Paper No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ARAGEN BIOSCIENCE, INC.
AND
TRANSPOSAGEN BIOPHARMACEUTICALS, INC.,

Petitioners,

v.

KYOWA HAKKO KIRIN CO., LTD.
Patent Owner

Patent No. 8,067,232
Issued: November 29, 2011
Filed: March 14, 2008
Inventors: Yutaka Kanda, Mitsuo Satoh, Kazuyasu Nakamura, Kazuhisa Uchida, Toyohide Shinkawa, Naoko Yamane, Emi Hosaka, Kazuya Yamano, Motoo Yamasaki, Nobuo Hanai
Title: Antibody Composition-Producing Cell with Inactivated A-1,6-Fucocyltransferase

_____

Inter Partes Review No. _____

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 8,067,232

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I. PRELIMINARY STATEMENT

Petitioners Aragen Bioscience, Inc. and Transposagen Biopharmaceuticals, Inc. ("Petitioners") hereby request *Inter Partes* Review ("IPR") of claims 1-5 of U.S. Pat. No. 8,067,232 ("Challenged Claims") to Kanda *et al.*, entitled *Antibody Composition-Producing Cell with Inactivated A-1,6-Fucocyltransferase* ("the '232 patent") (Ex. 1001), which is assigned to Kyowa Hakko Kirin Co., Ltd ("Patent Owner").

The Challenged Claims are directed to an isolated mammalian host cell producing antibodies that function more effectively because they do not have a particular fucose sugar on their F_c regions. But published art expressly taught that loss of the fucose would result in these more efficient antibodies. And the underlying genetic engineering technology to make host cells that produce these antibodies was routine as of the alleged priority date of the '232 patent, October 6, 2000 (hereinafter, "Priority Date").

The obviousness of the Challenged Claims is straightforward. The sole alleged point of novelty of the '232 patent is the purported discovery that removing a sugar—fucose—from antibodies makes them more effective (i.e., having more efficient antibody-dependent cellular cytotoxicity or "ADCC"). The '232 patent, however, acknowledges that a sugar-chain/antibody-function correlation was already known in the art as of the alleged Priority Date of the '232 patent:

> These [prior-art] reports indicate that the structure of the sugar chain plays an important role in the effector functions of human antibodies of IgGl subclass and that it is possible to prepare an antibody having more higher [sic] effector function by changing the structure of the sugar chain.

(Ex. 1001 at 2:34-38.) The '232 patent frames the problem in the art as a lack of specific guidance as to what ***particular*** structural changes to the sugar chain would make antibodies more effective:

> However, actually, structures of sugar chains are various and complex, and it cannot be said that an actual important structure for the effector function was identified.

(Ex. 1001 at 2:38-41; *see also* Ex. 1001 at 5:20-33.) However, the prior art establishes just the opposite. For instance, *Rothman*—prior art not discussed by the Examiner during prosecution—specifically identifies a sugar-chain structure that improves ADCC:

> Thus, ***absence of core fucosylation [i.e. no fucose] itself*** would appear to be a likely candidate ***as a structural feature necessary for enhancement of NK cell-mediated ADCC***.

(Ex. 1002 at 1122 (emphasis added).) *Harris*, which is also prior art to the '232 patent, likewise describes how the "***[t]he fucose residue may be of particular interest***," explaining that fucose is "near the Fcγ receptor binding site and ***could influence binding by the receptor***." (Ex. 1003 at 1592 (emphasis added).)

The Challenged Claims are rendered obvious by the art submitted in this Petition: art never discussed by the Examiner during patent prosecution—*Rothman* or *Harris*—in light of *Umaña*, which discloses mammalian host cells to produce modified-sugar antibodies with enhanced effector function (ADCC), as well as the common knowledge of a person of ordinary skill in the art (hereinafter, "POSA").

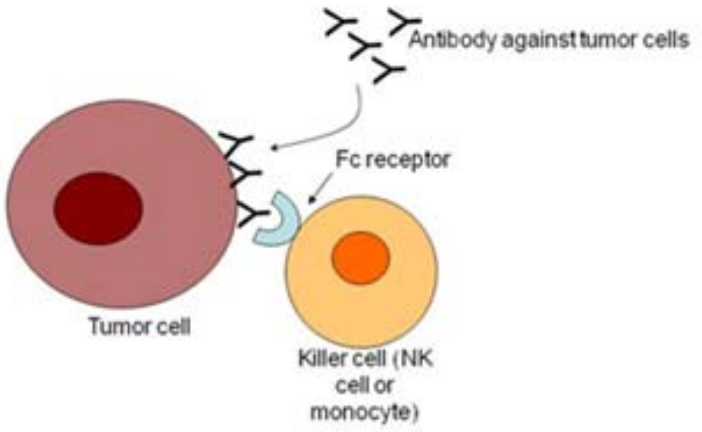
II. BACKGROUND OF THE RELEVANT ART

A.) Antibody Function and Structure

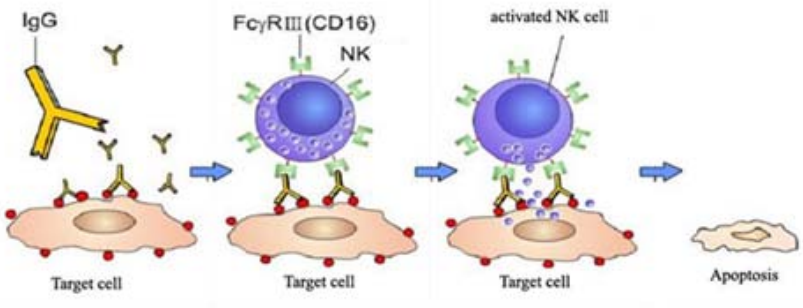
For centuries biologists have known that incursions by foreign bodies—particles and molecules—into the human body may cause disease. (Ex. 1026 at ¶¶ 15-16.) Humans fight back against these foreign bodies (called "antigens") via the immune system by producing "antibodies" that recognize and bind to the antigens to neutralize and expel them from the body. (*Id*.) Antibodies, which are also called immunoglobulins ("Ig" for short), come in many classes. (*Id*. at ¶¶ 16-20.) The class most commonly studied and most important for human immunology is the "IgG" class of antibodies. (*Id*.)

One mechanism by which antibodies facilitate the immune response and act to combat infection is called antibody-dependent cell-mediated cytotoxicity (ADCC). (Ex. 1026 at ¶¶ 21-24.) ADCC is mediated by NK ("Natural Killer") cells, which facilitate death of a target cell. NK cells express Fc receptors and bind

to the Fc portion on an antibody bound to the surface of an antigen, as shown below.

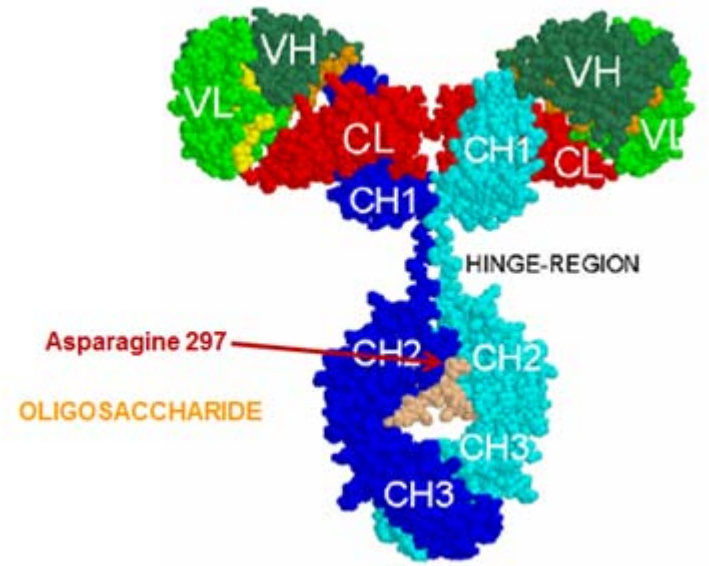


(*Id.*) The NK cell's Fc receptor recognizes and binds to the Fc portion of the antibody. (*Id.*) The most common Fc receptor on the surface of an NK cell is FcγRIII or CD16. (*Id.*) The efficacy of ADCC in a particular instance is measured by the binding efficiency of an IgG antibody to NK cells. (*Id.* at ¶¶ 22-23.) The binding efficiency of IgG and NKs cell is also considered a measurement of IgG "effector function." (*Id.*) The endpoint of ADCC is the death of the target cell ("cytotoxicity"), as depicted below.



(*Id.* at ¶ 23.)

Antibodies are comprised of four polypeptide chains forming an overall "Y" shape, as shown below. (Ex. 1026 at ¶ 17.)



The IgG polypeptide chains consist of two identical "light chains" and two identical "heavy chains." (*Id.* at ¶¶ 1719.) These chains fold to generate three-dimensional variable regions (VH & VL, above) and constant regions (CH & CL, above). (*Id.*) IgG may be cleaved at the "hinge" region to release two antigen binding fragments: (1) a Fab region (VHCH1/VLCL, above) and (2) an Fc region (CH2CH3/CH2CH3, above). (*Id.*) Each CH2 region bears an oligosaccharide (oligo: few; saccharide: sugar) attached at the asparagine 297 amino acid residue, as shown above. (*Id.* at ¶¶ 18-20.)

By October 6, 2000, it was well known in the art that the presence of oligosaccharide at the Fc region was essential for Fc receptor (FcγR) binding and

activation—i.e., the IgG/NK cell binding discussed above. (Ex. 1026 at ¶¶ 21-36.) It was also well known that the efficiency of these processes varied depending on the precise oligosaccharide sugars present. (*Id.* at ¶¶ 25-36.) Indeed, published research in the field long ago revealed that changes to oligosaccharide sugars—adding or removing particular sugars, whether enzymatically or genetically—may change (improve or lessen) the binding efficiency of IgG to NK cells. (*Id.*; *see also* Exs. 1002, 1003, 1004.) Even more specifically, published research that pre-dates the alleged Priority Date of the '232 patent explained that the removal of a ***particular*** sugar (the fucose sugar normally bound to N-acetyl glucosamine) would enhance the binding efficiency of IgG to NK cells—i.e, ADCC effector function. (See 1026 at ¶¶ 25-36; Ex. 1002 at 1122; Ex. 1003 at 1592; *see also* Ex. 1019.) Indeed, as explained by Professor Jefferis—a distinguished professor with more than fifty years' experience in the field of immunology—a POSA as of the alleged Priority Date of the '232 patent would certainly have understood the correlation between removing fucose from the sugar chain and improved ADCC. (Ex. 1026 at ¶¶ 4-6, 25-47.)

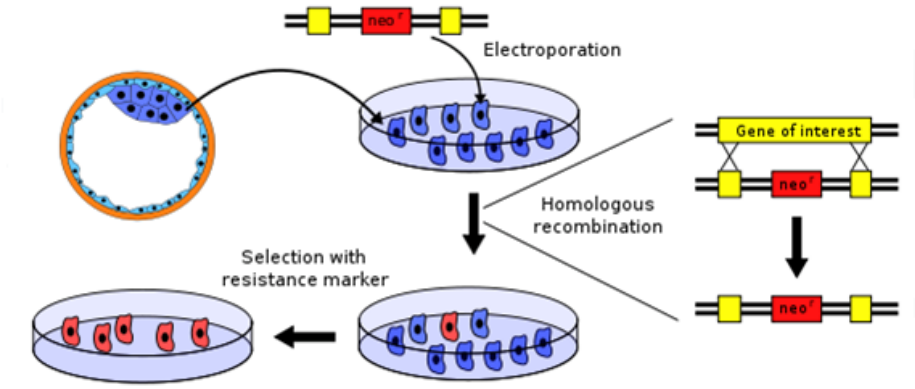
B.) Genetic Engineering in the Field of Immunology

The 1980s and 1990s saw an explosion of new genetic engineering techniques that allowed scientists to influence immunoglobulin (Ig) production in a variety of target cells. (Ex. 1007 at ¶¶ 21-42.) These innovations included, for

instance, new approaches that allowed scientists to modify sugar chains normally attached to amino acid residues in antibody molecules—new approaches that developed hand-in-hand with new discoveries in antibody structure and function, antibody engineering, and antibody therapeutics. (*Id.* at ¶¶ 35-42; *see also* Ex. 1018.)

As of the alleged Priority Date of the '232 patent, fucosyltransferase was known to be the enzyme that puts fucose on the antibody sugar chain. (Ex. 1007 at ¶¶ 39-41.) The human fucosyltransferase gene sequence was cloned in 1994. (*Id.*) And Patent Owner acknowledged during prosecution of the '232 patent's parent application that the gene sequence for α(1,6)-fucosyltransferase had already been published. (*Id.*; *see also* Ex. 1036 (selected pages), Aug. 12, 2004 Amend. at 33–34.) Knowing this sequence—which a POSA could have determined independently and routinely—would have allowed a POSA to target α(1,6)-fucosyltransferase and disable it by using well known "knock-out" techniques. (Ex. 1007 at ¶¶ 39-41.) By October 2000, the technologies of transfection and gene "knock-out" were routine. (*Id.* at ¶¶ 35-42.)

The figure below shows schematically how a gene "knock-out" would have been accomplished through a combination of techniques that were standard by 1995.



The above figure shows a homologous recombination to "knock-out" a target gene (e.g., α1,6-fucosyltransferase, shown in red) in a cell. (Ex. 1007 at ¶¶ 32-34.) Cells are grown in a culture dish, and a DNA construct is made that contains a selectable marker (in this case an antibiotic resistance gene, NEO, shown in red), flanked by sequences that will base pair with the target gene. (*Id.*) Enzymatic machinery in the cell catalyzes the exchange of the vector DNA into the host genome DNA by homologous recombination. (*Id.*) The host gene (e.g. α1,6-fucosyltransferase) is disrupted ("knocked-out") and the selectable marker (NEO) confers resistance of cells that have incorporated the NEO gene to the antibiotic, neomycin. (*Id.*) The only cells that survive are the red cells that, in the above example, (1) have had their α1,6-fucosyltransferase genes knocked out and (2) the NEO antibiotic-resistance gene inserted. (*Id.*)

As set forth in the Declaration of Professor Brian G. Van Ness, a distinguished professor at the University of Minnesota (Department of Genetics,

Cell Biology & Development), who has spent 35-plus-years in the field of genetic immunology, the above-described "knock-out" technology was routine by the mid-1990s. (Ex. 1007 at ¶¶ 4-12, 21-53.) One of thousands of published papers from that period succinctly describes the state of the art in 1995: "[i]ntroduction of defined modifications at a genomic level by gene targeting has become a widely used technique." (Ex. 1013.) Indeed, *Umaña*—one of the prior art references discussed in detail below—expressly teaches the creation of a host cell by inserting—or "knocking out"—sugar-adding genes (glycosyltransferases, of which fucosyltransferase is an example) to achieve antibodies with more effective ADCC. (Ex. 1004 at Abstract, 15:20-22, Cls. 1, 74.)

III. THE '232 PATENT AND THE PRIOR ART

The '232 patent is a continuation (divisional) of U.S. patent application No. 09/971,773, which issued as U.S. Patent No. 6,946,292. (Ex. 1001 at (60).) The '232 patent claims priority to a Japanese patent application filed October 6, 2000. At this time, Petitioners do not contest the alleged Priority Date of the Challenged Claims—October 6, 2000.

The '232 patent concerns antibody-producing cell lines, and more specifically cell lines with no α1,6-fucosyltransferase activity for adding α1,6-attached fucose sugar on their F_c sugar chain. (*See* Ex. 1001 at Cl. 1.) The creation of such cell lines is obvious in view of the prior art. The '232 patent itself

extensively describes (1) the known correlation between sugar-chain-structure and human IgG antibody function—as measured by ADCC—and, (2) the enabling biotechnology for making host cells having no α1,6-fucosyltransferase activity (e.g., a gene "knock-out"), including the cell lines recited in claims 1-5. The '232 patent specification describes the alleged problem in the art not as one of available techniques, but as lack of knowledge as to the specific structures on the IgG sugar chain that are important "for the effector function[.]" (Ex. 1001 at 2:38–41.) But as discussed extensively in this Petition and the accompanying expert declarations, published research and the knowledge of a POSA establishes that such a structure (fucose) was known.

A.) The '232 patent acknowledges that the correlation between sugar chain structure and human IgG function was well known in the art—a fact confirmed by the prior art.

The '232 patent details specific prior-art knowledge about sugar-structure/modification and its effect on antibody-effector-function. (Ex. 1001 at 2:11–39 (citing Exs. 1024, 1025).) The patent's citation to *Boyd* (Ex. 1024) confirms that the structure of the IgG antibody sugar chain—attached at the Asn297 position on the antibody—was fully characterized as of the alleged Priority Date of the '232 patent. (*See* Ex. 1024 at 1311.) The '232 patent further states that "the structure of the sugar chain plays an important role in the effector functions of human antibodies of IgG subclass and that it is possible to prepare an antibody

having more higher [sic] effector function by changing the structure of the sugar chain." (Ex. 1001 at 2:34–38.) The '232 patent even cites several prior-art examples of techniques for modifying the structure of the IgG sugar chain, including the technique of adding the fucose sugar to the "non-reducing" end (as opposed to the usual, reducing, end) of the sugar chain "by introducing human β-galactoside-2-αfucosyltransferase into mouse L cell [Science, 252, 1668 (1991)]." (Ex. 1001 at 4:65-5:2.)

Given these admissions, the '232 patent's sole alleged point of novelty is the "knock-out" of a specific sugar chain structure (fucose), which is important for effector function (ADCC). As alleged in the '232 patent specification, prior to the alleged invention, "it [could not] be said that an actual important structure for the effector function was identified," and "a truly important sugar chain structure has not been specified yet." (*Id.* at 2:38–41; 5:20–33.) In other words, the '232 patent frames the problem as a lack of specific guidance as to what actual structural changes to the sugar chain would provide higher effector function (ADCC). (*See* Ex. 1026 at ¶¶ 37-47; Ex. 1007 at ¶¶ 43-53.) But this guidance already existed in the art.

The correlation between removing fucose and improving ADCC was well known. Indeed, much published research supports the known existence of this correlation; for this IPR, Petitioners have focused on *Rothman* and *Harris.*

Rothman, which published in 1989, expressly found a link between loss of fucose from the sugar chain and enhanced ADCC: "Our data suggests a possible involvement of core fucosylation of IgG in NK cell-mediated ADCC." (Ex. 1002 at 1114.) *Rothman* concluded that "[the] absence of core fucosylation itself would appear to be a likely candidate as a structural feature necessary for enhancement of NK cell-mediated ADCC." (Ex. 1002 at 1122.) Similarly, *Harris*, which published in 1997, found that fucose "may be of particular interest" because the α-1,6-fucose molecule is positioned "near the Fcγ receptor binding site [(the functional antibody binding site)] and could influence binding by the receptor." (Ex. 1003 at 1592.) The published conclusions of *Rothman* and *Harris* are coextensive with the work (and findings) of Professor Jefferis, which confirms that by the alleged Priority Date of the '232 patent it was well known that the binding of the constant region of an antibody, as measured by ADCC, could be affected by modifications in the sugar chain attached at Asn297 (including removal of fucose). (Ex. 1026 at ¶¶ 21-36.) Thus, as of the alleged Priority Date of the '232 patent, a POSA would have been motivated to create the claimed host cells with "no α1,6-fucosyltransferase activity." (Ex. 1026 at ¶¶ 21-47; *see also* Ex. 1007 at ¶¶ 51-53.)

B.) The ’232 patent acknowledges that the technology necessary to “knock out” fucose was “quite advanced” as of the alleged Priority Date—a fact confirmed by the prior art.

The specification of the ’232 patent cites to several well-known treatises for the standard background procedures employed in selecting host cells and modifying genes to obtain antibodies that lack a fucose sugar. (*See, e.g.,* Ex. 1001 at 26:65-27:8, 32:15-24, 33:15-27.) Other prior-art references confirm the quite-advanced state of the enabling art for inserting and expressing genes in host cells, even finding it “routine.” (*See* Ex. 1007 at ¶¶ 21-42; Ex. 1026 at ¶¶ 21-36.) In his supporting Declaration, Professor Van Ness explains how the “knock-out” of the fucosyltransferase gene (as claimed in the ’232 patent) would have been obvious to a POSA as of the alleged Priority Date. (Ex. 1007 at ¶¶ 21-42.) As Professor Van Ness explains, the techniques for performing a gene “knock-out” were developed and refined throughout the 1980s and 1990s. (*Id*.) By the alleged Priority Date of the ’232 patent, the ability to “knock-out” the fucosyltransferase gene would have entailed use of techniques that had long since become routine. (*Id.* at ¶¶ 21-53.)

The prosecution history of the ’232 patent’s parent application further supports the advanced state of “knock-out” technology as of the alleged Priority Date. During prosecution, Patent Owner detailed just how “advanced” the

background enabling technology was.[1] Patent Owner explained that "the state of the art in the field of, for example, genetic manipulation techniques, at the time of the present invention, ***w[as] quite advanced***." (Ex. 1036 (selected pages), Aug. 12, 2004 Amend. at 32–35 (emphasis added).) Patent Owner further explained that "the knowledge in the art relating to antibody production from CHO cells, manipulation of CHO cells and enzymes relating to the synthesis of an intracellular sugar nucleotide, GDP-fucose and/or modification of a sugar chain in which fucose is bound to the 6-position of N-acetylglucosamine in the reducing end through an α(1-6)glycosyl bond in a complex N-glycoside-linked sugar chain, ***w[as] advanced at the time of the present invention***." (*Id.* (emphasis added).) Indeed, Patent Owner was clear in its position on the "advanced" state of the art: "[i]t will be apparent for [a POSA] that [the claimed] knock-out cell could be prepared, without an undue amount of experimentation[.]" (*Id.*)

[1] During prosecution, the Examiner focused almost exclusively on Section 112 rejections, especially on whether all types of fucosyltransferase-gene mutations were enabled for all levels of expression of fucosyltransferase enzymes in all types of cells. (Ex. 1036 at Feb. 13, 2004 Office Action, 11-12.) The Examiner discussed the correlation between the removal or "knock-out" of fucose and improved ADCC only in the context of section 112, and only in the context of a non-prior-art reference. (*Id.* at 11-13.)

Patent Owner's position as to the "advanced" state of the art even extends to other patents in the field. During prosecution of an earlier related patent application directed to no-fucose antibodies (U.S. Patent No. 7,214,775, claiming priority to April 9, 1999), Patent Owner submitted a declaration explaining how the construction of gene constructs and knock-out CHO cells constituted "standard methods" in the prior art. (Ex. 1035 (selected pages), May. 2, 2006 Shitara Decl. at 5 (citing presentation slides nos. 22–26 and 30–32).

As made clear above, the technology and methods for modifying genes to obtain antibodies that lack a fucose sugar was routine in the art as of the alleged Priority Date of the '232 patent. Many prior art references establish the obviousness of the genetic engineering techniques described in the Challenged Claims; for this IPR, Petitioners have focused on *Umaña*, which teaches the creation of mammalian host cells with a modified sugar chain (knocked out glycosyl transferases) to produce antibodies with enhanced ADCC effector function:

> [T]he present invention is directed, generally, to methods for the glycosylation engineering of proteins to alter and improve their therapeutic properties. More specifically, the present invention describes methods for producing in ***a host cell an antibody which has an altered glycosylation pattern resulting in an enhanced antibody dependent cellular cytotoxicity (ADCC)***.

(Ex. 1004 at 8:24–28 (emphasis added).) *Umaña*, which is representative of the state of the art, explains that "***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." (*Id.* at 15:20–22 (emphasis added).)

IV. PERSON OF ORDINARY SKILL IN THE ART

With respect to the '232 patent (Ex. 1001), 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. (*See* Ex. 1026 at ¶¶ 11-13; Ex. 1007 at ¶¶ 18-20.) The POSA would have a doctorate in molecular immunology or biochemistry of glycoproteins including antibodies, knowledge of routine genetic procedures including gene "knock-outs," and a few years' practical experience working on the genetics of antibodies. (*Id*.) This definition conforms to the level of skill and knowledge that Patent Owner itself noted had been reached by October 6, 2000. (*See Id.*; *see also* Ex. 1036 (selected pages), Aug. 12, 2004 Amend. at 32–35 (emphasis added).)

V. CLAIM CONSTRUCTION

In this proceeding, the claims of the '232 patent must be given their broadest

reasonable construction in light of the specification. *See* 37 C.F.R. 42.100(b). For the purposes of this proceeding only, the broadest reasonable construction of claims 1-5 of the '232 patent are their plain and ordinary meaning as understood by a person of ordinary skill in the art.[2]

VI. STATEMENT OF PRECISE RELIEF REQUESTED FOR EACH CLAIM CHALLENGED

Petitioners request review under 35 U.S.C. § 311 of the Challenged Claims and cancellation of these claims as unpatentable under 35 U.S.C. § 103 for the following reasons:

Ground	Proposed Statutory Rejections for the '232 Patent	Exhibit Nos.
1	Claims 1-5 are obvious under § 103(a) over *Rothman* in view of *Umaña* and the common knowledge	1002, 1004
2	Claims 1-5 are obvious under § 103(a) over *Harris* in view of *Umaña* and the common knowledge	1003, 1004
3	Claims 1-5 are obvious under § 103(a) over *Rothman* in view of *Umaña*, *Malý*, and the common knowledge	1002, 1004, 1005

[2] Petitioners' position in this particular proceeding may differ from that offered in any district court or ITC litigation, including related litigations. Petitioners reserve all rights in this regard. To the extent Patent Owner contends that the prior art references identified herein would not enable a POSA to make or use any element of the challenged claims, Petitioners reserve the right to assert that the challenged claim element(s) do not comply with the enablement, written description, and/or definiteness requirements of 35 U.S.C. § 112.

Ground	Proposed Statutory Rejections for the ’232 Patent	Exhibit Nos.
4	Claims 1-5 are obvious under § 103(a) over *Harris* in view of *Umaña*, *Malý*, and the common knowledge	1003, 1004, 1005
5	Claim 5 is obvious under § 103(a) over *Rothman* in view of *Umaña, Gao*, and the common knowledge	1002, 1004, 1006
6	Claim 5 is obvious under § 103(a) over *Harris* in view of *Umaña*, *Gao*, and the common knowledge	1003, 1004, 1006

The reasons for unpatentability and specific evidence supporting this request are detailed herein.

VII. CLAIMS 1-5 OF THE ’232 PATENT ARE UNPATENTABLE OVER THE PRIOR ART

A.) Ground 1: *Rothman* in view of *Umaña* and the Common Knowledge Renders Claims 1–5 Obvious

Claims 1-5 of the ’232 patent are obvious over *Rothman* in view of *Umaña* and the common knowledge of a POSA. (*See* Ex. 1026 at ¶¶ 49-66; Ex. 1007 at ¶¶ 55-78.) *Umaña* teaches the creation of mammalian host cells with modified sugar-adding genes (including “knock-outs”) to create sugar-modified antibodies with more efficient ADCC. (Ex. 1004.) *Rothman* teaches the correlation between a no-fucose sugar-chain structure and enhanced antibody function (ADCC): “[the] absence of core fucosylation itself would appear to be a likely candidate as a structural feature necessary for enhancement of NK cell-mediated ADCC. (Ex. 1002 at 1122.) In other words, *Rothman* teaches the sole alleged point of novelty of the ’232 patent—targeting the α1,6-fucosyltransferase gene for “knock-out,

resulting in no α1,6-fucosyltransferase activity for adding fucose to the antibody sugar chain.

Given the teachings of *Rothman***,** a POSA would be motivated to obtain host cells that have no α1,6-fucosyltransferase activity. (*See* Ex. 1026 at ¶¶ 21-36, 53-66; Ex. 1007 at ¶ 59.) A POSA would achieve this result by "knocking-out" the gene for the enzyme that adds the fucose to the sugar chain—α(1,6)-fucosyltransferase. (Ex. 1007 at ¶¶ 32-34, 39-42, 60-75.) The necessary steps for creating such a host cell (in a variety of target cells) were in the common knowledge. (*Id*.) As Patent Owner admitted during prosecution of the '232 patent's parent application, the state of the art was "quite advanced." *See supra* **Sections II**, **III**.

1.) Independent claim 1 is obvious over *Rothman, Umaña*, and the Common Knowledge.

With the above as a backdrop, claim 1 of the '232 patent is obvious over *Rothman*, *Umaña*, and the common knowledge. As set forth in the below claim chart, all limitations of claim 1 are taught by *Rothman* and *Umaña*. Given *Rothman's* teaching regarding the link between removal of fucose and improved ADCC, a POSA as of the alleged Priority Date of the '232 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* Ex. 1026 at ¶¶ 53-66; Ex. 1007 at ¶¶ 60-75.) 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.*)

Claim Language	**Evidence & Corresponding Disclosure**
[1.a] An isolated mammalian host cell which has no α-1,6-fucosyltransferase activity for adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked 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 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 at 15:20–22 (emphasis added).) "Our data suggests a possible involvement of core fucosylation of IgG in NK cell-mediated ADCC." (Ex. 1002 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 at 1122 (emphasis added).)
[1.b] by deleting a genomic gene encoding α-1,6-fucosyltransferase or	"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 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 at 7:15–18 (emphasis added).)

Claim Language	Evidence & Corresponding Disclosure
	"Our data suggests a possible involvement of core fucosylation of IgG in NK cell-mediated ADCC." (Ex. 1002 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 at 1122 (emphasis added).) (*See also* Ex. 1007 at ¶¶ 69-71.)
[1.c] by adding a mutation to said genomic gene to eliminate the α-1,6-fucosyltranferase 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 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 at 7:15–18 (emphasis added).) "Our data suggests a possible involvement of core fucosylation of IgG in NK cell-mediated ADCC." (Ex. 1002 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 at 1122 (emphasis added).) (*See also* Ex. 1007 at ¶¶ 69-71.)
[1.d] wherein said mammalian host cell is selected from the group consisting of a CHO cell, a NSO cell, an SP2/0 cell,	"***Mammalian cells are the preferred hosts for production of therapeutic glycoproteins***, due to their capability to glycosylate proteins in the most compatible form for human application." (Ex. 1004 at 2:4–6 (emphasis added).)

Claim Language	Evidence & Corresponding Disclosure
and a YB2/0 cell.	"More specifically, the present invention is directed to a ***method for producing altered glycoforms of proteins having improved therapeutic values, e.g., an antibody*** which has an enhanced antibody dependent cellular cytotoxicity (ADCC), ***in a host cell***. The invention provides ***host cells*** which harbor a nucleic acid encoding the protein of interest, e.g., an antibody, ***and at least one*** nucleic acid encoding a glycoprotein-modifying ***glycosyl transferase***." (Ex. 1004 *at* 3:6–11 (emphasis added).) "Furthermore, the present invention provides alternative glycoforms of proteins having improved therapeutic properties. ***The proteins of the invention include antibodies with an enhanced antibody-dependent cellular cytotoxicity (ADCC), which have been generated using the disclosed methods and host cells***." (Ex. 1004 at 3:17-20 (emphasis added); *see also* Ex. 1004 at 8:24-28.) "***Host cells include cultured cells, e.g., mammalian cultured cells***, such as ***CHO cells***, BHK cells, ***NSO cells***, ***SP2/0 cells***, or hybridoma cells, yeast cells, and insect cells, to name only few, but also cells comprised within a transgenic animal or cultured tissue." (Ex. 1004 at 7:31–8:1 (emphasis added).) "***Any type of cultured cell line can be used as background to engineer the host cell lines of the present invention***." (Ex. 1004 at 15:23-24 (emphasis added).) (*See also* Ex. 1007 at ¶¶ 72-75.)

For the foregoing reasons, claim 1 of the '232 patent is obvious over *Rothman*, *Umaña*, and the common knowledge.

2.) Dependent claims 2-5 are obvious over *Rothman*, *Umaña*, and the Common Knowledge.

Dependent Claims 2–5 of the ’232 patent identify particular mammalian cell lines, all of which were well known in the prior art. As Professor Van Ness explains, the source of cells was not a restriction in gene modification as of the alleged Priority Date of the ’232 patent, and various routine technologies existed to transfect virtually any DNA sequence into a variety of target cells. (Ex. 1007 at ¶¶ 25, 76-78.) A POSA was only limited by their ability to maintain and grow particular cells of interest in laboratory cultures. (*Id*.) *Umaña* confirms the state of the art:

> Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. In addition to giving suitable glycosylation patterns, these cells allow consistent generation of genetically stable, highly productive clonal cell lines. They can be cultured to high densities in simple bioreactors using serum-free media, and permit the development of safe and reproducible bioprocesses. ***Other commonly used animal cells include baby hamster kidney (BHK) cells, NSO- and SP2/0-mouse myeloma cells***.

(Ex. 1004 at 2:10-16 (emphasis added).) Indeed, *Umaña* is clear that “[a]ny type of cultured cell line can be used as background to engineer the host cell lines of [*Umaña’*s] invention.” (Ex. 1004 at 15:23-24.) As of the alleged Priority Date of the ’232 patent, mammalian cell targets of genetic engineering routinely included

CHO cells, NSO cells, SP2/0 cells, YB2/0 cells, among many others. (Ex. 1007 at ¶¶ 25, 76-78; *see also* Ex. 1006.) Thus, a POSA would find each of claims 2-5 obvious over *Rothman*, *Umaña*, and the common knowledge. (Ex. 1007 at ¶¶ 25, 76-78; *see also* Ex. 1026 at ¶¶ 64-66.) Set forth below is a claim chart that identifies the evidence and portions of *Rothman* and *Umaña* that correspond to dependent claims 2-5.

Claim 2	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a CHO cell.	"Among mammalian cells, Chinese hamster ovary ***(CHO) cells have been most commonly used during the last two decades***. . . . Other commonly used animal cells include baby hamster kidney (BHK) cells, NSO- and SP2/0-mouse myeloma cells." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 3	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a NSO cell.	"Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. . . . ***Other commonly used animal cells include*** baby hamster kidney (BHK) cells, ***NSO-*** and SP2/0-mouse myeloma cells." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 4	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein mammalian host cell is a SP2/0 cell.	"Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. . . . ***Other commonly used animal cells include*** baby hamster kidney (BHK) cells, NSO- and ***SP2/0-mouse myeloma cells***." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 5	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a YB2/0 cell.	"***Host cells include cultured cells, e.g., mammalian cultured cells***[.]" (Ex. 1004 at 7:31–8:1 (emphasis added).) "***Any type of cultured cell line can be used as background***

Claim 5	Evidence & Corresponding Disclosure
	to engineer the host cell lines of the present invention." (Ex. 1004 at 15:23-24 (emphasis added).) *As of the alleged Priority Date of the '232 patent, mammalian cell targets of genetic engineering routinely included CHO cells, NSO cells, SP2/0 cells, YB2/0 cells, among many others.* (Ex. 1007 at ¶¶ 77-78.)

For the foregoing reasons, claims 2-5 the '232 patent are obvious over *Rothman, Umaña*, and the common knowledge.

B.) Ground 2: *Harris* in view of *Umaña* and the Common Knowledge Renders Claims 1–5 Obvious

Claims 1-5 of the '232 patent are obvious over *Harris* in view of *Umaña* and the common knowledge of a POSA. (*See* Ex. 1026 at ¶¶ 67-84; Ex. 1007 at ¶¶ 79-102.) *Umaña* teaches the creation of mammalian host cells with modified sugar-adding genes (including "knock-outs") to create sugar-modified antibodies with more efficient ADCC. *Harris* teaches the correlation between fucose and antibody binding, of which ADCC is a function:

> ***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 at 1592 (emphasis added).) In other words, *Harris* teaches the sole alleged point of novelty of the '232 patent — targeting the α1,6-fucosyltransferase

gene for "knock-out, resulting in no α1,6-fucosyltransferase activity for adding fucose to the antibody sugar chain.

Given the teachings of *Harris*, a POSA would be motivated to obtain host cells that have no α1,6-fucosyltransferase activity. (*See* Ex. 1026 at ¶¶ 21-36, 71-81; Ex. 1007 at ¶ 83.) A POSA would achieve this result by "knocking-out" the gene for the enzyme that adds the fucose to the sugar chain—α(1,6)-fucosyltransferase. (Ex. 1007 at ¶¶ 32-34, 39-42, 60-75.) The necessary steps for creating such a host cell (in a variety of target cells) were in the common knowledge. (*Id*.) As Patent Owner admitted during prosecution of the '232 patent's parent application, the state of the art was "quite advanced." *See supra* **Sections II, III**.

1.) Independent claim 1 is obvious over *Harris, Umaña*, and the Common Knowledge.

With the above as a backdrop, claim 1 of the '232 patent is obvious over *Harris*, *Umaña*, and the common knowledge. As set forth in the below claim chart, all limitations of claim 1 are taught by *Harris* and *Umaña*. Given *Harris'* teaching regarding the link between removal of fucose and improved ADCC, a POSA as of the alleged Priority Date of the '232 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* Ex. 1026 at ¶¶ 71-81; Ex. 1007 at ¶¶ 84-99.) 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.*)

Claim Language	**Evidence & Corresponding Disclosure**
[1.a] An isolated mammalian host cell which has no α-1,6-fucosyltransferase activity for adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked 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 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 at 15:20–22 (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 at 1592 (emphasis added).)
[1.b] by deleting a genomic gene encoding α-1,6-fucosyltransferase or	"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 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 at 7:15–18 (emphasis added).) "***The fucose residue may be of particular interest***. In

Claim Language	Evidence & Corresponding Disclosure
	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 at 1592 (emphasis added).) (*See also* Ex. 1007 at ¶¶ 93-95.)
[1.c] by adding a mutation to said genomic gene to eliminate the α-1,6-fucosyltranferase 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 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 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 at 1592 (emphasis added).) (*See also* Ex. 1007 at ¶¶ 93-95.)
[1.d] wherein said mammalian host cell is selected from the group consisting of a CHO cell, a NSO cell, an SP2/0 cell, and a YB2/0 cell.	"***Mammalian cells are the preferred hosts for production of therapeutic glycoproteins***, due to their capability to glycosylate proteins in the most compatible form for human application." (Ex. 1004 at 2:4–6 (emphasis added).) "More specifically, the present invention is directed to a ***method for producing altered glycoforms of proteins having improved therapeutic values, e.g., an antibody*** which has an enhanced antibody dependent cellular cytotoxicity (ADCC), ***in a host***

Claim Language	Evidence & Corresponding Disclosure
	cell. The invention provides ***host cells*** which harbor a nucleic acid encoding the protein of interest, e.g., an antibody, ***and at least one*** nucleic acid encoding a glycoprotein-modifying ***glycosyl transferase***." (Ex. 1004 at 3:6–11 (emphasis added).) "Furthermore, the present invention provides alternative glycoforms of proteins having improved therapeutic properties. ***The proteins of the invention include antibodies with an enhanced antibody-dependent cellular cytotoxicity (ADCC), which have been generated using the disclosed methods and host cells***." (Ex. 1004 at 3:17-20 (emphasis added); *see also* Ex. 1004 at 8:24-28.) "***Host cells include cultured cells, e.g., mammalian cultured cells***, such as ***CHO cells***, BHK cells, ***NSO cells***, ***SP2/0 cells***, or hybridoma cells, yeast cells, and insect cells, to name only few, but also cells comprised within a transgenic animal or cultured tissue." (Ex. 1004 at 7:31–8:1 (emphasis added).) "***Any type of cultured cell line can be used as background to engineer the host cell lines of the present invention***." (Ex. 1004 at 15:23-24 (emphasis added).) (*See also* Ex. 1007 at ¶¶ 96-99.)

For the foregoing reasons, claim 1 of the '232 patent is obvious over *Harris*, *Umaña*, and the common knowledge.

2.) Dependent claims 2-5 are obvious over *Harris*, *Umaña*, and the Common Knowledge.

Dependent Claims 2–5 of the '232 patent identify particular mammalian cell lines, all of which were well known in the prior art. As Professor Van Ness

explains, the source of cells was not a restriction in gene modification as of the alleged Priority Date of the ’232 patent, and various routine technologies existed to transfect virtually any DNA sequence into a variety of target cells. (Ex. 1007 at ¶¶ 25, 100-102.) A POSA was only limited by their ability to maintain and grow particular cells of interest in laboratory cultures. (*Id*.) *Umaña* confirms the state of the art:

> Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. In addition to giving suitable glycosylation patterns, these cells allow consistent generation of genetically stable, highly productive clonal cell lines. They can be cultured to high densities in simple bioreactors using serum-free media, and permit the development of safe and reproducible bioprocesses. ***Other commonly used animal cells include baby hamster kidney (BHK) cells, NSO- and SP2/0-mouse myeloma cells***.

(Ex. 1004 at 2:10-16 (emphasis added).) Indeed, *Umaña* is clear that “[a]ny type of cultured cell line can be used as background to engineer the host cell lines of [*Umaña’s*] invention.” (Ex. 1004 at 15:23-24.) As of the alleged Priority Date of the ’232 patent, mammalian cell targets of genetic engineering routinely included CHO cells, NSO cells, SP2/0 cells, YB2/0 cells, among many others. (Ex. 1007 at ¶¶ 25, 100-102; *see also* Ex. 1006.) Thus, a POSA would find each of claims 2-5 obvious over *Rothman*, *Umaña*, and the common knowledge. (Ex. 1007 at ¶¶ 25,

100-102; *see also* Ex. 1026 at ¶¶ 82-84.) Set forth below is a claim chart that identifies the evidence and portions of *Harris* and *Umaña* that correspond to dependent claims 2-5.

Claim 2	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a CHO cell.	"Among mammalian cells, Chinese hamster ovary ***(CHO) cells have been most commonly used during the last two decades***. . . . Other commonly used animal cells include baby hamster kidney (BHK) cells, NSO- and SP2/0-mouse myeloma cells." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 3	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a NSO cell.	"Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. . . . ***Other commonly used animal cells include*** baby hamster kidney (BHK) cells, ***NSO-*** and SP2/0-mouse myeloma cells." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 4	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein mammalian host cell is a SP2/0 cell.	"Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. . . . ***Other commonly used animal cells include*** baby hamster kidney (BHK) cells, NSO- and ***SP2/0-mouse myeloma cells***." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 5	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a YB2/0 cell.	"***Host cells include cultured cells, e.g., mammalian cultured cells***[.]" (Ex. 1004 at 7:31–8:1 (emphasis added).) "***Any type of cultured cell line can be used as background to engineer the host cell lines of the present invention***." (Ex. 1004 at 15:23-24 (emphasis added).) *As of the alleged Priority Date of the '232 patent, mammalian cell targets of genetic engineering routinely included CHO cells, NSO cells, SP2/0 cells, YB2/0 cells,*

Claim 5	Evidence & Corresponding Disclosure
	among many others. (Ex. 1007 at ¶¶ 101-102.)

For the foregoing reasons, claims 2-5 the ’232 patent are obvious over *Harris, Umaña*, and the common knowledge.

C.) Ground 3: *Rothman* in view of *Umaña, Malý*, and the Common Knowledge Renders Claims 1–5 Obvious

Claims 1-5 of the ’232 patent are obvious over *Rothman* in view of *Umaña*, *Malý*, and the common knowledge of a POSA. (*See* Ex. 1026 at ¶¶ 85-101; Ex. 1007 at ¶¶ 103-125.) *Umaña* teaches the creation of mammalian host cells with modified sugar-adding genes (including “knock-outs”) to create sugar-modified antibodies with more efficient ADCC. *Rothman* teaches the correlation between a no-fucose sugar-chain structure and enhanced antibody function (ADCC): “[the] absence of core fucosylation itself would appear to be a likely candidate as a structural feature necessary for enhancement of NK cell-mediated ADCC. (Ex. 1002 at 1122.) In other words, *Rothman* teaches the sole alleged point of novelty of the ’232 patent— targeting the α1,6-fucosyltransferase gene for “knock-out, resulting in no α1,6-fucosyltransferase activity for adding fucose to the antibody sugar chain.

Given the teachings of *Rothman*, a POSA would be motivated to obtain host cells that have no α1,6-fucosyltransferase activity. (*See* Ex. 1026 at ¶¶ 88-101; Ex. 1007 at ¶¶ 106.) A POSA would achieve this result by “knocking-out” the gene for

the enzyme that adds the fucose to the sugar chain—α(1,6)-fucosyltransferase. (Ex. 1007 at ¶¶ 32-34, 39-42, 106-122.) The necessary steps for creating such a host cell (in a variety of target cells) were in the common knowledge. (*Id*.) As Patent Owner admitted during prosecution of the '232 patent's parent application, the state of the art was "quite advanced." *See supra* **Sections II, III**. Indeed, *Malý* already accomplished a knockout of the gene for α(1,3)-fucosyltransferase in mouse embryos (Ex. 1005 at 644.) ("Targeted Disruption of the Mouse Fuc-TVII Gene . . . approximately 26% of the progeny were Fuc-TVII (-/-)"). The "knock-out" performed by *Malý* further demonstrates the routine nature of completing the claimed "knock-out" of α1,6-fucosyltransferase in CHO cells as of the alleged Priority Date, and this success would have only emboldened a POSA to pursue "knock-out" of α-1,6-fucosyltransferase. (*See* Ex. 1007 at ¶¶ 103-122.)

1.) Independent claim 1 is obvious over *Rothman, Umaña, Malý,* and the Common Knowledge.

With the above as a backdrop, claim 1 of the '232 patent is obvious over *Rothman*, *Umaña*, *Malý* and the common knowledge. As set forth in the below claim chart, all limitations of claim 1 are taught by *Rothman, Umaña,* and *Malý*. Given *Rothman's* teaching regarding the link between removal of fucose and improved ADCC, a POSA as of the alleged Priority Date of the '232 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* Ex. 1026 at

¶¶ 88-98; Ex. 1007 at ¶¶ 106-122.) 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.*)

Claim Language	**Evidence & Corresponding Disclosure**
[1.a] An isolated mammalian host cell which has no α-1,6-fucosyltransferase activity for adding fucose to N-acetylglucosamine of a reducing terminus of N-glycoside-linked 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 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 at 15:20–22 (emphasis added).) "Our data suggests a possible involvement of core fucosylation of IgG in NK cell-mediated ADCC." (Ex. 1002 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 at 1122 (emphasis added).) "Southern blot analysis identified embryonic stem (ES) **cell transfectants** containing homologous integration . . . approximately 26% of the progeny **were Fuc-TVII (-/-)**." (Ex. 1005 at 644.)
[1.b] by deleting a genomic gene encoding α-1,6-fucosyltransferase or	"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

Claim Language	Evidence & Corresponding Disclosure
	the invention." (Ex. 1004 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 at 7:15–18 (emphasis added).) "Our data suggests a possible involvement of core fucosylation of IgG in NK cell-mediated ADCC." (Ex. 1002 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 at 1122 (emphasis added).) (*See also* Ex. 1007 at ¶¶ 116-118.)
[1.c] by adding a mutation to said genomic gene to eliminate the α-1,6-fucosyltranferase 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 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 at 7:15–18 (emphasis added).) "Our data suggests a possible involvement of core fucosylation of IgG in NK cell-mediated ADCC." (Ex. 1004 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 at 1122 (emphasis added).)

Claim Language	Evidence & Corresponding Disclosure
	(*See also* Ex. 1007 at ¶¶ 116-118.)
[1.d] wherein said mammalian host cell is selected from the group consisting of a CHO cell, a NSO cell, an SP2/0 cell, and a YB2/0 cell.	"***Mammalian cells are the preferred hosts for production of therapeutic glycoproteins***, due to their capability to glycosylate proteins in the most compatible form for human application." (Ex. 1004 at 2:4–6 (emphasis added).) "More specifically, the present invention is directed to a ***method for producing altered glycoforms of proteins having improved therapeutic values, e.g., an antibody*** which has an enhanced antibody dependent cellular cytotoxicity (ADCC), ***in a host cell.*** The invention provides ***host cells*** which harbor a nucleic acid encoding the protein of interest, e.g., an antibody, ***and at least one*** nucleic acid encoding a glycoprotein-modifying ***glycosyl transferase***." (Ex. 1004 at 3:6–11 (emphasis added).) "Furthermore, the present invention provides alternative glycoforms of proteins having improved therapeutic properties. ***The proteins of the invention include antibodies with an enhanced antibody-dependent cellular cytotoxicity (ADCC), which have been generated using the disclosed methods and host cells***." (Ex. 1004 at 3:17-20 (emphasis added); *see also* Ex. 1004 at 8:24-28.) "***Host cells include cultured cells, e.g., mammalian cultured cells***, such as ***CHO cells***, BHK cells, ***NSO cells***, ***SP2/0 cells***, or hybridoma cells, yeast cells, and insect cells, to name only few, but also cells comprised within a transgenic animal or cultured tissue." (Ex. 1004 at 7:31–8:1 (emphasis added).) "***Any type of cultured cell line can be used as background to engineer the host cell lines of the present invention***." (Ex. 1004 at 15:23-24 (emphasis

Claim Language	Evidence & Corresponding Disclosure
	added).) (*See also* Ex. 1007 at ¶¶ 119-122.)

For the foregoing reasons, claim 1 of the ’232 patent is obvious over *Rothman*, *Umaña*, *Malý*, and the common knowledge.

2.) Dependent claims 2-5 are obvious over *Rothman*, *Umaña*, *Malý*, and the Common Knowledge.

Dependent Claims 2–5 of the ’232 patent identify particular mammalian cell lines, all of which were well known in the prior art. As Professor Van Ness explains, the source of cells was not a restriction in gene modification as of the alleged Priority Date of the ’232 patent, and various routine technologies existed to transfect virtually any DNA sequence into a variety of target cells. (Ex. 1007 at ¶¶ 25, 123-125.) A POSA was only limited by their ability to maintain and grow particular cells of interest in laboratory cultures. (*Id*.) *Umaña* confirms the state of the art:

> Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. In addition to giving suitable glycosylation patterns, these cells allow consistent generation of genetically stable, highly productive clonal cell lines. They can be cultured to high densities in simple bioreactors using serum-free media, and permit the development of safe and reproducible bioprocesses. ***Other commonly used animal cells***

include baby hamster kidney (BHK) cells, NSO- and SP2/0-mouse myeloma cells.

(Ex. 1004 at 2:10-16 (emphasis added).) Indeed, *Umaña* is clear that "[a]ny type of cultured cell line can be used as background to engineer the host cell lines of [*Umaña's*] invention." (Ex. 1004 at 15:23-24.) As of the alleged Priority Date of the '232 patent, mammalian cell targets of genetic engineering routinely included CHO cells, NSO cells, SP2/0 cells, YB2/0 cells, among many others. (Ex. 1007 at ¶¶ 25, 123-125; *see also* Ex. 1006.) Thus, a POSA would find each of claims 2-5 obvious over *Rothman*, *Umaña*, *Malý*, and the common knowledge. (Ex. 1007 at ¶¶ 25, 123-125; *see also* Ex. 1026 at ¶¶ 99-101.) Set forth below is a claim chart that identifies the evidence and portions of *Rothman* and *Umaña* that correspond to dependent claims 2-5.

Claim 2	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a CHO cell.	"Among mammalian cells, Chinese hamster ovary ***(CHO) cells have been most commonly used during the last two decades***. . . . Other commonly used animal cells include baby hamster kidney (BHK) cells, NSO- and SP2/0-mouse myeloma cells." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 3	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a NSO cell.	"Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. . . . ***Other commonly used animal cells include*** baby hamster kidney (BHK) cells, ***NSO-*** and SP2/0-mouse myeloma cells." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 4	Evidence & Corresponding Disclosure
The isolated host cell of [claim 1], wherein said mammalian host cell is a SP2/0 cell.	"Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. . . . ***Other commonly used animal cells include*** baby hamster kidney (BHK) cells, NSO- and ***SP2/0-mouse myeloma cells***." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 5	Evidence & Corresponding Disclosure
The isolated host cell of [claim 1], wherein said mammalian host cell is a YB2/0 cell.	"***Host cells include cultured cells, e.g., mammalian cultured cells***[.]" (Ex. 1004 at 7:31–8:1 (emphasis added).) "***Any type of cultured cell line can be used as background to engineer the host cell lines of the present invention***." (Ex. 1004 at 15:23-24 (emphasis added).) *As of the alleged Priority Date of the '232 patent, mammalian cell targets of genetic engineering routinely included CHO cells, NSO cells, SP2/0 cells, YB2/0 cells, among many others.* (Ex. 1007 at ¶¶ 124-125.)

For the foregoing reasons, claims 2-5 the '232 patent are obvious over *Rothman, Umaña*, *Malý*, and the common knowledge.

D.) Ground 4: *Harris* in view of *Umaña, Malý*, and the Common Knowledge Renders Claims 1-5 Obvious

Claims 1-5 of the '232 patent are obvious over *Harris* in view of *Umaña, Malý*, and the common knowledge of a POSA. (*See* Ex. 1026 at ¶¶ 102-118; Ex. 1007 at ¶¶ 126-148.) *Umaña* teaches the creation of mammalian host cells with modified sugar-adding genes (including "knock-outs") to create sugar-modified antibodies with more efficient ADCC. *Harris* teaches the correlation between fucose and antibody binding, of which ADCC is a function:

> ***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 at 1592 (emphasis added).) In other words, *Harris* teaches the sole alleged point of novelty of the '232 patent — targeting the α1,6-fucosyltransferase gene for "knock-out, resulting in no α1,6-fucosyltransferase activity for adding fucose to the antibody sugar chain.

Given the teachings of *Harris*, a POSA would be motivated to obtain host cells that have no α1,6-fucosyltransferase activity. (*See* Ex. 1026 at ¶¶ 21-36, 105-118; Ex. 1007 at ¶ 129.) A POSA would achieve this result by "knocking-out" the gene for the enzyme that adds the fucose to the sugar chain—α(1,6)-fucosyltransferase. (Ex. 1007 at ¶¶ 32-34, 39-42, 129-145.) The necessary steps for creating such a host cell (in a variety of target cells) were in the common knowledge. (*Id*.) As Patent Owner admitted during prosecution of the '232 patent's parent application, the state of the art was "quite advanced." *See supra* Sections II, III. Indeed, *Malý* already accomplished a knockout of the gene for α(1,3)-fucosyltransferase in mouse embryos (Ex. 1005 at 644.) ("Targeted Disruption of the Mouse Fuc-TVII Gene . . . approximately 26% of the progeny were Fuc-TVII (-/-)"). The "knock-out" performed by *Malý* further demonstrates the routine nature

of completing the claimed "knock-out" of α1,6-fucosyltransferase in CHO cells as of the alleged Priority Date, and this success would have only emboldened a POSA to pursue "knock-out" of α-1,6-fucosyltransferase. (*See* Ex. 1007 at ¶¶ 126-145.)

1.) Independent claim 1 is obvious over *Harris, Umaña, Malý*, and the Common Knowledge.

With the above as a backdrop, claim 1 of the '232 patent is obvious over *Harris*, *Umaña*, *Malý*, and the common knowledge. As set forth in the below claim chart, all limitations of claim 1 are taught by *Harris*, *Umaña*, and *Malý*. Given *Harris'* teaching regarding the link between removal of fucose and improved ADCC, a POSA as of the alleged Priority Date of the '232 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* Ex. 1026 at ¶¶ 105-115; Ex. 1007 at ¶¶ 129-145.) 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.*)

Claim Language	**Evidence & Corresponding Disclosure**
[1.a] An isolated mammalian host cell which has no α-1,6-fucosyltransferase activity for adding fucose to N-acetylglucosamine of a	"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 at 3:9–11 (emphasis added).)

Claim Language	Evidence & Corresponding Disclosure
reducing terminus of N-glycoside-linked sugar chains	"***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 at 15:20–22 (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 at 1592 (emphasis added).) "Southern blot analysis identified embryonic stem (ES) **cell transfectants** containing homologous integration . . . approximately 26% of the progeny **were Fuc-TVII (-/-)**." (Ex. 1005 at 644.)
[1.b] by deleting a genomic gene encoding α-1,6-fucosyltransferase or	"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 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 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 at 1592 (emphasis added).) (*See also* Ex. 1007 at ¶¶ 139-141.)

Claim Language	Evidence & Corresponding Disclosure
[1.c] by adding a mutation to said genomic gene to reduce or eliminate the α-1,6-fucosyltranferase 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 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 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 at 1592 (emphasis added).) (*See also* Ex. 1007 at ¶¶ 139-141.)
[1.d] wherein said mammalian host cell is selected from the group consisting of a CHO cell, a NSO cell, an SP2/0 cell, and a YB2/0 cell.	"***Mammalian cells are the preferred hosts for production of therapeutic glycoproteins***, due to their capability to glycosylate proteins in the most compatible form for human application." (Ex. 1004 at 2:4–6 (emphasis added).) "More specifically, the present invention is directed to a ***method for producing altered glycoforms of proteins having improved therapeutic values, e.g., an antibody*** which has an enhanced antibody dependent cellular cytotoxicity (ADCC), ***in a host cell.*** The invention provides ***host cells*** which harbor a nucleic acid encoding the protein of interest, e.g., an antibody, ***and at least one*** nucleic acid encoding a glycoprotein-modifying ***glycosyl transferase***." (Ex. 1004 at 3:6–11 (emphasis added).) "Furthermore, the present invention provides

Claim Language	Evidence & Corresponding Disclosure
	alternative glycoforms of proteins having improved therapeutic properties. ***The proteins of the invention include antibodies with an enhanced antibody-dependent cellular cytotoxicity (ADCC), which have been generated using the disclosed methods and host cells***." (Ex. 1004 at 3:17-20 (emphasis added); *see also* Ex. 1004 at 8:24-28.) "***Host cells include cultured cells, e.g., mammalian cultured cells***, such as ***CHO cells***, BHK cells, ***NSO cells***, ***SP2/0 cells***, or hybridoma cells, yeast cells, and insect cells, to name only few, but also cells comprised within a transgenic animal or cultured tissue." (Ex. 1004 at 7:31–8:1 (emphasis added).) "***Any type of cultured cell line can be used as background to engineer the host cell lines of the present invention***." (Ex. 1004 at 15:23-24 (emphasis added).) (*See also* Ex. 1007 at ¶¶ 142-145.)

For the foregoing reasons, claim 1 of the '232 patent is obvious over *Harris*, *Umaña*, *Malý*, and the common knowledge.

2.) Dependent claims 2-5 are obvious over *Harris*, *Umaña*, *Malý*, and the Common Knowledge.

Dependent Claims 2–5 of the '232 patent identify particular mammalian cell lines, all of which were well known in the prior art. As Professor Van Ness explains, the source of cells was not a restriction in gene modification as of the alleged Priority Date of the '232 patent, and various routine technologies existed to transfect virtually any DNA sequence into a variety of target cells. (Ex. 1007 at ¶¶

25, 146-148.) A POSA was only limited by their ability to maintain and grow particular cells of interest in laboratory cultures. (*Id*.) *Umaña* confirms the state of the art:

> Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. In addition to giving suitable glycosylation patterns, these cells allow consistent generation of genetically stable, highly productive clonal cell lines. They can be cultured to high densities in simple bioreactors using serum-free media, and permit the development of safe and reproducible bioprocesses. ***Other commonly used animal cells include baby hamster kidney (BHK) cells, NSO- and SP2/0-mouse myeloma cells***.

(Ex. 1004 at 2:10-16 (emphasis added).) Indeed, *Umaña* is clear that "[a]ny type of cultured cell line can be used as background to engineer the host cell lines of [*Umaña's*] invention." (Ex. 1004 at 15:23-24.) As of the alleged Priority Date of the '232 patent, mammalian cell targets of genetic engineering routinely included CHO cells, NSO cells, SP2/0 cells, YB2/0 cells, among many others. (Ex. 1007 at ¶¶ 25, 146-148; *see also* Ex. 1006.) Thus, a POSA would find each of claims 2-5 obvious over *Rothman*, *Umaña*, *Malý*, and the common knowledge. (Ex. 1007 at ¶¶ 25, 146-148; *see also* Ex. 1026 at ¶¶ 116-118.) Set forth below is a claim chart that identifies the evidence and portions of *Harris* and *Umaña* that correspond to dependent claims 2-5.

Claim 2	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a CHO cell.	"Among mammalian cells, Chinese hamster ovary ***(CHO) cells have been most commonly used during the last two decades***. . . . Other commonly used animal cells include baby hamster kidney (BHK) cells, NSO- and SP2/0-mouse myeloma cells." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 3	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a NSO cell.	"Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. . . . ***Other commonly used animal cells include*** baby hamster kidney (BHK) cells, ***NSO-*** and SP2/0-mouse myeloma cells." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 4	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a SP2/0 cell.	"Among mammalian cells, Chinese hamster ovary (CHO) cells have been most commonly used during the last two decades. . . . ***Other commonly used animal cells include*** baby hamster kidney (BHK) cells, NSO- and ***SP2/0-mouse myeloma cells***." (Ex. 1004 at 2:10–16 (emphasis added).)

Claim 5	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a YB2/0 cell.	"***Host cells include cultured cells, e.g., mammalian cultured cells***[.]" (Ex. 1004 at 7:31–8:1 (emphasis added).) "***Any type of cultured cell line can be used as background to engineer the host cell lines of the present invention***." (Ex. 1004 at 15:23-24 (emphasis added).) *As of the alleged Priority Date of the '232 patent, mammalian cell targets of genetic engineering routinely included CHO cells, NSO cells, SP2/0 cells, YB2/0 cells, among many others.* (Ex. 1007 at ¶¶ 147-148.)

For the foregoing reasons, claims 2-5 the ’232 patent are obvious over *Harris, Umaña*, *Malý*, and the common knowledge.

E.) Ground 5: *Rothman* in view of *Umaña, Gao,* and the Common Knowledge Renders Dependent Claim 5 Obvious

Dependent claim 5 of the ’232 patent identifies a particular mammalian cell line, a YB2/0 cell line. As Professor Van Ness explains, the source of cells was not a restriction in gene modification as of the alleged Priority Date of the ’232 patent, and various routine technologies existed to transfect virtually any DNA sequence into a variety of target cells. (Ex. 1007 at ¶¶ 25, 149-154.) Accordingly, a POSA would have found it obvious and further would have been motivated (based upon their specific research needs) to create the claimed host cell in a YB2/0 cell. (Ex. 1007 at ¶¶ 25, 149-154; Ex. 1026 at ¶¶ 119-124.)

Umaña confirms the state of the art, and expressly teaches that “[a]ny type of cultured cell line can be used as background to engineer the host cell lines of [*Umaña’s*] invention.” (Ex. 1004 at 15:23-24.) Indeed, as of the alleged Priority Date of the ’232 patent, mammalian cell targets of genetic engineering routinely included YB2/0 cells, among many others. (Ex. 1007 at ¶¶ 25, 149-154; Ex. 1026 at ¶¶ 119-124; *see also* Ex. 1006.) *Gao*, for instance, explicitly described the “[c]haracterization of YB2/0 cell line by counterflow centrifugation elutriation” in 1992. (Ex. 1006 at Title.) Set forth below is a claim chart that identifies the evidence and portions of *Rothman, Umaña,* and *Gao* that corresponds to claim 5.

Claim 5	Evidence & Corresponding Disclosure
The isolated host cell of [claim 1], wherein said mammalian host cell is a YB2/0 cell.	"*Characterization of **YB2/0 cell line** by counterflow centrifugation elutriation*[.]" (Ex. 1006 at Title (emphasis added).) "The non-secreting rat myeloma clone ***YB 2/0 is a highly efficient fusion partner for the production of hybridomas***. ***YB 2/0*** was initially derived from the hybrid myeloma YB 2/3 HL cell line after cloning in soft agar multiple times and selecting for the absence of immunoglobulin secretion. ***The YB2/0 cell line*** and its derivatives, moreover, can be propagated in (LOU X AO)F1 hybrid rats, ***making it a useful, model for the study of neoplasms of the immune system***." (Ex. 1006 at 435 (emphasis added); *see also* Ex. 1007 at ¶¶ 25, 149-154.)

For the foregoing reasons, claim 5 of the '232 patent is obvious over *Rothman, Umaña*, *Gao*, and the common knowledge.

F.) Ground 6: *Harris* in view of *Umaña, Gao,* and the Common Knowledge Renders Dependent Claim 5 Obvious

Dependent claim 5 of the '232 patent identifies a particular mammalian cell line, a YB2/0 cell line. As Professor Van Ness explains, the source of cells was not a restriction in gene modification as of the alleged Priority Date of the '232 patent, and various routine technologies existed to transfect virtually any DNA sequence into a variety of target cells. (Ex. 1007 at ¶¶ 25, 155-160.) Accordingly, a POSA would have found it obvious and further would have been motivated (based upon their specific research needs) to create the claimed host cell in a YB2/0 cell. (Ex. 1007 at ¶¶ 25, 155-160; Ex. 1026 at ¶¶ 125-130.)

Umaña confirms the state of the art, and expressly teaches that "[a]ny type of cultured cell line can be used as background to engineer the host cell lines of [*Umaña's*] invention." (Ex. 1004 at 15:23-24.) Indeed, as of the alleged Priority Date of the '232 patent, mammalian cell targets of genetic engineering routinely included YB2/0 cells, among many others. (Ex. 1007 at ¶¶ 25, 155-160; Ex. 1026 at ¶¶ 125-130; *see also* Ex. 1006.) *Gao*, for instance, explicitly described the "[c]haracterization of YB2/0 cell line by counterflow centrifugation elutriation" in 1992. (Ex. 1006 at Title.) Set forth below is a claim chart that identifies the evidence and portions of *Rothman, Umaña,* and *Gao* that corresponds to claim 5.

Claim 5	**Evidence & Corresponding Disclosure**
The isolated host cell of [claim 1], wherein said mammalian host cell is a YB2/0 cell.	"*Characterization of **YB2/0 cell line** by counterflow centrifugation elutriation*[.]" (Ex. 1006 at Title.) "The non-secreting rat myeloma clone ***YB 2/0 is a highly efficient fusion partner for the production of hybridomas***. ***YB 2/0*** was initially derived from the hybrid myeloma YB 2/3 HL cell line after cloning in soft agar multiple times and selecting for the absence of immunoglobulin secretion. ***The YB2/0 cell line*** and its derivatives, moreover, can be propagated in (LOU X AO)F1 hybrid rats, ***making it a useful, model for the study of neoplasms of the immune system***." (Ex. 1006 at 435 (emphasis added); *see also* Ex. 1007 at ¶¶ 25, 155-160.)

For the foregoing reasons, claim 5 of the '232 patent is obvious over *Harris, Umaña*, *Gao*, and the common knowledge.

VIII. SECONDARY CONSIDERATIONS DO NOT REBUT THE STRONG *PRIMA FACIE* CASE OF OBVIOUSNESS

Secondary considerations—such as unexpected results, skepticism by experts, and commercial success—may be used to give light to the circumstances surrounding the origin of the subject matter sought to be patented, and may be relevant in determining obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1 (1966); *see also Stratoflex, Inc., v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983). But where the three primary factors of the obviousness inquiry—(1) the scope and content of the art when the invention was made; (2) the differences between that art and the claim(s) at issue and (3) the level of ordinary skill in the pertinent art when the invention was made—are strong, these factors are enough to overcome any secondary considerations favoring obviousness. *Rothman v. Target Corp.*, 556 F.3d 1310 (Fed. Cir. 2009); *Leapfrog Enterprises Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). Such is the case here: the strong *prima facie* showing of obviousness is sufficient to overcome any secondary considerations evidence. Still, should the Board consider secondary considerations, none weighs in favor of non-obviousness.

A.) No Unexpected Results

First, the record shows no allegedly unexpected results (e.g., antibody effector function or ADCC by removal of fucose) as against the closest prior art, *i.e., Rothman*, *Harris*, and *Umaña*. *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir.

1984) ("When an article is said to achieve unexpected (i.e. superior) results, those results must logically be shown superior compared to the results achieved with other articles. Moreover, an applicant relying on comparative tests to rebut a *prima facie* case of obviousness must compare his claimed invention to the closest prior art."). There is no such comparison here against *Rothman, Harris,* and *Umaña*, with their mammalian host cells producing antibodies—including "knock-outs" of glycosyltransferases, which by definition include α(1,6)-fucosyltransferase—with improved effector function. (*See* Ex. 1007 at ¶¶ 161-162; Ex. 1026 at ¶¶ 131-132.)

Second, unexpected results are only relevant if a significant aspect of the invention is unexpected. *See In re Eli Lilly & Co.*, 902 F.2d 943, 948 (Fed. Cir. 2008) (rejecting evidence of unexpected results when inventor had "not claim[ed] a narrow improvement limited to details not shown in the prior art ... not shown unexpected superiority over the property in the prior art ... [and] not shown that a significant aspect of his claimed invention is unexpected in light of the prior art"); *In re Nolan*, 553 F.2d 1261, 1267 (C.C.P.A 1977) (holding evidence of unexpected results unpersuasive when the prior art showed that results for the invention's "most significant improvement" were expected). Here—in light of *Rothman* or *Harris* and *Umaña*—the POSA would precisely expect antibody function modification with removal of fucose. (*See* Ex. 1007 at ¶¶ 161-162; Ex. 1026 at ¶¶ 14-47, 131-132.)

B.) No Skepticism by Experts

The prior art—*Rothman* or *Harris*—give every reason to expect that a knockout cell for fucosyltransferase would produce an improved antibody. And the Patent Owner itself said that the enabling state of the art was "quite advanced." The record does not—and would not—show skepticism by experts. Experts, rather, would expect the improved antibody effector function with 6-position fucose removed. (*See* Ex. 1007 at ¶¶ 170, 172; Ex. 1026 at ¶¶ 155-157.)

C.) No Commercial Success

The record does not establish commercial success due to the '232 patent. Patent Owner would need to show that any commercial success was not caused by economic or commercial factors unrelated to the technical quality of the patented subject matter. *See Sjolund v. Musland*, 847 F.2d 1573, 1582, (Fed. Cir. 1988) ("Nor could the jury, from the bare evidence of units sold and gross receipts, draw the inference that the popularity of the [sold units] was due to the merits of the invention."). To date, there is but a single example of a commercialized product allegedly using the '232 patent.

Nor is there any nexus. The claims of the '232 patent require there to be ***no*** fucose bound to the Fc sugar chain on the antibody: "wherein the sugar chains do not contain fucose bound to the 6-position…" Indeed, Patent Owner amended the claims in the '232 patent parent application to exclude any level of fucose in

response to the Examiner's non-enablement rejection for merely decreased amounts of fucosylation:

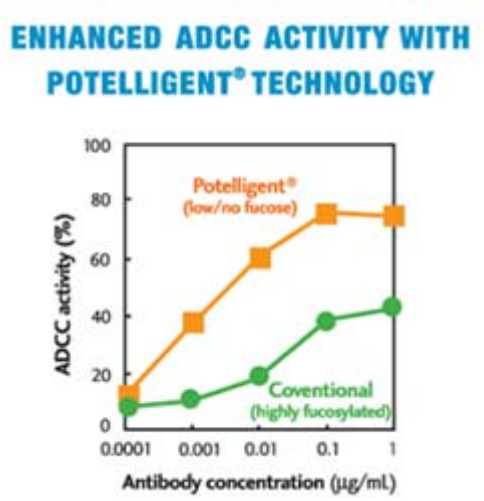
> It is maintained that Applicant still has not provided an enabling disclosure based on even one single enzyme mutation that decreases the activity of such enzyme to the proper amount, in CHO cells and thereby allows such cells to produce the claimed characteristic [some-fucose] glycosylations (e.g., Official Action of 13 February 2004, p. 7, first paragraph, "... that produces any decrease in such enzyme [activity] . . ."). Applicant has only demonstrated the ability to completely remove activity in a reasonably predictable manner.

(Ex. 1036 at Nov. 3, 2004 final office action at 11.) In response, the patentee filed an Amendment under 37 C.F.R. § 1.116, which cancelled the previously pending claims. The first of the new claims inserted a no-fucose limitation; all decreased-fucose limitations were removed:

> 69. (New) 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 antibody molecule comprising a Fc region comprising complex N-glycoside.
>
> linked sugar chains bound to the Fe region, said sugar chains comprising a reducing end which contains an N-acetylglucosamine, ***wherein the sugar chains do not contain fucose*** bound to N-acetylglucosamine in the reducing end of the sugar chains.

(Ex. 1036 at Dec. 17, 2004 Amend. at 2 (emphasis added).) And the claims in the '232 patent are clear about exclusion of fucose: "wherein the sugar chains do not contain fucose bound to the 6-position…" (Ex. 1001 at Cl. 1.)

But, as the Patent Owner's website admits, POTELLIGENT®, in contrast to "conventional highly fucosylated" antibodies, includes "low" levels of fucose on the antibody sugar chains:



Accordingly, there is no nexus between the invention as claimed and the commercial embodiment that would weigh in favor of non-obviousness. Ultimately, even were the Board somehow to find commercial success and nexus, the '232 patent would still be invalid as obvious. Where, as here, there's a strong case of *prima facie* obviousness, the Board has found obviousness despite a demonstration of commercial success and nexus: "In the alternative, Patent Owner's evidence of commercial success does not outweigh the strong showing of

obviousness made out by Petitioner in view of Kanebo." *Conopco, Inc. v. The Procter & Gamble Company*, No. IPR2013-00505, Paper No. 69 (P.T.A.B. Feb. 10, 2015) (citing *Sud-Chemie, Inc. v. Multisorb Techs., Inc.*, 554 F.3d 1001, 1009 (Fed. Cir. 2009) ("evidence of unexpected results and other secondary considerations will not necessarily overcome a strong prima facie showing of obviousness")). In sum, any showing of commercial success and nexus cannot overcome the strong showing of obviousness.

D.) No Failure of Others

The record shows no evidence of failure of others to obtain cells producing the improved, no-fucose, antibodies. Rather, the record—including the Patent Owner's own admissions during prosecution—show that it would have been routine to obtain such cells once the no-fucose/improved antibody correlation (*Rothman* or *Harris*) was appreciated.

E.) No Praise by Others

Patent Owner here may point to some awards that the Patent Owner/Plaintiff in the related judicial action set forth in the complaint:

> The inventions underlying the Patents-in-Suit form the basis of the Plaintiffs' award-winning POTELLIGENT® Technology, which applies an "intelligent" approach to creating more potent antibodies. Plaintiffs' proprietary FUT8 knockout CHO cell line produces 100% fucose-free antibodies that have markedly higher ADCC than their fucosylated counterparts. POTELLIGENT® Technology, for which

> KHK employees received Japan Bioindustry Association's Kei Arima Memorial Award in 2005 and the Okochi Memorial Technology Prize in 2016, has been recognized as the global standard technology to enhance ADCC in therapeutic antibodies and has led to the development of antibodies that themselves have received commendation from government and industry bodies. BioWa possesses an exclusive worldwide license to POTELLIGENT® Technology.[3]

These citations do not support the bare attorney allegation that the POTELLIGENT® Technology is a "recognized global standard," or indicate what criteria were applied to have Japanese national organizations award a Japanese company the cited awards. But far more importantly, it is apparent that the POTELLIGENT® Technology is ***not*** the same as what is claimed in the '232 patent claims. The POTELLIGENT® Technology—contrary to the allegations in the above-cited passage—is not limited to "knockout CHO cell line [that] produce 100% fucose-free antibodies." As shown on its own website, discussed *supra* in connection with the lack of commercial success, POTELLIGENT® contains fucose. Accordingly, even if the cited awards were relevant for POTELLIGENT® Technology, which includes low amounts of fucose, they are not relevant for the '232 patent claims, in which the subject sugar chains have no fucose.

[3] Complaint at ¶ 25, 5:16-cv-05993 (N.D. Cal. Oct. 17, 2016).

IX. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A.) Real Party-in Interest

Each Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)) is: Aragen Bioscience, Inc.; Transposagen Biopharmaceuticals, Inc.; GVK Biosciences, Private Limited; and GVK Davix Technologies Private Limited.

B.) Related Matters

Related Matters (37 C.F.R. § 42.8(b)(2)) are: Judicial matters: *Kyowa Hakko Kirin Co., Ltd. and BioWa, Inc. v. Aragen Bioscience, Inc. and Transposagen Biopharmaceuticals, Inc.*, Case No. 3-16-cv-05993-JD (N.D. Cal.); Administrative matters: *Inter Partes* Reviews for related U.S. Pats. Nos. 7,425,446 and 6,946,292, which are being concurrently filed.

C.) Lead and Backup Counsel, and Service Information

Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)):

Lead Counsel	Back-up Counsel
Bryan J. Vogel (Reg. No. 44,389) ROBINS KAPLAN LLP 399 Park Avenue, Suite 3600 New York, NY 10022 212.980.7400 (telephone) 212.980.7499 (fax) bvogel@robinskaplan.com	Miles Finn (Reg. No. 54,098) ROBINS KAPLAN LLP 399 Park Avenue, Suite 3600 New York, NY 10022 212.980.7400 (telephone) 212.980.7499 (fax) mfinn@robinskaplan.com

Notice of Service Information (37 C.F.R. § 42.8(b)(4)): Please direct all correspondence regarding this Petition to lead counsel at the above address. Petitioners consent to service by e-mail at the e-mail addresses listed above

X. GROUNDS FOR STANDING

Petitioners certify that the ’232 patent is available for IPR and that Petitioners are not barred or estopped from requesting IPR of the ’232 patent and challenging the patent claims on the grounds identified herein.

XI. CONCLUSION

Knowing loss of fucose made a better antibody, a POSA would have been directly motivated to use routine methods to create host cells that made no-fucose antibodies to obtain the improved-ADCC antibodies that *Rothman* found and *Harris* predicted. Claims 1–5 of the ’232 patent would have been obvious over *Rothman* or *Harris* in view of *Umaña*’s host cells for producing better antibodies with modified sugar chains, in light of the common knowledge for the enabling biotechnology (including *Malý*). Petitioners have established a reasonable likelihood of prevailing on each ground. Accordingly, prompt and favorable consideration of this Petition is respectfully requested.

RESPECTFULLY SUBMITTED,

ROBINS KAPLAN LLP

Date: April 6, 2017

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Aragen Bioscience, Inc. and
Transposagen Biopharmaceuticals, Inc.

WORD COUNT CERTIFICATION

I hereby certify that this Corrected Petition complies with the word count limit, and contains 13,444 words, excluding any Mandatory Notices. I further certify that, in preparation of this Corrected Petition, I used Microsoft Word, Version 2010, and that this word processing program has been applied specifically to include all text, including headings, footnotes, and quotations in the following word count.

Dated: April 6, 2017

/ Bryan J. Vogel /

Bryan J. Vogel
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Robins Kaplan LLP
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Attorney for Petitioners

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4)(i) and 42.105(b), the undersigned certifies that on April 6, 2017, a copy of the foregoing Petition, and its transmittal letter, was served by Federal Express on Patent Owner:

KYOWA HAKKO KIRIN CO., LTD.

at the correspondence address of record for the subject patent:

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