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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 IPR2017-01262
U.S. Patent No. 7,425,446

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)
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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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2011	Excerpts of Transcript of June 23, 2017 Deposition of Dr. Brian Van Ness Deposition in *Kyowa Hakko Kirin Co., Ltd. v. Aragen Bioscience, Inc.*, No. 3:16-cv-05993-JD (N.D. Cal.)
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. 7,425,446 (the "'446 Patent," Ex. 1001).

The Board should decline to institute *inter partes* review. The Petition challenging claims 1-6 of the '446 Patent suffers from fundamental inadequacies. Importantly, the single independent claim requires "decreased or no α1,6-fucosyltransferase activity" as a result of "deleting a gene encoding α1,6-fucosyltransferase or by adding a mutation to said gene . . . ." Yet the Petition fails to identify a single reference in the alleged obviousness combinations that discloses the claimed gene encoding α1,6-fucosyltransferase, or any method of deleting or adding a mutation to the gene encoding α1,6-fucosyltransferase to reduce or eliminate α1,6-fucosyltransferase activity.

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 elements of the α1,6-fucosyltransferase activity/enzyme, the α1,6-fucosyltransferase gene, or any method of deleting or adding a mutation to the α1,6-fucosyltransferase gene. Nor does the Petition include any analysis of why the selected quotes allegedly disclose each of the elements of the claim.

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 '446

Patent over the asserted grounds. Patent Owner respectfully submits that the Board should decline to institute *inter partes* review.

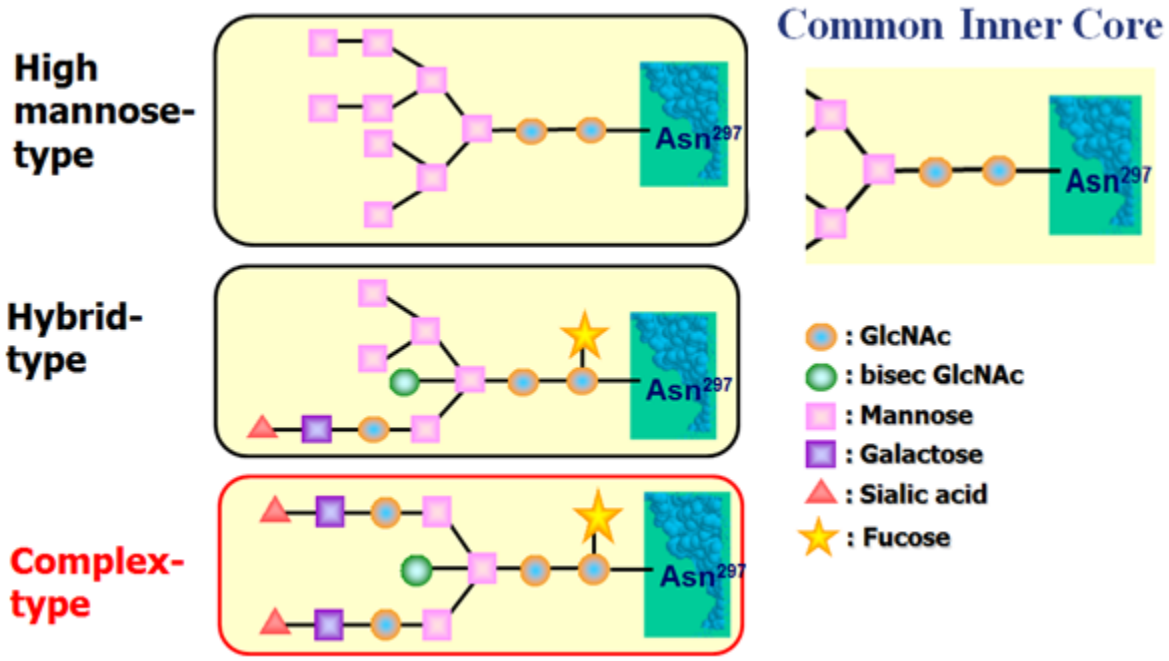
II. Background

A. The State of the Art at the Priority Date of the '446 Patent

At the time of the invention, no one had engineered a mammalian host cell lacking a functional FUT8 gene, the gene that encodes the enzyme α-1,6-fucosyltransferase. α-1,6-fucosyltranferase is 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 sugar chain attached to the amino acid designated Asn297 of an antibody's constant (Fc) region.

The sugar chain attached to antibodies is called "N-linked oligosaccharide." As explained in the specification of the '446 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, 2:39-3:4 (the '446 Patent uses the alternative wording "N-glycoside-linked sugar chain).) 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.)[1] 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:



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, 2:50-58 (formula (I)).) The sugar chain terminus at the right is called the

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

"reducing end" of the sugar chain, and the opposite side is called the "non-reducing end." (*Id.*, 2:59-61.)

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.*, 2:62-63; 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, 2:63–3:1; 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, 3:1-4; 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-fucosyltranferase 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, 3:65-67.) 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 '446 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 deleted or had a mutation added such that the process of adding fucose was disrupted by reducing or eliminating the activity of the enzyme α1,6-fucosyltransferase. The inventors were the first to develop this novel solution. In fact, none of the references cited by Petitioners disclose reducing or eliminating α1,6-fucosyltransferase enzyme activity, the FUT8 gene or any method of deleting or adding a mutation to the FUT8 gene.

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, 2:11-38.) However, these prior studies did not focus on reducing or eliminating the activity of the enzyme α1,6-fucosyltransferase by deleting or adding a mutation to 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,[2] it is undisputed that neither Rothman nor Harris discusses making antibodies with decreased or no amount of fucose by reducing or eliminating the activity of the enzyme α1,6-fucosyltransferase. Nor do they discuss the FUT8 gene whatsoever—let alone address any method of deleting or adding a mutation to 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 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

[2] 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.

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 '446 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., 21.)

But Rothman does not mention the FUT8 gene, targeting the gene or limiting or reducing the activity of α1,6-fucosyltransferase. (*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, none of these inhibitors results in the production of fucose-free antibodies having complex type N-linked oligosaccharides—complex type N-linked oligosaccharides are the overwhelming majority of antibodies produced by mammalian cells. 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 genetically engineering a mammalian cell by deleting or adding a mutation to the FUT8 gene to obtain no or decreased activity of α-1,6 fucosyltransferase.

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.

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 '446 Patent. (*See* Ex. 1037, IDS filed Nov. 28, 2005.)

"[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 deleting or adding a mutation to the FUT8 gene in order to obtain no or decreased activity of α-1,6 fucosyltransferase.

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 '446 Patent. (*See* Ex. 1037, IDS filed Nov. 28, 2005.)

Malý studies α-1,3 fucosyltransferase. According to Malý, α-1,3 fucosyltransferase catalyzes the formation of α-1,3 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, α-1,3 fucosyltransferase is a completely different enzyme from α-1,6 fucosyltransferase, is unrelated to the synthesis of sugar chain of an antibody, and has nothing to do with adding fucose to the 6 position of N-acetylglucosamine in the reducing end of the sugar chain on an antibody. (*See id.*) Malý does not discuss α-1,6 fucosyltransferase or the FUT8 gene.

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., 51.) 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 '446 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, 2:39-3:4.) 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 '446 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 deleting or adding a mutation to the α1,6-fucosyltransferase encoding gene (FUT8) to decrease or eliminate α1,6-

fucosyltransferase activity. (*See* Ex. 1001, cols. 5-13.) The end result would be the production of antibodies that either lack or have a decreased fucose content on the complex type sugar chain structures attached to the Fc region. (*See*, *e.g.*, col. 8.) At the time of the invention, no one had engineered a mammalian host cell lacking a functional FUT8 gene.

D. The Claims of the '446 Patent

The '446 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 a specific position within complex type sugar chains attached to antibodies. The '446 Patent has six claims and its sole independent claim reads as follows:

> 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-fucosyltranferase activity, wherein said mammalian host cell produces an antibody molecule.

(Ex. 1001, 183:30-36.)

Dependent claims 2-5 specify that the mammalian 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.

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., 16:1-5.) 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., 16:5-7.) But Dr. Van Ness[3] 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. 2011 (Van Ness Depo.), 47:23-48:3.[4]) 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.

[3] 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).

[4] 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.

F. Claim Construction

Patent Owner believes that Petitioners' attempt to construe the phrases "which has decreased or no α1,6-fucosyltransferase activity for adding fucose" and "deleting a gene encoding α1,6-fucosyltransferase or by adding a mutation to said gene to reduce or eliminate the α1,6-fucosyltranferase activity" such that "decreased" means "zero" and "reduced" means "remove" is unnecessary at this stage. No construction is needed to evaluate whether the Petition has shown a reasonable likelihood that any challenged claim is unpatentable. Nonetheless, Patent Owner reserves the right to challenge Petitioners' proposed constructions because they are, among other things, illogical, lead to redundant claim language and are unsupported by the specification and prosecution history.

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 a gene encoding α1,6-fucosyltransferase, 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 claim 1 are taught by Rothman and Umaña" and, in the very next sentence, concludes that "given Rothman's teaching regarding the link between removal of fucose and improved ADCC, a POSA as of the alleged Priority Date of the '446 patent would have

found it obvious—with at least a reasonable expectation of success—to apply routine 'knock-out' techniques to create the host cell of claim 1." (*See* Pet., 22.) 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 known correlation between removal of fucose and improved ADCC, the myriad of research uses for such cells, and 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, ¶¶ 60–113 *with* Ex. 1026, ¶¶ 55–94.) Without articulating any explanation of how any particular reference contributes to the alleged obviousness of claims 1-6, 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.[5] 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 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." A

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

central requirement of the claimed mammalian host cell is that it has "decreased or no α1,6-fucosyltransferase activity for adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked sugar chains." Further, the mammalian host cell is prepared "by deleting a gene encoding α1,6-fucosyltransferase or by adding a mutation to said gene to reduce or eliminate the α1,6-fucosyltranferase activity."

Stated differently, 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, is a central element of claims 1-6 of the '446 Patent. Indeed, Petitioners' expert Dr. Van Ness confirmed at deposition that "one of the important pieces in claim 1 [of the '446 Patent] is a gene encoding alpha-1,6-fucosyltransferase." (Ex. 2011, 61:19-24.) Dr. Van Ness admitted that "one of the important pieces of that claim is that gene, correct." (*Id*.)

Notably, as detailed below, none of the cited prior art references ***for any of Grounds 1-6*** even contains the terms " decreased or no α1,6-fucosyltransferase activity," "a gene encoding α1,6-fucosyltransferase," or "deleting . . . or adding a mutation to said gene . . . ." This fact 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 claim 1 are taught by Rothman and Umaña" is untenable. (*See* Pet., 22.) The following claim elements are missing: "decreased or no α1,6-fucosyltransferase activity," "a gene encoding α1,6-fucosyltransferase activity," and "deleting . . . or adding a mutation" to such a gene. Petitioners rely on the following four excerpts from Rothman and Umaña for these claim elements:

> "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).)

> "Examples of glycoprotein-modifying glycosyl transferases include, ***but are not limited to*** glycosyl transferases such as GnT III, GnT V, GalT, and Man II." (Ex. 1004 [Umaña] at 7:15-18 (emphasis added).)[6]
>
> "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., 23-24 (emphasis in original, footnote added).)

The first quotation above from Umaña (Ex. 1004) 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. Umaña is further relied upon for providing a list of four glycosyl transferases that notably ***does not include α1,6-fucosyltransferase*** (*Id.*) (the second quotation above), forcing the Petition to use the open-ended phrase "but are not limited to" to contend that Umaña discloses the central claim element "a gene encoding α1,6-fucosyltransferase." 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

[6] GnT III, GnT V, GalT, and Man II stand for GlcNAc-transferase III, β(1,4)-N-acetylglucosamine-transferase V, β(1,4)-galactosyl-transferase, and mannosidase II. (Ex. 1004, 9:9-12; 13:18-23.)

gene encoding α1,6-fucosyltransferase," much less to a deletion of or addition of a mutation to such a gene to reduce or eliminate α1,6-fucosyltransferase activity. In fact, Petitioners' expert Dr. Van Ness agreed that Umaña does not disclose these central claim elements. (Ex. 2011, 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. 2011, 95:18-96:21 (objections omitted, discussing Ex. 1004 [Umaña]).)

Rothman, the other reference cited for Ground 1, also does not disclose the key claim element "a gene encoding 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 deleting or adding a mutation to the gene encoding α1,6-fucosyltransferase. Nor does Rothman discuss a mammalian host cell having "decreased or no α1,6-fucosyltransferase activity." 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. 2011, 89:1-90:10 (objections omitted, discussing Ex. 1002 [Rothman]).)

Accordingly, Petitioners' assertion that "all limitations of claim 1 are taught by Rothman and Umaña" has no basis in fact. The Petition fails to articulate where the central claim elements "decreased or no α1,6-fucosyltransferase activity" and "deleting a gene encoding α1,6-fucosyltransferase" or "adding a mutation to said gene to reduce or eliminate α1,6-fucosyltransferase activity" are found.

The only remaining purported support Petitioners provide are Paragraphs 74-76 of the declaration of Dr. Van Ness. (Ex. 1007.) 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 claim 1 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 Claim 1 is obvious based on Ground 1 and since claims 2-6 depend from claim 1, Petitioner has also failed on those claims.

2. Ground 2: Petitioners' assertion that Harris teaches targeting α1,6-fucosyltransferase for knock-out is demonstrably false

Petitioners' claim that "Harris teaches the sole alleged point of novelty of the '446 patent—targeting α1,6-fucosyltransferase activity for 'knock-out'" also lacks merit. (Pet., 29.) Petitioners rely on the following three excerpts from

Umaña and Harris for the central elements "decreased or no α1,6-fucosyltransferase activity," "a gene encoding α1,6-fucosyltransferase" and "by deleting . . . or by adding a mutation to said gene to reduce or eliminate α1,6-fucosyltransferase activity":

> "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).)
>
> "Examples of glycoprotein-modifying glycosyl transferases include, ***but are not limited to*** glycosyl transferases such as GnT III, GnT V, GalT, and Man II." (Ex. 1004 [Umaña] at 7:15-18 (emphasis added).)
>
> "***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., 30-31 (emphasis in original).)

The two 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 the central claim elements "decreased or no α1,6-fucosyltransferase activity" or "a gene encoding α1,6-fucosyltransferase," much

less a deletion of or an addition of a mutation to such a gene to reduce or eliminate α1,6-fucosyltransferase activity.

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 (emphasis added).) Contrary to Petitioners' argument, Harris suggests that the ***presence*** of the fucose residue is important for binding to Fc receptors.

Moreover, the Petition fails to provide any reference to "a gene encoding α1,6-fucosyltransferase," much less to a deletion or mutation in such a gene to reduce or eliminate α1,6-fucosyltransferase activity. Petitioners' declarant Dr. Van

Ness also admitted that Harris does not disclose α1,6-fucosyltransferase, the FUT8 gene, or a knock-out or any mutations to 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. 2011, 92:17-93:10 (objections omitted, discussing Ex. 1003 [Harris]).)

Accordingly, Petitioners' claim that "Harris teaches . . . targeting α1,6-fucosyltransferase activity for 'knock-out'" has no basis in fact. (Pet., 29.) The only remaining purported support Petitioners provide are Paragraphs 101-103 of the declaration of Dr. Van Ness. (Ex. 1007.) 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 claim 1 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 Claim 1 is obvious based on Ground 2 and since claims 2-6 depend from claim 1, 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), which Petitioners cited in the corresponding claim charts as being relevant to the first part of claim 1—"[a]n 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." (*See* Pet., 37, 45.) However, Malý does not disclose "α1,6-fucosyltransferase," let alone any level of "α1,6-fucosyltransferase activity," and any impact on this activity "by deleting a gene encoding α1,6-fucosyltransferase" or "by adding a mutation to said gene to reduce or eliminate α1,6-fucosyltransferase activity." Even Petitioners' expert Dr. Van Ness admits that Malý does not disclose these key claim elements:

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. 2011, 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 fucosyltranferase [was] involved in adding fucose to the complex sugar chain in antibodies." (Ex. 2011, 98:17-20.)

The only other purported support Petitioners provide are Paragraphs 127-129 and Paragraphs 153-155 of Dr. Van Ness' Declaration (for Grounds 3 and 4, respectively). (Ex. 1007.) 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 claim 1 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 Claim 1 (or dependent claims 2-6) are is 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 (Exhibit 1006.) Petitioners cite Gao in the claim charts as being relevant to the YB2/0 cell recited in dependent claim 5. (*See* Pet., 51-53.) However, Gao discloses a YB2/0 cell in a completely difference context. Although Petitioners only cite Gao for claim 5, Gao also does not disclose "α1,6-fucosyltransferase," let alone any level of "α1,6-fucosyltransferase activity," and any impact on this activity "by deleting a gene encoding α1,6-fucosyltransferase" or "by adding a mutation to said gene to reduce or eliminate α1,6-fucosyltransferase activity." 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. 2011, 99:14-100:11.)

As with their other Grounds, the only other purported support Petitioners provide are Paragraphs 25, 166-171 and Paragraphs 172-177 of Dr. Van Ness' Declaration (for Grounds 5 and 6 respectively). 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 claim 1, on which claim 5 depends, reliance on common knowledge is not legally sufficient to support institution against claim 5.

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 claim 1, 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 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-fucosyltranferase activity***, wherein said mammalian host cell produces an antibody molecule.

(Ex. 1001, 183:30-36.)

Petitioners' claim charts cite a few paragraphs of Dr. Van Ness' declaration for the proposition that "the knowledge of POSA"—*i.e.*, common knowledge—would have supplied the missing claim elements "deleting a gene encoding α1,6-fucosyltransferase" or "adding a mutation to said gene to reduce or eliminate α1,6-fucosyltransferase activity." (Ex. 1007, ¶¶75, 102, 128, 154; *see also* Pet., 22-23, 101-103, 127-129, 153-155.) 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 missing elements were evidently and indisputably within the common knowledge of those skilled in the art. *See 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 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 claim 1 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 "deleting a gene encoding α1,6-fucosyltransferase" or "adding a mutation to said gene to reduce or eliminate α1,6-fucosyltransferase activity" were common knowledge. (Ex. 1007, ¶¶75, 102, 128, 154.) 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 to the recited α1,6-fucosyltransferase activity of claim 1. (Ex. 2011, 97:16-98:20.)

Second, Dr. Van Ness alleges that during prosecution of the '446 Patent's grandparent application 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 '446 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 '446 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) (emphasis added). Here, the Petition does not demonstrate that a POSA would have conceived of

obtaining a mammalian host cell with "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-fucosyltranferase activity" without the express teachings in the '446 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 apply routine 'knock-out' techniques to create the host cell of claim 1." (*See* Pet., 36-37.) Likewise, for Grounds 2, 4, and 6, Petitioners assert in a conclusory manner that, in view of Harris, "POSA would be motivated to obtain host cell that have decreased or no α1,6-fucosyltransferase activity." (*Id.*, 29.) 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 reduced or eliminated α1,6-fucosyltransferase activity, the α1,6-fucosyltransferase gene, and deleting or adding a mutation to the α1,6-fucosyltransferase gene. 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 antibodies by deleting or adding a mutation to the α1,6-fucosyltransferase gene to reduce or eliminate the α1,6-fucosyltranferase activity. Nor does Rothman's observations lead to the

conclusion that lack of fucose results in increased ADCC activity in antibodies that are produced by mammalian host cells as claimed by the '446 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 Biotechnol.* (1997) 15, 26-32 (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 reducing or eliminating α1,6-fucosyltransferase activity and to create the claimed mammalian 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 reducing or eliminating α1,6-fucosyltransferase activity by creating the claimed mammalian host cells.

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 '446 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 cee 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: July 26, 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 10,524 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 July 26, 2017, at the following email addresses of record:

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