceeding, we agree with Patent Owner, and find that no explicit construction of any 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 on October 6, 2000 (the earliest possible filing date of the invention) would have had "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." Pet. 16 (citing Ex. 1026 ¶¶ 12–14; Ex. 1007 ¶¶ 18–20). The hypothetical person of ordinary skill in the art would have also had "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." *Id*. 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. 17–20. Patent Owner argues, however, that Petitioners' attempt to read into their definition of the level of skill in the art knowledge of knocking out the gene for "the fucose-adding enzyme fucosyltransferase," thereby "resulting in a modified sugar chain, giving improved antibodies," is improper and contrary to the evidence. Prelim. Resp. 17.

We agree with Patent Owner to the extent that Petitioner's proposed definition attempts to avoid a requirement of proof. More specifically, Petitioner attempts to sidestep the issue of whether 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. Genetic manipulation techniques may have been "quite advanced," but some credible evidence that the FUT8 gene was known is necessary.

Accordingly, on this record, we adopt only a portion 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 this 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 1–6 of the '466 Patent would have been obviousness to a person of ordinary skill in the art at the time of the invention over Rothman or Harris in view of Umaña and the knowledge of a person of ordinary skill in the art (Grounds 1 and 2); Umaña and Malý and the knowledge of a person of ordinary skill in the art (Grounds 3 and 4) or, in the case of claim 5 alone, Umaña and Gao and the knowledge of a person of ordinary skill in the art (Grounds 5 and 6). Pet. 20.

Briefly, Petitioner contends that Rothman and Harris each suggest a link between removal of fucose and improved ADCC—and thus motivation to generate IgG-type antibodies cells lacking α1,6-fucosyltransferase activity—, whereas "*Umaña*, teaches the creation of mammalian host cells with modified sugar-adding genes (including 'knock-outs') to create sugar-modified antibodies with more efficient ADCC" properties." Pet. 21–53. According to Petitioner, "[t]he necessary steps for creating such a host

cell. . . were in the common knowledge." *Id.* 21–22 (citing Ex. 1007 ¶¶ 32–34, 39–42, 60–75).

With respect to Grounds 3 and 4, Petitioner further argues that one of ordinary skill in the art would have been motivated by the teachings of Rothman to obtain host cells that had decreased or no α1,6-fucosyltransferase activity and "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.* 35–50.[13]

Patent Owner responds that the challenged claims are not obvious because none of the cited references disclose "decreased or no α1,6-fucosyltransferase activity," the "gene encoding fucosyltransferase," and "deleting . . . or . . . adding a mutation" to such a gene. Prelim. Resp. 27–38.

We address the dispositive issue below.

i. Grounds 1 – 6 and "Common Knowledge"

Common knowledge is a component of each of Grounds 1–6. Pet. 20. We address only Ground 1 to illustrate the deficiency of the asserted "common knowledge," but note that grounds 2–6 fail for the same reason.

In Ground 1, Petitioner asserts that Umaña teaches the creation of mammalian host cells with modified sugar adding genes (including "knock-outs") to create sugar-modified antibodies with more efficient ADCC. Pet. 21, citing Ex. 1004 generally. Petitioner relies on Rothman as teaching the correlation between a no-fucose sugar-chain structure and enhanced antibody function ADCC. More specifically, Petitioner cites the reference's

[13] Petitioner further references Gao, in Grounds 5 and 6, to highlight the applicability of cell line YB2/0 for production of IgG-secreting hybridomas. *Id.* 50–53.

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." *Id*., citing Ex. 1002 at 1122. Accordingly, Petitioner reasons that Rothman provides motivation to target the α1,6-fucosyltransferase gene for genetic knockout. Pet. 21. The "necessary steps for creating a host cell with a knocked out gene for the enzyme that adds fucose to the sugar chain" are said to be in the "common knowledge." Pet. 21, citing Ex. 1007, ¶¶ 32–34, 39–42, 65–81, which is the testimony of Dr. Van Ness.

Patent Owner, on the other hand, asserts that the Petition fails to point out where key claim elements can be found in the prior art. Prelim. Resp. 25. More specifically, Patent Owner asserts that claims 1–6 contain a critical element of the gene encoding α1,6-fucosyltransferase, which is either deleted or has a mutation added to it resulting in the claimed mammalian host cell with reduced or eliminated α1,6-fucosyltransferase activity. *Id.* According to the Patent Owner, none of the references contain any identification of this gene, and the absence of identification of the gene is fatal to the Petition. *Id.* 26.

We agree with Patent Owner.

The claims of the '446 Patent are directed to an isolated "mammalian host cell which has decreased or no α1,6-fucosyltransferase activity." *See* Ex. 1001, 183:30–31. This decreased activity is by virtue of a modification to the gene encoding α1,6-fucosyltransferase, the enzyme which permits fucose to be added to the sugar chain. 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). In support of

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 (emphasis added).

This is the heart of the evidence supporting "common knowledge" in each of Grounds 1–6. However, no copy of the evidence cited was provided as an exhibit by Petitioner. Exhibit 2009, a copy of Sasaki, was in fact supplied by the Patent Owner in its Preliminary Response.

After careful review of the evidence of record, we find it to be contrary to the assertion of Dr. Van Ness.

First, claim 1 recites α1,6-fucosyltransferase. Our review of Sasaki fails to turn up mention of α1,6-fucosyltransferase, but instead we find it discloses the cloning of Fuc-TVII, a member of "a unique class of the α1,3-fucosyltransferase family." Ex. 2009, 14730. Malý discloses that there are *five* human fucosyltransferase genes encoding α1,3-fucosyltransferases alone. Ex. 1005, 649. Dr. Van Ness's statement glosses over these facts.

Petitioner presents no persuasive evidence suggesting that the nucleotide sequence of any α1,3-fucosyltransferase is related to that of the α1,6-fucosyltransferase recited in claim 1. Moreover, Petitioner does not establish that any of the α1,3-fucosyltransferases are involved in the fucosylation of antibodies. *See* Ex. 1038 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. 36.

Petitioner alternatively contends in support of its position 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). Asserting that the genetic sequence of α1,6-fucosyltransferase was "known," Petitioner's witness Dr. Van Ness further testifies that "a POSA could have determined [the sequence of α1,6-fucosyltransferase] independently and routinely." Ex. 1007 ¶¶ 41, 68.

Dr. Van Ness's evidentiary support for this positon is that "during prosecution of the '446 patent's parent application, 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 by the evidence in the record before us.

According to the Specification, the inventors of the '446 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, 99:3–111:46.

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, *based on the present specification*." Ex. 1036, Aug. 12, 2004 Amendment at 33 (emphasis added). Applicants additionally 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*. 33–34 (emphasis added).

Thus, contrary to Petitioner's argument, Applicants did not admit that the genetic sequence of α1,6-fucosyltransferase was known or published, 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 with persuasive evidence that DNA encoding any portion of the FUT8 gene was in the prior art.

Because knowledge of at least some portion of this sequence is necessary for "deleting a gene encoding α1,6-fucosyltransferase or by adding a mutation to said gene to reduce or eliminate the α1,6-fucosyltransferase activity" as set forth in claim 1, we find unsupported Petitioner's blanket assertion that "all limitations of claim 1 are taught by Rothman and Umaña," with or without the "common knowledge" of one of ordinary skill in the art. *See* Pet. 22.

With respect to his testimony 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 with credible evidence or persuasive argument 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 persuasive 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 and are unpersuaded by it in view of the documentary evidence of record. *See* Ex. 1007 ¶ 41; *cf.* Ex. 1038.

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, 13–14 (arguing that techniques for knocking out targeted genes were routine).

We find that 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 the "gene

encoding fucosyltransferase," necessary for "deleting a gene encoding α1,6-fucosyltransferase or by adding a mutation to said gene to reduce or eliminate the α1,6-fucosyltransferase activity," in the "isolated mammalian host cell which has decreased or no α1,6-fucosyltransferase activity" of independent claim 1. Prelim. Resp. 22–50.

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 or Umaña. Harris, Malý, and Gao also fail to cure the deficiencies found in Ground 1. As a consequence, Grounds 2–6 also fail to show that the subject matter of any claim would have been obvious.

ii. Additional Deficiencies Concerning Grounds 2, 4, and 6

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. 28–32 (quoting Ex. 1003, 1592) (emphasis removed); *see also* Ex. 1026 ¶¶ 71, 105 (asserting that Harris "describes the correlation between sugar chain modification—including the removal of fucose, particularly—and improved ADCC"); Ex. 1007 ¶¶ 83, 129 (same).

We do not find Petitioner's arguments in this regard to be 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. 12, 33.

For this additional reason, the Petition fails to show sufficiently that the subject matter of claims 1–6 would have been obvious over Harris, in view of Umaña, Malý, and/or Gao.

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 1–6 of the '446 Patent.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner's request for *inter partes* review of claims 1–6 of the '446 Patent is denied and no *inter partes* review is instituted.

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