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Filed on behalf of : Kyowa Hakko Kirin Co., Ltd.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Aragen Bioscience Inc.,

and

Transposagen Biopharmaceuticals, Inc.,
Petitioners,

v.

Kyowa Hakko Kirin Co., Ltd.,
Patent Owner.

Case IPR2017-01252
U.S. Patent No. 6,946,292

PATENT OWNER'S PRELIMINARY RESPONSE

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2002	Jefferis, *et al.*, "Glycosylation of Antibody Molecules: Structural and Functional Significance," *Chem. Immunol. 65*, 111-28 (1997)
2003	Jefferis, "Glycosylation of Recombinant Antibody Therapeutics," *Biotechnol. Prog. 21*(1), 11-16 (2005)
2004	Wright*, et al*., "Effect of Glycosylation on Antibody Function: Implications for Genetic Engineering," *Trends Biotechnol. 15*, 26-32 (1997)
2005	Hubbard, *et al.*, "Synthesis and Processing of Asparagine-Linked Oligosaccharides," *Ann. Rev. Biochem. 50*, 555-83 (1981)
2006	Shields, *et al.*, "Lack of Fucose on Human IgG1 *N*-Linked Oligosaccharide Improves Binding to Human FcγRIII and Antibody-Dependent Cellular Toxicity," *J. Biol. Chem. 277*(30), 26733-40 (2002)
2007	Fukao, *et al.*, "Effect of Monensin on Secretion of t-PA from Melanoma (Bowes)," *Cell Structure & Function 14*(6), 673-84 (1989)
2008	Schachter, "Biosynthetic Controls That Determine the Branching and Microheterogeneity of Protein-Bound Oligosaccharides," *Biochem. Cell Biol. 64*(3), 163-81 (1986)
2009	Sasaki, *et al*., "Expression Cloning of a Novel α1,3-Fucosyltransferase That Is Involved in Biosynthesis of the Sialyl Lewis x Carbohydrate Determinants in Leukocytes," *J. Biol. Chem. 269*(20), 14730-37 (1994)

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2010	Shinkawa, *et al.*, "The Absence of Fucose But Not the Presence of Galactose or Bisecting *N*-Acetylglucosamine of Human IgG1 Complex-Type Oligosaccharides Shows the Critical Role of Enhancing Antibody-Dependent Cellular Cytotoxicity," *J. Biol. Chem. 278*(5), 3466-73 (2003)
2011	*Not used*
2012	Schachter, *et al*., "Mammalian Glycosyltransferases," *The Biochemistry of Glycoproteins and Proteoglycans*, Chap. 3, 85-160 (Plenum Press, New York, 1980)

I. Introduction

Pursuant to 35 U.S.C. § 313 and 37 C.F.R. § 42.107(a), Patent Owner Kyowa Hakko Kirin Co., Ltd. (the "Patent Owner") submits this Preliminary Response to the Petition for *Inter Partes* Review (the "Petition" or "Pet."), filed by Aragen Bioscience Inc. and Transposagen Biopharmaceuticals, Inc. (collectively, "Petitioners"), of U.S. Patent No. 6,946,292 (the "'292 Patent," Ex. 1001).[1]

The Board should decline to institute *inter partes* review. The Petition challenging claims 1-12 of the '292 Patent suffers from fundamental inadequacies. Importantly, each of the two independent claims require "a fucosyltransferase knock-out host cell" that can produce an antibody 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."[2] Yet the Petition fails to identify a single reference in the alleged obviousness combinations that discloses the claimed fucosyltransferase knock-out host cell or a fucosyltransferase

[1] Petitioners have also filed co-pending petitions, IPR2017-01262 and IPR2017-01254, challenging related patents U.S. Patent Nos. 7,425,446 (the '446 Patent) and 8,067,232 (the '232 Patent).

[2] The only difference between the two independent claims is that claim 1 does not require that the knock-out host cell produces an antibody composition, while claim 7 does recite that the host cell produces an antibody composition.

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, *i.e.* an α1,6-fucosyltransferase knock-out host cell.[3]

The Petition's claim charts reveal the gaping holes in their obviousness grounds. While the left column in each chart lists the claim language, the selected quotes from the relied-upon references in the right column do not disclose the missing elements. For example, there is no quote from any reference that matches the required element of 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 any method of creating such a fucosyltransferase knock-out host cell, which requires knocking out the gene encoding α1,6-fucosyltransferase. Nor does the Petition include any

[3] α1,6-fucosyltransferase is the fucosyltransferase responsible for adding fucose to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains. (*See*, *e.g.*, Ex. 1001, 3:65-67.) Thus, the "fucosyltransferase knock-out host cell" recited in the claims is an α1,6-fucosyltransferase knock-out host cell, as acknowledged by Petitioners and their declarants. (*See*, *e.g.*, Pet., 19; Ex. 1007, ¶ 45; Ex. 1026, ¶ 45.)

analysis of why the selected quotes allegedly disclose each of the elements of the claims.

Recognizing these critical deficiencies, the Petition attempts to fill the gaps by alleging that a person of ordinary skill in the art ("POSA") would have had knowledge of the missing elements. The missing elements go to the heart of the claimed invention. Yet, Petitioners fail to provide the reasoned analysis and evidentiary support, such as scientific literature, necessary to show that the missing elements were within the common knowledge of a POSA at the time of the invention.

Finally, even if the missing elements were individually known to a POSA, the Petition still fails to establish that a POSA would have had motivation to combine them to come up with the claimed invention. The Petition relies exclusively on conclusory allegations of motivation to combine and reasonable expectation of success without providing any analysis or evidence with regard to either.

For these and other reasons detailed below, Petitioners have failed to establish a reasonable likelihood of prevailing in challenging the claims of the '292 Patent over the asserted grounds. Patent Owner respectfully submits that the Board should decline to institute *inter partes* review.

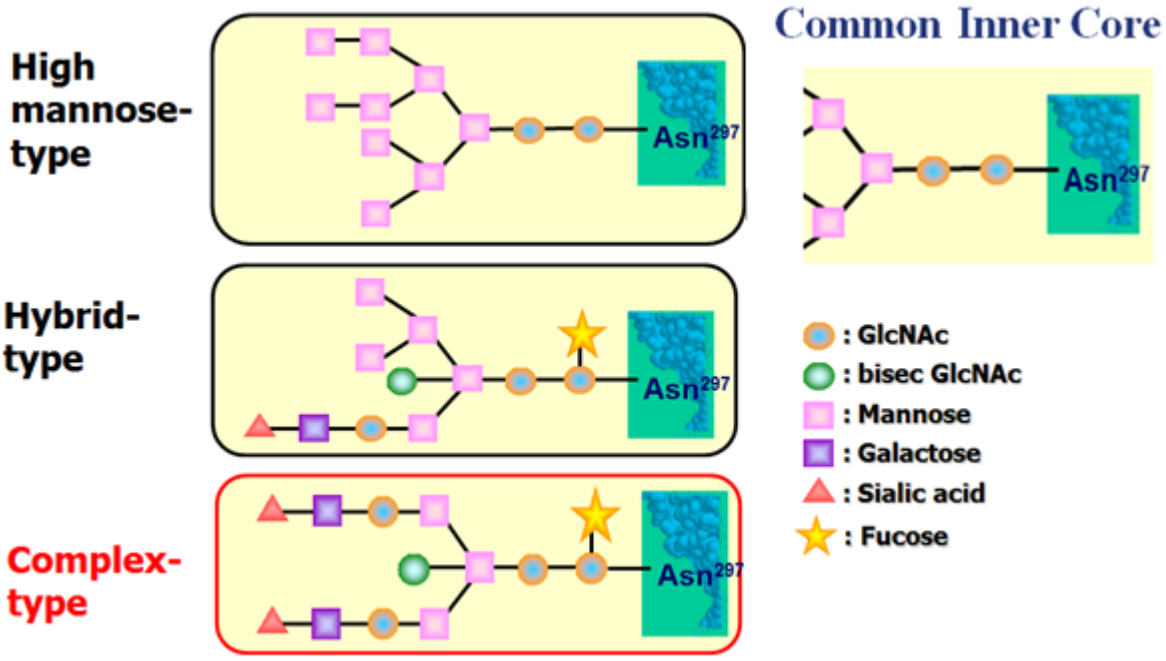
II. Background

A. The State of the Art at the Priority Date of the '292 Patent

At the time of the invention, no one had engineered a mammalian 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 complex sugar chains. α1,6-Fucosyltransferase, encoded by the FUT8 gene, is the enzyme responsible for catalyzing the transfer of fucose, from the nucleotide sugar GDP-fucose, to the 6-position of N-acetylglucosamine in the reducing end of a complex sugar chain attached to the amino acid designated Asn297 of an antibody's constant (Fc) region. (*See*, *e.g.*, Ex. 1001, 3:66-4:1, 20:46-55, 23:21-25.) It is undisputed that 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 is necessarily an *α1,6*-fucosyltransferase knock-out host cell. (*See*, *e.g.*, Pet., 19; Ex. 1007, ¶ 45; Ex. 1026, ¶ 45.)

The sugar chain attached to antibodies is called "N-linked oligosaccharide." As explained in the specification of the '292 Patent, at the time of the invention, it was known that three main classes of N-linked oligosaccharides exist: "high-mannose type," "hybrid type," and "complex type." (Ex. 1001, 2:59-3:2 (the '292

Patent uses the alternative wording "N-glycoside-linked sugar chain).) Claims 1 and 7 of the '292 Patent recite "complex" type sugar chains. Complex type oligosaccharides are the predominant naturally occurring type and are structurally very different from both hybrid type and high-mannose type oligosaccharides. (*See* Ex. 2001, 22; Ex. 2005, 572.)[4] Each type of sugar chain is further heterogeneous with respect to its sugar composition. Representative complex type, hybrid type and high-mannose type sugar chains are illustrated in the diagram below:



[4] All citations herein refer to the exhibits' native page numbers.

The three types of N-linked oligosaccharides share the same inner core structure of mannose3N-acetylglucosamine2 (*i.e.*, three mannose sugars and two N-acetylglucosamine sugars) as shown in the top right of the diagram above. (*See* Ex. 1001, 2:50-56 (formula (I)).) The sugar chain terminus at the right is called the "reducing end" of the sugar chain, and the opposite side is called the "non-reducing end." (*Id.*, 2:57-59.)

High-mannose type sugar chains contain additional mannose residues at the non-reducing end of the core structure (usually two to six in vertebrate cells). (*See id.*, 2:59-61; Ex. 2005, 556, 570.) Complex type sugar chains contain additional external sugars, such as N-acetylglucosamine (GlcNAc), galactose (Gal), fucose (Fuc), and sialic acid (SA). (*See* Ex. 1001, 2:61-67; Ex. 2001, 22.) Hybrid type sugar chains have one "arm" similar to the high-mannose type (additional mannose residues) and one "arm" similar to the complex type (additional GlcNAc and other external sugar residues). (*See* Ex. 1001, 2:67-3:2; Ex. 2001, 22.)

High-mannose type, hybrid type, and complex type N-linked oligosaccharides are synthesized sequentially from a common large, high-mannose precursor during a biosynthesis process called "N-linked oligosaccharide processing" involving multiple enzymes. (Ex. 2001, 22-24.) The precursor oligosaccharide is typically processed in an ordered sequence, first into a high-mannose type oligosaccharide, then a hybrid type oligosaccharide, and eventually

to a complex type oligosaccharide. (*See id.*) Most N-linked oligosaccharides made in mammalian cells do not retain a high-mannose or hybrid structure, but instead are converted to complex type oligosaccharides, which makes them the predominate type in mammals. (*See* Ex. 2005, 572.)

Many enzymes are involved in the N-linked oligosaccharide processing and each enzyme plays a different role. (*See id.*) Among these enzymes are glycosyltransferases, a genus of various different enzymes responsible for mediating glycosylation reactions that result in the addition of different sugars to and elongation of sugar chains of a variety of molecules, including glycoproteins—molecules that modulate or mediate a wide variety of interactions in multicellular organisms. (*See* Ex. 2012.)

Fucosyltransferases are a subclass of glycosyltransferases and there are different ones. (*See*, *e.g.*, Ex. 1001, Ex. 1005.) While fucosyltransferases mediate the transfer of a particular sugar residue called fucose (hence the name fucosyltransferase), different fucosyltransferases do so in unrelated biochemical pathways. For example, α1,3-fucoslytransferase catalyzes the transfer of fucose from GDP-beta-fucose to sialyl-Lewis X, a carbohydrate often found on the surface of cells involved in processes such as inflammation and cancer metastasis. (Ex. 1005.) In a different biochemical process, α1,6-fucosyltransferase catalyzes the transfer of fucose from the nucleotide sugar GDP-fucose to the 6-position of N-

acetylglucosamine in the reducing end of a sugar chain attached to the amino acid designated Asn297 of an antibody's constant (Fc) region. (*See*, *e.g.*, Ex. 1001, 3:66-4:1, 20:46-55, 23:21-25.) Accordingly, the fact that fucosyltransferases have similar sounding names does not mean that different fucosyltransferases catalyze the same reaction or have homology in their genetic code. (*See*, *e.g.*, Ex. 1001, Ex. 1005.)

The '292 Patent's inventors discovered that the antibody-dependent cell-mediated cytotoxicity ("ADCC")—which is the killing of an antibody-coated target cell by a class of cells called "effector cells" through a process that involves releasing a substance toxic to the target cells or by expression of cell death inducing molecules—could be significantly improved by preventing the addition of the sugar residue fucose to an antibody's complex type N-linked oligosaccharide chains. Fucose is added to the sugar chain by the enzyme α1,6-fucosyltransferase very late in the N-linked oligosaccharide processing. High-mannose type oligosaccharides, for example, do not contain fucose. To take advantage of this discovery, the inventors designed a mammalian host cell line for producing antibodies where the FUT8 gene—the gene encoding α1,6-fucosyltransferase—was knocked out such that the process of adding fucose was disrupted. The inventors were the first to develop this novel solution. In fact, none of the references cited by Petitioners disclose the FUT8 gene or any method of knocking

out the FUT8 gene to create the claimed fucosyltransferase knock-out host cell.

At the time of the invention, scientists had been focusing on antibody sugar chains to determine a causal relationship with the antibody's effector functions, including ADCC. (Ex. 1001, 2:9-37.) However, these prior studies did not focus on the enzyme α1,6-fucosyltransferase, much less on knocking out the FUT8 gene. Petitioners' two primary references, Rothman and Harris, illustrate this point. While Patent Owner disagrees with Petitioners' argument that Rothman and Harris identify a relationship between a fucose residue and ADCC,[5] it is undisputed that neither Rothman nor Harris discusses making antibodies with complex sugar chains that lack fucose by knocking out α1,6-fucosyltransferase. Nor do they discuss α1,6-fucosyltransferase or the FUT8 gene whatsoever—let alone address any method of knocking out that gene.

To the extent the discussion in Rothman or Harris is considered relevant to the claims—and the Patent Owner contends they are not given the missing elements—Harris contradicts Petitioners' allegation that Rothman teaches

[5] Rothman's speculation regarding fucose as a likely candidate, which is relied upon by Petitioners, is unsupported by the data presented in the paper itself and was subsequently criticized and/or ignored by those of ordinary skill in the art, including Petitioners' expert Dr. Jefferis. (Ex. 2002; Ex. 2003.) Harris, the alternative primary reference relied upon by the Petitioners does not even mention ADCC.

removing fucose from the specific region of a sugar chain. Harris states that fucose could ***influence Fc receptor binding*** and never suggests removing fucose to increase Fc receptor binding. (Ex. 1003, 1592.) Further, Rothman and Harris were not understood by a POSA to suggest defucosylated antibodies (as Petitioners attempt to argue) as evidenced by research and review articles, including those authored by Petitioners' declarant Dr. Jefferis. Indeed, in a 2005 review article describing the research history of antibody glycosylation, Dr. Jefferis attributes the Patent Owner and other references published ***after the priority date*** of the '292 Patent for reporting the correlation between enhanced ADCC and absence of the specific fucose residue added by α1,6-fucosyltransferase. (Ex. 2003.) In the article, Dr. Jefferis never mentions Rothman or Harris as discovering such a correlation. (*See id.*) This is also consistent with other research and review articles. (*See*, *e.g.*, Ex. 2004; Ex. 2005; Ex. 2006.) Simply put, no one interpreted Rothman and Harris as Petitioners do now.

B. The Asserted Prior Art

1. Rothman

Rothman (Ex. 1002), titled "Antibody-Dependent Cytotoxicity Mediated by Natural Killer Cells Is Enhanced by Castanospermine-Induced Alterations of IgG Glycosylation" and published in 1989, is the primary reference for Grounds 1, 3, and 5. The Petition alleges that Rothman teaches targeting the α1,6-

fucosyltransferase (FUT8) gene for "knock-out." (*See* Pet., 19.)

But Rothman does not mention an α1,6-fucosyltransferase knock-out host cell, the FUT8 gene, or knocking out the FUT8 gene to create a mammalian 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* Ex. 1002.) Instead, Rothman describes the production of antibodies by culturing cells in the presence of six inhibitors that each inhibit enzymes in the early steps of N-linked oligosaccharide processing, such as α-glucosidases I and II, α-mannosidase I, and α-mannosidase II. (*See id.*, 1114.) Because the focus of Rothman's study was the early steps of N-linked oligosaccharide processing, none of the inhibitors addressed in the study inhibits α1,6-fucosyltransferase (an enzyme relevant to a subsequent step of N-linked oligosaccharide processing), nor do they have anything to do with α1,6-fucosyltransferase or its activity. (*See id.*)

Even more significantly, the claims of the '292 Patent require that the antibodies produced by the claimed mammalian cell have ***complex type*** sugar chains. Yet, none of these inhibitors results in the production of fucose-free antibodies having ***complex type*** N-linked oligosaccharides. Rather, antibodies produced in the presence of these inhibitors have: (a) no N-linked oligosaccharides

(*see* Ex. 1002, 1121, right col.); or (b) high-mannose type N-linked oligosaccharides (*see* Ex. 2001; Ex. 2005; Ex. 2007); or (c) hybrid type N-linked oligosaccharides (*see* Ex. 2008). Indeed, Rothman explains that the high-mannose structures "are ***not*** substrates for the core fucosyl transferase." (Ex. 1002, 1122 (citations omitted, emphasis added).) Ultimately, Rothman presented data that high-mannose type antibodies have enhanced ADCC whereas antibodies without N-linked oligosaccharides or with hybrid oligosaccharides had the same level of ADCC as natively produced antibodies (which are predominantly antibodies having complex type structures). (*See id*.) Rothman speculated that the natural absence of core fucosylation in high-mannose type antibodies may have been related to enhanced ADCC. (*See id.*) Contrary to Petitioners' suggestion, however, Rothman did not address or contemplate knocking out the FUT8 gene to create the claimed "fucosyltransferase knock-out host cell" that can produce an antibody 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," *i.e*., an *α-1,6*-fucosyltransferase knock-out host cell.

2. Harris

Harris (Ex. 1003) is relied on for Grounds 2, 4, and 6 as an alternative primary reference to Rothman. Harris was published in 1997, and is titled "Refined Structure of An Intact IgG2a Monoclonal Antibody."

Harris describes visualization by X-ray analysis of a murine Fc segment. (Ex. 1003, 1581.) The CH2 domains of the Fc region are described to show substantial rigid body conformational changes with respect to the human Fc, while the oligosaccharides were found to be similar to those of the free human Fc fragment although differences are present in the terminal residues. (*Id.*) Notably, Harris does not contain any discussion of α1,6-fucosyltransferase or the FUT8 gene, let alone knocking out the FUT8 gene to create the claimed "fucosyltransferase knock-out host cell" that can produce an antibody 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."

In the seventeen-page article of Harris, "fucose" is mentioned in only two places. The first instance is in the "Materials and Methods" section and simply informs the reader that carbohydrate analysis confirmed the presence of fucose in the antibody being analyzed. (*Id.*, 1582, left col.)

The second instance states that "[t]he fucose residue may be of particular interest. In both this [murine] antibody and the human Fc it ***interacts*** with Tyr313, 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, right col. (emphases added).) 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.

Furthermore, Harris devotes an entire section to "Effector Functions," which emphasizes the importance of the ***presence*** and ***integrity*** of carbohydrates on antibody functions, stating that "***[d]egradation or modification*** of the carbohydrate has, however, been clearly shown to ***eliminate or reduce effector functions*** such as complement activation, binding to Fc receptors, induction of antigen-dependent cellular cytotoxicity, and feedback immunosuppression." (*Id.*, 1593-94 (emphases added).) Thus, Harris suggests the importance of retaining, not removing, carbohydrate residues.

3. Umaña

Umaña (Ex. 1004), a secondary reference for all six of Petitioners' obviousness grounds, is an international application published in 1999 as WO 99/54342 and titled "Glycosylation Engineering of Antibodies for Improving Antibody-Dependent Cellular Cytotoxicity." Umaña was before the Examiner during examination of the application leading to the '292 Patent. (*See* Ex. 1036, IDS filed Aug. 12, 2004.)

"[T]he invention [in Umaña] is directed to host cells that have been engineered such that they are capable of expressing a preferred range of a glycoprotein-modifying glycosyl transferase activity which increases complex N-

linked oligosaccharide carrying bisecting GlcNAc." (Ex. 1004, 2.) "The invention is based, in part, on the inventors' discovery that there is an optimal range of glycoprotein-modifying glycosyl transferase expression for the maximization of complex N-linked oligosaccharide carrying bisecting GlcNAc." (Ex. 1004, 3.) Umaña focuses on the effect of a bisecting GlcNAc on ADCC. Umaña, however, does not contain any discussion of the FUT8 gene, let alone knocking out the FUT8 gene to create the claimed "fucosyltransferase knock-out host cell" that can produce an antibody 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," *i.e.*, an *α1,6*-fucosyltransferase knock-out host cell.

4. Malý

Malý (Ex. 1005), another secondary reference relied on by Petitioners for Grounds 3 and 4, was published in 1996 and titled "The α(1,3) Fucosyltransferase Fuc-TVII Controls Leukocyte Trafficking through an Essential Role in L-, E-, and P-selectin Ligand Biosynthesis." Malý was before the Examiner during examination of the application leading to the '292 Patent. (*See* Ex. 1036, IDS filed Aug. 12, 2004.)

Malý studies α1,3 fucosyltransferase. According to Malý, α1,3 fucosyltransferase catalyzes the formation of α1,3 linked fucose residue on oligosaccharides, and its function is required for leukocyte trafficking through E-

and P-selectin ligands. (*See* Ex. 1005, 643, 645.) However, α1,3 fucosyltransferase is a completely different enzyme from α-1,6 fucosyltransferase, is unrelated to the synthesis of an antibody's sugar chains, and has nothing to do with adding fucose to the 6 position of N-acetylglucosamine in the reducing end of the complex sugar chain on an antibody. (*See id.*) Malý does not discuss α1,6 fucosyltransferase or the FUT8 gene, let alone knocking out the FUT8 gene to create the claimed "fucosyltransferase knock-out host cell" that can produce an antibody 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," *i.e.*, an *α1,6*-fucosyltransferase knock-out host cell.

5. Gao

Gao (Ex. 1006), a third secondary reference relied on by Petitioners for Grounds 5 and 6, was published in 1992 and titled "Characterization of YB2/0 Cell Line by Counterflow Centrifugation Elutriation."

Gao describes the characterization of the YB2/0 cell line by counterflow centrifugation elutriation. (*See* Pet., 23.) More specifically, Gao describes using counterflow centrifugation elutriation to separate different cell fractions according to cell cycle stages. Gao does not discuss antibody glycosylation, much less any enzymes or genes involved therein.

C. The ’292 Patent

ADCC, a type of lytic attack on antibody-targeted cells, is considered one of the major immunologic mechanisms in tumor cell eradication. ADCC is induced by binding of an antibody’s Fc region to lymphocyte receptors (Fc receptors). (*See* Ex. 1001, 1:64-67.)

N-linked oligosaccharides fall into three types (high-mannose type, hybrid type, and complex type). (Ex. 1001, 2:59-3:2.) The vast majority of antibodies produced in mammalian cells have complex type sugar chains that are attached to the Fc region and the majority of the complex type sugar chains carry a fucose residue. (*See* Ex. 2005, 572.) The inventors of the ’292 Patent discovered that an antibody’s ADCC can be greatly enhanced by preventing the addition of fucose in complex type N-linked oligosaccharides. (*See*, *e.g.*, Ex. 1001, Examples 7, 8, 13.) The inventors then set out to genetically engineer mammalian host cells that produce more effective antibodies by knocking out the α1,6-fucosyltransferase encoding gene (FUT8). (*See* Ex. 1001, cols. 5-13.) The end result would be the production of antibodies 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*, *e.g.*, col. 8.) At the time of the invention, no one had knocked out the FUT8 gene to engineer a “fucosyltransferase knock-out host cell” that can produce an antibody 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," *i.e.*, an *α1,6*-fucosyltransferase knock-out host cell.

D. The Claims of the '292 Patent

The '292 Patent describes, among other things, genetically-altered mammalian host cells that lack a functional FUT8 gene encoding α1,6-fucosyltransferase, the enzyme responsible for the transfer of fucose to the 6 position of N-acetylglucosamine in the reducing end of complex type sugar chains attached to antibodies. The '292 Patent has twelve claims and two independent claims (claims 1 and 7) read as follows:

> 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.

> 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, 183:26-39, 184:25-37.)

Claims 2-6 depend from claim 1. Dependent claims 2-5 specify that the fucosyltransferase host cell is a CHO cell, an NS0 cell, an SP2/0 cell and a YB2/0 cell, respectively, while dependent claim 6 specifies that the antibody molecule is an IgG antibody.

Claims 8-12 depend from claim 7. Dependent claims 8-11 specify that the fucosyltransferase host cell is a CHO cell, an NS0 cell, an SP2/0 cell and a YB2/0 cell, respectively, while dependent claim 12 specifies that the antibody molecule is an IgG antibody.

E. Level of Ordinary Skill in the Art

Petitioners state "a POSA would have had knowledge of the scientific literature no later than October 6, 2000 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., 15, 16.) However, there was no such knowledge in the scientific literature at the time. For the limited purpose of this Preliminary Response, Patent Owner deems it unnecessary to contest at this time Petitioners' allegations regarding what a POSA knew regarding the means or methods for creating cells in which a gene is knocked out.

However, Patent Owner opposes Petitioners' improper 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," since this is contrary to the evidence. Moreover, Patent Owner objects to Petitioners' attempt to use their definition to make up for the missing elements and the missing motivation to combine in the prior art references they cite. *See Al-Site Corp. v. VSI Int'l, Inc*., 174 F.3d 1308, 1324 (Fed. Cir. 1999) (rejecting argument that the level of skill in the art would supply the missing suggestion to combine references to arrive at the claimed invention).

In *Al-Site*, the Federal Circuit explained that "the level of skill in the art is a prism or lens through which a judge or jury views the prior art and the claimed invention." *Id*. Thus, "[s]kill in the art does not act as a bridge over gaps in

substantive presentation of an obviousness case, but instead supplies the primary guarantee of objectivity in the process." *Id*. (citing *Ryko Mfg. v. Nu-Star, Inc*., 950 F.2d 714, 718 (Fed. Cir. 1991)). Here, Petitioners' attempt to "bridge over gaps" in their obviousness case by reading missing limitations into the level of skill in the art should be rejected. This is especially important where, as here, the missing limitations play a major role in the claimed subject matter. *See Arendi S.A.R.L. v. Apple Inc*., 832 F.3d 1355, 1361-63 (Fed. Cir. 2016) (holding that where common knowledge is used to supply a missing limitation, a thorough inquiry is required "particularly . . . where the missing limitation goes to the heart of an invention"); *Robert Bosch Tool Corp. v. SD3, LLC*, No. IPR2016-01753, Paper 15, at 26-27 (P.T.A.B. Mar. 22, 2017) (rejecting Petitioner's argument that a POSA's common knowledge would supply a missing limitation where "the [] limitations are important structural limitations that are not evidently and indisputably within the common knowledge of those skilled in the art").

The gaps in Petitioners' obviousness arguments are so wide that, in order to bridge them with the purported common knowledge of those skilled in the art, Petitioners had to elevate the purported level of ordinary skill in the art to the point that Petitioners' own declarants fail to meet it. Petitioners state that "[t]he POSA

would have a doctorate in molecular immunology or biochemistry of glycoproteins including antibodies." (Pet., 16.) But Dr. Van Ness[6] testified that, not only does he not have a Ph.D. in molecular immunology, he also does not know if a Ph.D. in the biochemistry of glycoproteins even exists. (Ex. 1038 (Van Ness Depo.), 47:23-48:3.[7]) Likewise, Dr. Royston Jefferis has a Ph.D. in chemistry, but not in molecular immunology or biochemistry of glycoproteins. To support their obviousness position, Petitioners elevate ***ordinary*** skill in the art to a level of ***super*** skill in the art. That Petitioners' own proffered experts cannot qualify as a POSA, as posited by Petitioners, only underscores Petitioners' improper attempt to use their definition of POSA to read in limitations missing from their asserted prior art references.

F. Claim Construction

Patent Owner believes that Petitioners' attempt to construe the term "knock-out" is unnecessary at this stage. No construction is needed to evaluate whether

[6] Dr. Van Ness, one of Petitioners' declarants in the Petition, is also Petitioners' claim construction expert in the co-pending district court litigation. Dr. Van Ness was recently deposed in the co-pending district court action (Case No. 3-16-cv-05993-JD).

[7] Q. Do you have a Ph.D. in molecular immunology?
A. I do not.
Q. Do you have a Ph.D. in the biochemistry of glycoproteins?
A. I do not. I don't know if such a Ph.D. exists.

the Petition has shown a reasonable likelihood that any challenged claim is unpatentable. Nonetheless, to the extent that Petitioners' proposed construction requires "gene deletion" as the only means to knock-out the FUT8 gene, Patent Owner disagrees with the proposed construction and reserves the right to challenge Petitioners' construction. For the limited purposed of this response, even under Petitioners' proposed construction, the Petition still fails for the reasons detailed in this Preliminary Response.

III. The Petition Fails to Establish a Reasonable Likelihood of Prevailing in Challenging Any of the Claims Over the Asserted Grounds

A. To Prevail in Their Obviousness Allegations, Petitioners Must Show that Each Element of the Claimed Invention Was Known in the Prior Art and There Was Motivation to Combine Them

A *prima facie* case of obviousness requires that each element of the claimed invention was known in the prior art. *ArcelorMittal France v. AK Steel Corp.*, 700 F.3d 1314, 1323 (Fed. Cir. 2012). In particular, a petition for *inter partes* review of a patent on obviousness grounds "must specify where each element of the claim is found in the prior art patents or printed publications relied upon." 37 C.F.R. § 42.104(b)(4). Furthermore, "mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole." *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("A patent composed of several elements is

not proved obvious merely by demonstrating that each element was, independently, known in the prior art."). "Rather, to establish a *prima facie* case of obviousness based on a combination of elements disclosed in the prior art," Petitioners must "explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious." *In re Kahn,* 441 F.3d at 986.

Generally speaking, the Board "can rely on common sense to inform its obviousness analysis 'if explained with sufficient reasoning.'" *Paice LLC v. Ford Motor Co.*, Nos. 2016-1412/-1415/-1745, 2017 WL 900062, at *5 (Fed. Cir. Mar. 7, 2017) (quoting *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1361 (Fed. Cir. 2016)). In cases in which common sense is used to supply a missing limitation, however, as distinct from a motivation to combine, "our search for a reasoned basis for resort to common sense must be searching. And, this is particularly true where the missing limitation goes to the heart of an invention." *Arendi*, 832 F.3d at 1363, 1367 (reversing the Board's obviousness finding because its presumption that common knowledge would supply a missing limitation "was conclusory and unsupported by substantial evidence"); *see also In re NuVasive, Inc.*, 842 F.3d 1376, 1381-82 (Fed. Cir. 2016) (reviewing obviousness finding for substantial evidence and noting "'the factual inquiry . . . must be thorough and searching,' and

'the need for specificity pervades our authority'") (quoting *In re Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002)).

B. Fundamental Inadequacies in the Petition's Obviousness Analysis Warrant Dismissal of the Petition Without Institution of an IPR

Even without reviewing the merits of Grounds 1-6, the Petition suffers from fundamental inadequacies that make it impossible to establish a reasonable likelihood that Petitioners will prevail in challenging any of the claims.

First, central elements of the challenged claims are missing entirely from the asserted prior art references.

Second, as a result of this, the Petition resorts exclusively to an unsupported, overly elevated level of ordinary skill in the art, to make up for the missing claim elements. The Petition and its expert declarations provide only conclusory assertions with no guidance for the Board on the key missing elements.

Third, the Petition fails to provide a reasoned explanation of how a POSA would have combined any of the elements purportedly disclosed or known in the prior art to come up with the claimed inventions. Nowhere does the Petition acknowledge any challenges that such modifications would have presented, 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 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. Indeed, Petitioners make no effort to explain how or where the asserted references differ from the challenged claims, a prerequisite to any articulated reasoning for combining the asserted references. The Board has repeatedly denied petitions like this where "[t]he inadequacy of the obviousness analysis in the Petition and accompanying Declarations is readily apparent when the disparate elements of the references are scrutinized closely, as in Patent Owner's response, and we decline to search through the record and piece together those teachings that might support Petitioner's position." *Ariosa Diagnostics v. Verinata Health, Inc.*, No. IPR2013-00276, Paper 64 (P.T.A.B. Aug. 15, 2016); *Ariosa Diagnostics v. Verinata Health, Inc*., No. IPR2013-00277, Paper 62 (P.T.A.B. Aug. 15, 2016).

To support each obviousness ground, the Petition includes nothing more than a single short paragraph of hindsight-driven word play consisting of conclusory sentences offering no reasoning beyond buzzwords like "motivation" and "reasonable expectation of success." The Petition's "analysis" for Ground 1, for example, begins with an assertion that "all limitations of claims 1 and 7 are taught by Rothman and Umaña" and, in the very next sentence, concludes that

"[g]iven Rothman's teaching regarding the link between removal of fucose and improved ADCC, a POSA as of the alleged Priority Date of the '292 Patent would have found it obvious—with at least a reasonable expectation of success—to apply routine 'knock-out' techniques to create the 'isolated fucosyltransferase knock-out host cell' of claims 1 and 7." (*See* Pet., 19.) Rather than articulating any reasoned analysis for this conclusion, the Petition moves immediately to another conclusion that a "POSA would have been motivated to create the claimed host cell given the myriad of research uses for such cells, as well as the potential therapeutic benefits (*e.g.*, a more effective immune response to antigens)." (*Id.*) The "analysis" for Ground 1 then concludes without providing any reasoning to support that claim.

Likewise, the Petition's accompanying Declarations merely repeat the same superficial assertions and quotes in each of the asserted grounds, and provide unsupported conclusions without any analysis or detailed articulation. The lack of any detailed analysis of the various references is evident from the fact that entire sections of the expert "analysis" from both Dr. Van Ness and Dr. Jefferis are repeated verbatim for different grounds, replacing only the names of the asserted references and corresponding single sentence quotes. (*Compare*, *e.g.*, Ex. 1007, ¶¶ 58-82 *with* Ex. 1026, ¶¶ 53-75.) Without articulating any explanation of how any particular reference contributes to the alleged obviousness of claims 1-12, the declarations offer only general conclusions, which results in the same conclusory

assertions being repeated verbatim throughout the different grounds. The Board should reject Petitioners' wishful attempt to leave the task of finding the missing elements and combining them to the Board.[8] The Petition should have connected the dots—but it did not, because it could not.

C. The Petition Fails to Point Out—Because It Cannot—Where Key Elements Can Be Found in the Asserted Prior Art for Grounds 1-6

Petitioners must identify where every limitation of the claims is located in the prior art. 37 C.F.R. § 42.104(b)(4) (requiring that "petition must specify where each element of the claim is found in the prior art patents or printed publications relied upon"); *see also CB Distribs., Inc. v. Fontem Holdings 1 B.V.*, No. IPR2013-00387, Paper 43 at 30-31 (P.T.A.B. Dec. 24, 2014) (finding that a claim is not obvious in view of the asserted prior art because the petitioner did not "contend or point us to where Hon '494 discloses or suggests a restriction component 'detachably set on one end' of the porous component"). Petitioners have not done so, and indeed, cannot do so.

Claim 1 is directed to "[a]n isolated [mammalian] fucosyltransferase knock-out host cell wherein when a gene encoding an antibody molecule is introduced in

[8] Of course, the elements are not in the references.

to said host cell, said host cell produces . . . antibody molecule . . . [having] complex N-glycosidase-linked sugar chains . . . said sugar chain do not contain fucose bound to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains."

As discussed above, α1,6-fucosyltransferase is the fucosyltransferase that adds fucose to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains attached to antibodies. (*See*, *e.g.*, Ex. 1001, 3:65-67.) Therefore, the "fucosyltransferase knock-out host cell" recited in the claims is an α1,6-fucosyltransferase knock-out host cell, as acknowledged by Petitioners and their declarants. (*See*, *e.g.*, Pet., 19; Ex. 1007, ¶ 45; Ex. 1026, ¶ 45.) Accordingly, a central requirement of the claimed fucosyltransferase knock-out host cell is that the FUT8 gene, which encodes α1,6-fucosyltransferase is knocked out so that the host cell can produce antibodies having no fucose in the complex type sugar chains attached to the antibodies.

Stated differently, the ***gene encoding α1,6-fucosyltransferase***, which is knocked out in the claimed fucosyltransferase knock-out host cell, is a central element of claims 1-12 of the '292 Patent. Indeed, Petitioners' expert Dr. Van Ness confirmed at deposition that "the fucosyltransferase [*i.e.*, alpha-1,6-fucosyltransferase] knockout language is one of the important pieces in [claim 1 of

the ’292 Patent]. (Ex. 1038, 59:9-17.) Dr. Van Ness admitted that “it’s an important component of the claim” (*Id*.)

Notably, as detailed below, none of the cited support from the prior art references ***for any of Grounds 1-6*** even contains the term “α1,6-fucosyltransferase,” the fucosyltransferase that adds fucose to the 6 position of N-acetylglucosamine in the reducing end of the complex sugar chains attached to an antibody or contains any mention of a fucosyltransferase knock-out host cell that can produce an antibody 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,” *i.e*., an *α1,6*-fucosyltransferase knock-out host cell. Each of these omissions alone is fatal to the Petition.

The table below summarizes the references relied on by Petitioners for each of the six grounds in the Petition. Rothman and Harris are relied on as two alternative primary references. Umaña, Malý, and Gao are cited as secondary references. In all of these grounds, common knowledge was used to attempt to supply the missing claim elements. This does not meet Petitioners’ burden under 37 C.F.R. § 42.104(b)(4) and justifies denial of the Petition.

Ground	Rothman (1002)	Harris (1003)	Umaña (1004)	Malý (1005)	Gao (1006)	Common Knowledge
1	X		X			X
2		X	X			X
3	X		X	X		X
4		X	X	X		X
5	X		X		X	X
6		X	X		X	X

1. Ground 1: Rothman and Umaña do not teach all limitations of the claims

Petitioners' assertion that "all limitations of claims 1 and 7 are taught by Rothman and Umaña" is untenable. (*See* Pet., 19.) The following central claim elements are missing: "a fucosyltransferase knock-out host cell" that can produce an antibody 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." Neither Rothman nor Umaña discloses a gene encoding α1,6-fucosyltransferase, much less to knocking out a gene encoding α1,6-fucosyltransferase 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."

Petitioners rely on the following five excerpts from Rothman and Umaña for these claim elements:

> "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***." (Ex. 1004 [Umaña] at 3:9-11 (emphasis added).)
>
> "Also ***the use of gene knockout technologies or the use of ribozyme methods may be used to tailor the host cell's glycosyl transferase and/or glycosidase expression levels***, and is therefore within the scope of the invention." (Ex. 1004 [Umaña] at 15:20-22 (emphasis added).)
>
> "In one specific embodiment, the invention is directed to host cells that have been engineered such that they are capable of expressing a preferred range of a glycoprotein-modifying glycosyl transferase activity which increases complex N-linked oligosaccharides carrying bisecting GlcNAc (N-acetylglucosamine)." (Ex. 1004 [Umaña] at 2:28-31.)
>
> "Our data suggests a possible involvement of core fucosylation of IgG in NK cell-mediated ADCC." (Ex. 1002 [Rothman] at 1114.)
>
> "Thus, ***absence of core fucosylation*** itself would appear to be a likely candidate as a structural feature necessary for enhancement of NK cell-mediated ADCC." (Ex. 1002 [Rothman] at 1122 (emphasis added).)

(*See* Pet., 20-22 (emphases in original).)

The first quotation above from Umaña (Ex. 1004) is cited for a passing reference to the "host cells" which have a nucleic acid encoding the protein of interest. The second quotation above from Umaña is cited for a passing reference

to the "use of gene knockout technologies," which is the only mention of the term "knockout" in the entire publication. (*Id.*) Umaña is further relied upon for providing engineered host cells that has increased complex N-linked oligosaccharides carrying bisecting GlcNAc. (*Id.*) However, none of these excerpts from Umaña mentions the term "fucosyltransferase," much less α1,6-fucosyltransferase, the specific fucosyltransferase required in claims 1 and 7 that catalyzes the addition of fucose to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains. It is not the case that the Petition neglected to cite an excerpt of Umaña more helpful to Petitioners' position. Rather, Umaña simply does not contain any mention of a gene encoding α1,6-fucosyltransferase, much less to knocking out a gene encoding α1,6-fucosyltransferase 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." In fact, Petitioners' expert Dr. Van Ness agreed that Umaña does not disclose α1,6-fucosyltransferase. (Ex. 1038, 95-96.) Dr. Van Ness offered the following testimony:

> Q: Sure. Does the Umana reference, Exhibit 11, discuss alpha-1,6-fucosyltransferase?

A: Okay. I see no evidence of alpha-1,6-fucosyltransferase in this document.

Q: And do you see any discussion of the FUT8 gene?

A: I do not.

Q: Do you see any discussion of knocking out the FUT8 gene?

A: I do not.

Q: With respect to the Umana reference, does it describe knocking out the FUT8 gene?

A: Doesn't -- it does not.

Q: Does it describe deleting the FUT8 gene?

A: It does not.

Q: Does it describe mutating the FUT8 gene?

A: It does not.

(Ex. 1038, 95:18-96:21 (objections omitted, discussing Ex. 1004 [Umaña]).)

Rothman, the other reference cited for Ground 1, also does not disclose the fucosyltransferase that catalyzes the addition of fucose to the 6 position of N-acetylglucosamine in the reducing end of the sugar chains, *i.e.*, α1,6-fucosyltransferase.

Rothman is cited for its speculation regarding a possible relationship between absence of core fucosylation and enhancement of NK cell-mediated

ADCC. Rothman does not mention ***any*** gene, let alone knocking out the gene encoding α1,6-fucosyltransferase. Petitioners' declarant Dr. Van Ness agrees:

> Q. Does the Rothman reference, Exhibit 9, discuss alpha-1,6-fucosyltransferase?
>
> A. In my review of the paper right now, which was a scan review, recalling the paper, I don't see any indication of the word alpha-1,6-fucosyltransferase.
>
> Q. If reviewing Exhibit 9, is there any discussion of the FUT8 gene?
>
> A. I don't recall any discussion of the FUT8 gene in this reference.
>
> Q. Is there any discussion in this reference about knocking out the FUT8 gene?
>
> A. There is not.
>
> Q. Is there any discussion about adding a mutation in the FUT8 gene?
>
> A. There is not.
>
> Q. Is there any discussion of deleting the FUT8 gene?
>
> A. There is not.

(Ex. 1038, 89:1-90:10 (objections omitted, discussing Ex. 1002 [Rothman]).)

Accordingly, Petitioners' assertion that "all limitations of claims 1 and 7 are taught by Rothman and Umaña" has no basis in fact. The Petition fails to articulate where the central claim elements of a "fucosyltransferase knock-out host cell," that can produce an antibody 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 chain" are found.

The only remaining purported support for these central claim elements is common knowledge of a POSA allegedly provided in the declarations of Dr. Van Ness and Dr. Jefferis (Ex. 1026, ¶¶ 53-75; Ex. 1007, ¶¶ 58-82.) However, these are merely conclusory assertions regarding what a POSA allegedly knew as discussed in Section III.D below. Petitioners' reliance on common knowledge to supply central elements of claims 1 and 7 is not legally sufficient to support institution. 37 C.F.R. § 42.104(b)(4); *Arendi*, 832 F.3d at 1361-63. Petitioner has not shown a reasonable likelihood that claims 1 and 7 are obvious based on Ground 1 and since claims 2-6 and 8-12 depend from claims 1 and 7, respectively, Petitioner has also failed on those claims.

2. Ground 2: Harris and Umaña do not teach all limitations of the claims

Petitioners' claim that "all limitations of claims 1 and 7 are taught by Harris and Umaña" also lacks merit. (Pet., 26.) Petitioners rely on the following four excerpts from Umaña and Harris for the central elements central claim elements of a "fucosyltransferase knock-out host cell," that can produce an antibody 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":

> "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***." (Ex. 1004 [Umaña] at 3:9-11 (emphasis added).)
>
> "Also ***the use of gene knockout technologies or the use of ribozyme methods may be used to tailor the host cell's glycosyl transferase and/or glycosidase expression levels***, and is therefore within the scope of the invention." (Ex. 1004 [Umaña] at 15:20-22 (emphasis added).)
>
> "In one specific embodiment, the invention is directed to host cells that have been engineered such that they are capable of expressing a preferred range of a glycoprotein-modifying glycosyl transferase activity which increases complex N-linked oligosaccharides carrying bisecting GlcNAc (N-acetylglucosamine)." (Ex. 1004 [Umaña] at 2:28-31.)
>
> "***The fucose residue may be of particular interest***. In both this antibody and the human Fc it interacts with Tyr313, 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***." (Ex. 1003 [Harris] at 1592 (emphases added).)

(*See* Pet., 26-28 (emphases in original).)

The three excerpts from Umaña (Ex. 1004) are the same as the ones used in Ground 1. As explained in the previous section, Umaña does not contain any reference to or disclose a gene encoding α1,6-fucosyltransferase, much less

knocking out a gene encoding α1,6-fucosyltransferase to create the claimed fucosyltransferase knock-out host cell that can produce an antibody 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."

Harris, the other reference cited for Ground 2, also does not disclose these central claim elements. Petitioners, without providing any context, quote Harris as stating that the "fucose residue may be of particular interest" and that "fucose is also near the Fcγ receptor binding site and could influence binding by the receptor." (Ex. 1003, 1592, right col.)

However, when read in context, Harris shows that it discusses fucose in the context of its potential importance to Fcγ receptor binding. In fact, Harris emphasizes the importance of retaining carbohydrates on antibody functions, stating that "***[d]egradation or modification*** of the carbohydrate has, however, been clearly shown to ***eliminate or reduce effector functions*** such as complement activation, binding to Fc receptors, induction of antigen-dependent cellular cytotoxicity, and feedback immunosuppression." (*Id.*, 1593-94 (emphases added).) Contrary to Petitioners' argument, Harris suggests that the ***presence*** of the fucose residue is important for binding to Fc receptors.

Moreover, Harris fails to provide any reference to "α1,6-fucosyltransferase," much less to knocking out a gene encoding α1,6-fucosyltransferase to create the

claimed "fucosyltransferase knock-out host cell" that can produce an antibody 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." Petitioners' declarant Dr. Van Ness also admitted that Harris does not disclose α1,6-fucosyltransferase, the FUT8 gene, or a knock-out of the FUT8 gene:

> Q. Does the Harris reference, Exhibit 10, discuss alpha-1,6-fucosyltransferase?
>
> A. I am pretty confident it does not.
>
> Q. Does the Harris reference discuss the FUT8 gene?
>
> A. It does not.
>
> Q. Does the Harris reference discuss knocking out the FUT8 gene?
>
> A. It does not.
>
> Q. Does the Harris reference discuss deleting the FUT8 gene?
>
> A. It does not.
>
> Q. Does it discuss adding mutation to the FUT8 gene?
>
> A. It does not.

(Ex. 1038, 92:17-93:10 (objections omitted, discussing Ex. 1003 [Harris]).)

Accordingly, Petitioners' claim that "all limitations of claims 1 and 7 are taught by Harris and Umaña" has no basis in fact. (Pet., 26.) Again, the only remaining purported support is common knowledge of a POSA allegedly provided

in the declarations of Dr. Van Ness and Dr. Jefferis (Ex. 1026, ¶¶ 76-98; Ex. 1007, ¶¶ 83-107.) However, these are merely conclusory assertions regarding what a POSA knew, and as discussed in Section III.D below. Petitioners' reliance on common knowledge to supply central elements of claims 1 and 7 is not legally sufficient to support institution. 37 C.F.R. § 42.104(b)(4); *Arendi*, 832 F.3d at 1361-63. Petitioner has not shown a reasonable likelihood that Claims 1 and 7 are obvious based on Ground 2 and since claims 2-6 and 8-12 depend from claims 1 and 7, respectively, Petitioner has also failed on those claims. Having failed to "specify where each element of the claim is found in the prior art patents or printed publications relied upon," Ground 2 of the Petition fails as well. 37 C.F.R. § 42.104(b)(4).

3. Grounds 3 and 4: Malý does not cure the deficiencies of Grounds 1 and 2 by supplying the central elements not found in Rothman/Harris and Umaña

Grounds 3 and 4 are identical to Grounds 1 and 2, respectively, except for the addition of the Malý reference (Ex. 1005). Malý is relied on by Petitioners for demonstrating knocking out a gene in mouse embryos. (*See* Pet., 32.) However, Malý does not disclose α1,6-fucosyltransferase, let alone knocking out an α1,6-fucosyltransferase gene, prerequisites for describing the claimed "fucosyltransferase knock-out host cell" that can produce an antibody 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." Even Petitioners' expert Dr. Van Ness admits that Malý does not disclose α1,6-fucosyltransferase:

> Q. And does the Maly reference discuss alpha-1,6-fucosyltransferase?
>
> THE WITNESS: It does not.
>
> Q. And does the Maly reference discuss the FUT 8 gene?
>
> THE WITNESS: It does not.
>
> Q. Does the Maly reference discuss knocking out the FUT 8 gene?
>
> THE WITNESS: It does not.
>
> Q. Does the Maly reference discuss deleting the FUT 8 gene?
>
> THE WITNESS: It does not.
>
> Q. Does the Maly reference discuss adding mutation to the FUT 8 gene?
>
> THE WITNESS: It does not.

(Ex. 1038, 97:16-98:15 (objections omitted, discussing Ex. 1005).)

In fact, Malý discloses a different enzyme—α1,3-fucosyltransferase, which is unrelated to "adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked sugar chains" or to making sugar chains in antibodies (Ex. 1005, 643.) At his deposition in the co-pending district court litigation, Dr. Van Ness

testified that he was "not aware" that "alpha 1,3 fucosyltransferase [was] involved in adding fucose to the complex sugar chain in antibodies." (Ex. 1038, 98:17-20.)

The only other purported support is common knowledge of a POSA allegedly provided in the declarations of Dr. Jefferis and Dr. Van Ness (Ex. 1026, ¶¶ 99-142; Ex. 1007, ¶¶ 108-157.) However, these are merely conclusory assertions regarding what a POSA allegedly knew, and as discussed in Section III.D below, Petitioner's reliance on common knowledge to supply central elements of claims 1 and 7 is not legally sufficient to support institution. 37 C.F.R. § 42.104(b)(4); *Arendi*, 832 F.3d at 1361-63. Petitioner simply has not shown any likelihood, much less a reasonable likelihood, that Claims 1 and 7 (or dependent claims 2-6 and 8-12) are obvious based on either Ground 3 or 4.

4. Grounds 5 and 6: Gao does not cure the deficiencies of Grounds 1 and 2 by supplying the central elements not found in Rothman/Harris and Umaña

Grounds 5 and 6 are identical to Grounds 1 and 2, respectively, except for the addition of the Gao reference (Ex. 1006.) Petitioners cite Gao in the claim charts as being relevant to the YB2/0 cell recited in dependent claims 5 and 11. (*See* Pet., 46-48.) However, Gao discloses a YB2/0 cell in a completely difference context. Although Petitioners only cite Gao for claims 5 and 11, Gao also does not disclose α1,6-fucosyltransferase, let alone knocking out an α1,6-fucosyltransferase gene, prerequisites for describing the claimed "fucosyltransferase knock-out host

cell" that can produce an antibody 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." Even Petitioners' expert declarant Dr. Van Ness admits that Gao does not disclose α1,6-fucosyltransferase:

> Q. And does the Gao reference discuss alpha-1,6-fucosyltransferase?
>
> THE WITNESS: It does not.
>
> Q. Does the Gao reference discuss the FUT 8 gene?
>
> THE WITNESS: It does not.
>
> Q. Does the Gao reference discuss knocking out the FUT 8 gene?
>
> THE WITNESS: It does not.
>
> Q. Does the Gao reference discuss deleting the FUT 8 gene?
>
> THE WITNESS: It does not.
>
> Q. Does the Gao reference discuss adding mutation to the FUT 8 gene?
>
> THE WITNESS: It does not.

(Ex. 1038, 99:14-100:11.)

As with their other grounds, the only other purported support is common knowledge allegedly provided in the declarations of Dr. Jefferis and Dr. Van Ness (Ex. 1026, ¶¶ 143-154; Ex. 1007, ¶¶ 158-169.) Again, however, these are merely

conclusory assertions regarding what a POSA knew, and without citing references that teach or suggest any of the central elements of claims 1 and 7, on which claims 5 and 11 depend respectively, reliance on common knowledge is not legally sufficient to support institution against claim 5 or claim 11.

D. The Petition Improperly Relies on Common Knowledge to Supply Central Elements of the Claims

Unable to show the cited references disclose the central elements of claims 1 and 7, Petitioners resort to the "common knowledge" of a POSA. The elements missing in the cited prior art references, however, go to the heart of the claimed invention. To illustrate this, the missing elements of claim 1 are shown emphasized below:

> 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 (emphases added).)

The Petition cites a few paragraphs of Dr. Van Ness' declaration to support the proposition that "the common knowledge of a POSA"—*i.e.*, common knowledge—would have supplied the missing claim elements so that "[a] POSA would achieve [the claimed host cell] by 'knocking-out' the gene for the enzyme that adds the fucose to the sugar chain—α1,6-fucosyltransferase." (Pet., 19-20, 25, 31-32, 38-39; *see also* Ex. 1007, ¶¶ 32-34, 39-42, 70-77, 95-102, 119-127, 144-152.) Petitioners' reliance on common knowledge is misplaced as a matter of law and fact.

The Petition fails to provide any reasoned analysis or evidentiary support to show that "the gene for the enzyme that adds the fucose to the sugar chain—α1,6-fucosyltransferase" was evidently and indisputably within the common knowledge of those skilled in the art. *See Robert Bosch,* No. IPR2016-01753, Paper 15, at 26-27 (rejecting Petitioner's argument that a POSA's common knowledge would supply a missing limitation because "the [missing] limitations are important structural limitations that are not evidently and indisputably within the common knowledge of those skilled in the art").

Petitioners' reliance on common knowledge to supply key central elements of claims 1 and 7 is not legally sufficient to support institution. *Arendi*, 832 F.3d at 1362 (common knowledge inappropriate to supply missing claim limitation that

"plays a major role in the subject matter claimed," and should apply only where the missing limitation is "unusually simple and the technology particularly straightforward."). In *Arendi*, the Federal Circuit distinguished *Perfect Web Technologies, Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1329 (Fed. Cir. 2009), in which common knowledge was invoked to supply a limitation missing from the prior art where "the missing claim limitation—step D of steps A–D—was nothing more than an instruction to repeat steps A, B, and C until a particular quantity of email was sent in accordance with the claim." *Id.* In *Arendi*, as here, "[b]y contrast, the missing [limitation] at issue [] plays a major role in the subject matter claimed." *Id.* The Federal Circuit cautioned that *Perfect Web* "ought to be treated as the exception, rather than the rule." *Id.* The importance of the missing elements shows that this Petition is not such an exception to the rule.

Moreover, Dr. Van Ness' claim that the key claim elements existed in the common knowledge lacks any support or analysis. Dr. Van Ness refers to "Section IV" of his Declaration as supporting his assertion that knocking out a gene encoding α1,6-fucosyltransferase was common knowledge. (Ex. 1007, ¶¶ 70-77, 95-102, 119-127, 144-152.) But Section IV contains only two misleading characterizations of the state of the art.

First, Dr. Van Ness alleges that the "human fucosyltransferase gene sequence had been cloned in 1994 by Sasaki *et al*. (269 (20) J. Biol. Chem. 14730-

37 (1994)).” (Ex. 1007, ¶ 40.) But the Sasaki reference actually describes cloning of the gene for ***α1,3-***fucosyltransferase, which as explained above is a different enzyme involved in the biosynthesis of an E-selectin ligand involved in leukocyte trafficking to lymphoid tissues and sites of inflammation. (Ex. 2009.) The ***α1,3-*** fucosyltransferase enzyme is ***not*** related to N-linked oligosaccharide processing and has no involvement with the presence or absence of fucose at the 6 position of N-acetylglucosamine in the reducing end of an antibody’s complex sugar chains as recited in claims 1 and 7. (Ex. 1038, 97:16-98:20.)

Second, Dr. Van Ness alleges that during prosecution of the ’292 Patent the patentee cited articles “that confirm sufficient information of the gene sequence for α1,6-fucosyltransferase had already been published.” (Ex. 1007, ¶ 40.) The patentee, however, cited the articles to show that a POSA would be enabled by the teachings of the cDNA encoding α1,6 fucosyltransferase in the ’292 Patent’s specification to prepare a cell with decreased or deleted α1,6-fucosyltransferase activity. (Ex. 1036, Response filed Aug. 12, 2004 at 33-34.) The patentee explained that the “inventors of the presently claimed invention found cDNA encoding α1,6-fucosyltransferase in CHO cells and the exon 2 genomic region,” which enabled preparation of a cell in which the enzyme for α1,6-fucosyltransferase is decreased or deleted. (Ex. 1036, Response filed Aug. 12, 2004 at 35.) The patentee was clearly referring to its own findings and work.

Even if the Petition demonstrated, which it has not, that the α1,6-fucosyltransferase gene sequence was well-known in the prior art, that would still be insufficient to show that a person of ordinary skill in the art would have both been motivated and able to conceive the ***claimed*** host cell, something achieved by the inventors as taught and described in the '292 Patent's specification. For example, in *Kyocera Corp. v. Adaptix, Inc.*, the Board denied a request for rehearing relating to a denial of institution because common knowledge could not "bridge the gap" where "the use of [radio] pilot symbols was known [but] [t]he ***claimed*** use of pilot symbols is ***not*** acknowledged as well-known prior art." No. IPR2015-00318, Paper 17, at 5-6 (P.T.A.B. Nov. 13, 2015) (emphases added). Here, the Petition does not demonstrate that a POSA would have conceived of obtaining a "fucosyltransferase knock-out host cell" that can produce 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" by knocking out a specific fucosyltransferase—α1,6-fucosyltransferase—without the express teachings in the '292 Patent's specification. Ultimately, Petitioners' resort to "common knowledge" to fill the gaps in their cited references is unavailing.

E. The Petition Discloses No Motivation to Combine

"[T]o establish a *prima facie* case of obviousness based on a combination of elements disclosed in the prior art," Petitioners must "explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious." *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). "The showing of a motivation to combine must be clear and particular, and it must be supported by actual evidence." *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1334 (Fed. Cir. 2002) (citation omitted). "[B]road conclusory statements about the teaching of multiple references, standing alone, are not 'evidence.'" *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000) (citation omitted).

Here, the Petition cites isolated sentences of the allegedly invalidating references without any accompanying analysis or evidence as to why a POSA would have been motivated to make the alleged combinations, let alone with a reasonable expectation of success. Consequently, the Petition leaves the Board with the task of attempting to connect the various dots and determine whether the claims at issue are obvious rather than making a determination of whether Petitioners have satisfied their burden. Of course, there are simply not enough dots for the Board to do such an analysis.

For example, Petitioners offer no "actual evidence" (as the Federal Circuit requires) for their assertion in Grounds 1, 3, and 5, that, in light of Rothman, a POSA would have found it obvious to obtain the claimed host cell by "'knocking-out' the gene for the enzyme that adds the fucose to the sugar chain—α(1,6)-fucosyltransferase." (*See*, *e.g.*, Pet., 19, 32.) Likewise, for Grounds 2, 4, and 6, Petitioners assert in a conclusory manner that, in view of Harris, a POSA would be motivated to obtain the claimed host cell by "'knocking-out' the gene for the enzyme that adds the fucose to the sugar chain—α(1,6)-fucosyltransferase." (*See, e.g.*, *id.*, 25, 39.) Petitioners' accompanying declarations provide no more support either, for they too contain the same conclusory assertions repeated in each of the asserted grounds in the Petition.

Thus, the Petition does not articulate any motivation to combine the prior art references and thereby fails to provide the "clear and particular" showing that is an "essential evidentiary component of an obviousness holding." *See C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998) (reversing judgment of invalidity based on obviousness because "[n]o prior art provided a teaching or suggestion or motivation" that the claimed invention should be made).

To show motivation to combine, Petitioners would have had to provide clear and particular evidence that suggested, taught, or motivated a POSA to combine the prior art to render obvious the required, yet missing, elements of a

"fucosyltransferase knock-out host cell," that can produce 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."

However, none of Petitioners' references even discloses these elements, thus simply claiming there was motivation to combine, without showing any reasoning or support, is insufficient.

F. Rothman and Harris Were Not Read as Petitioners Suggest

A closer look at the isolated sentences Petitioners cherry-picked from Rothman and Harris confirms that they do not support their suggested meaning, much less a legally required motivation to combine with expectation of success.

First, Rothman was not read the way Petitioners now read it by other scientists. Rothman does not provide any motivation to a POSA to genetically engineer a mammalian cell to produce fucose free antibodies by knocking out a specific fucosyltransferase—α1,6-fucosyltransferase. Nor does Rothman's observations lead to the conclusion that lack of fucose results in increased ADCC activity in antibodies that are produced by fucosyltransferase host cells as claimed by the '292 Patent. In fact, neither Petitioners' declarant nor research and review articles read Rothman the way Petitioners now urge. (*See*, *e.g.*, Ex. 2002; Ex. 2003; Ex. 2004; Ex. 2005; Ex. 2006.)

For example, Wright and Morrison, *Trends in Biotechnology 15*(1), 26-32 (1997) (Ex. 2004), which is an unsolicited, peer-reviewed review article, confirms that Rothman does not establish any causal relationship between lack of fucosylation and enhanced ADCC. Wright and Morrison reflect the understanding by a POSA that Rothman's antibodies with high-mannose structures, beyond lacking fucose, differ substantially in their overall structure as well as in their sugar composition. Indeed, their peer-reviewed article demonstrates that Rothman was not read by a POSA to suggest that fucosylation is responsible for increasing ADCC.

> Rothman *et al.*[30] tested the capacity of ADCC of monoclonal murine IgG antibodies that were purified from hybridomas grown in the presence of glycosidase inhibitors that acted at different steps in the oligosaccharide-processing pathway. These inhibitors included Sw (see above) and castanospermine (Cs), which inhibits the removal of glucose residues from the oligosaccharide newly attached to the peptide…Compared with wild-type antibodies, those treated with Cs showed enhanced ADCC mediated NK cells but no by other types of effector cells such as monocytes. By contrast, Sw-treated antibodies failed to induce enhanced NK-cell-mediated ADCC. Through lectin-binding analysis the oligosaccharides on Sw-treated and wild-type IgGs were shown to contain fucose, which was lacking on the Cs-treated antibodies. It was ***suggested*** that recognition by IgG Fc of the type of Fc receptor present on NK cells, leading to enhanced ADCC,

> was glycosylation dependent, requiring the absence of fucose. ***However***, both Sw-treated and wild-type oligosaccharides contain at least one complex "arm", which would produce an overall conformation, as well as several sugar residues, that differs from the oligosaccharides produced by Cs treatment.

(*Id.*, 29. (emphases added).)

Those in the art did not conclude that Rothman provided any motivation to a POSA to remove fucose by knocking out an α1,6-fucosyltransferase gene and to create the claimed fucosyltransferase knock-out host cell.

Further, Harris is actually at odds with what Petitioners argue. The quotes from Harris that fucose is important for Fc receptor binding suggest the presence of fucose is necessary—teaching away from its removal. (Ex. 1003, 1592, right col.) Accordingly, Petitioners' alleged "link between removal of fucose and improved ADCC" could not have been gleaned from the contents of Harris. Petitioners' assertion to the contrary is based on hindsight knowledge of the present invention and is entirely unsupported by Harris. Harris does not provide any motivation to a POSA to prevent or decrease the addition of fucose by knocking out α1,6-fucosyltransferase and by creating the claimed fucosyltransferase knock-out host cells 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."

G. Petitioners' Expert Dr. Jefferis Ignored Rothman and Harris in His Review Articles

In his declaration in support of the Petition, Dr. Jefferis declares that Rothman and Harris each teach the correlation between removing fucose from the sugar chain and improved ADCC, so as to motivate a POSA to make fucose-free antibodies to achieve higher ADCC. (Ex. 1026, 2.) However, the positions Dr. Jefferis advocates here cannot be reconciled with the views he expressed in his own review articles published after Rothman and Harris.

In a review article published in 1997 (Ex. 2002), Dr. Jefferis provides a detailed review of the functions of N-linked oligosaccharides in the section "Functional Consequence of Asn297 Glycosylation." While he remained ***completely silent on Rothman and any relationship between fucose and ADCC***, Dr. Jefferis discussed the relevance of several other glycosylation structures, including bisecting GlcNAc, galactose, and sialic acid, to the ADCC activity of the antibodies. (*See id.*, 117.)

After the '292 Patent's priority date, Dr. Jefferis provided another detailed review on the same topic in 2005. (Ex. 2003.) In this later review article, Dr. Jefferis again ignored Rothman and Harris. With regard to fucosylation, Dr. Jefferis discussed a study published in a 2002 article, which reports that lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human

FcγRIII and ADCC. (*See* Ex. 2006.) Dr. Jefferis further discussed a study by the Patent Owner published in a 2003 article, which reports that the absence of fucose in complex type oligosaccharides, but not the presence of galactose or bisecting N-acetylglucosamine of human IgG1 complex type oligosaccharides shows the critical role of enhancing ADCC. (*See* Ex. 2010, 3466.)

Dr. Jefferis singles out these post-filing publications for providing the "***obvious incentive***" to generate a new production cell line by knock-out of the appropriate fucosyltransferase:

> Further exploration of the influence of rMAb glycoform on effector functions was reported from Genentech. A mutant CHO cell line (LEC 13) was employed that does not add fucose to the primary N-acetylglucosamine residue to produce nonfucosylated glycoforms of Herceptin. They report a 40- to 50-fold increase in the efficacy of FcgRIII-mediated ADCC and some improvement in binding to certain polymorphic forms of FcgRII but no effect on binding to FcgRI or C1q (28 [the 2002 article]); the LEC 13 cell line was reported not to be suitable for development as a production vehicle. ***These findings provide an obvious incentive to generate a new production cell line by knockout of the appropriate fucosyltransferase***. A similar improvement of ADCC was reported for the nonfucosylated fraction of a recombinant anti-human IL-5 receptor (rhIL-5-R) antibody (29 [Patent Owner's 2003 article]) produced in the rat-derived YB2/0 cell line.

(Ex. 2003, 14, left col. (emphasis added).)

Dr. Jefferis' review publications in the same area as the claimed inventions do not credit Rothman or Harris with having found the correlation between defucosylation and enhanced ADCC, much less with making cell line. Instead, Dr. Jefferis attributed the provision of the incentive to make a cell line by knock-out of the appropriate fucosyltransferase to generate fucose free antibodies to much later studies, including Patent Owner's study.

IV. Conclusion

Petitioners fail to show that that any challenged claim would have been obvious over the asserted references for Grounds 1-6. For these reasons, the Petition fails to establish a reasonable likelihood that any challenged claim is unpatentable. The Board should therefore deny institution of the Petition.

Dated: August 14, 2017

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the above Preliminary Response to Petition complies with the applicable type-volume limitations of 37 C.F.R. § 42.24(b)(1). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Preliminary Response, including footnotes, contains 11,860 words, as counted by the word count function of Microsoft Word. This is less than the limit of 14,000 words as specified by 37 C.F.R. § 42.24(a)(1)(i).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served on the counsel for Petitioners a true and correct copy of the foregoing Patent Owner's Preliminary Response by electronic means on August 14, 2017, at the following email addresses of record:

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