UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENZYME CORPORATION,
Petitioner

v.

GENENTECH, INC. AND CITY OF HOPE,
Patent Owners

U.S. Patent No. 6,331,415
Appl. No. 07/205,419, filed June 10, 1988
Issued: Dec. 18, 2001

Title: Methods of Producing Immunoglobulins, Vectors and Transformed Host Cells for Use Therein

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IPR Trial No. IPR2016-00383

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,331,415

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PETITION EXHIBIT LIST

Exhibit No.	Description	Abbreviation
1001	U.S. Patent No. 6,331,415	'415 patent
1002	U.S. Patent No. 4,495,280	Salser, or the Salser patent
1003	Ochi et al., *Transfer of a Cloned Immunoglobulin Light-Chain Gene to Mutant Hybridoma Cells Restores Specific Antibody Production*, Nature, 302:340-342 (1983)	Ochi (I)
1004	Southern and Berg, *Transformation of Mammalian Cells to Antibiotic Resistance with a Bacterial Gene Under Control of the SV40 Early Region Promoter*, Journal of Molecular and Applied Genetics, 1:327-41 (1982)	Southern
1005	U.S. Patent No. 4,816,657	Cabilly I patent
1006	'415 reexamination, Ex Parte Reexamination Certificate	Reexam Cert.
1007	U.S. Patent No. 4,816,397	Boss patent
1008	Final Order After District Court Judgment, Patent Interference 102,572, Paper No. 70 (Jul. 25, 2001)	Interference Final Order
1009	'415 patent reexamination, Appeal Brief	Appeal Br.
1010	Alberts et al., *Molecular Biology of the Cell* (1983) (excerpts)	Alberts (1983)
1011	Huber, *Spatial Structure of Immunoglobulin Molecules*, Klinische Wochenschrift, 58:1217-31 (1980)	Huber

1012	National Library of Medicine, *Medical Subject Headings Tree Structures, 1984* (excerpts)	MeSH
1013	Kuby, *Immunology* (2007) (excerpts)	Kuby
1014	Malcolm et al., *Localization of Human Immunoglobulin κ Light Chain Variable Region Genes to the Short Arm of Chromosome 2 by in Situ Hybridization*, Proceedings of the National Academy of Sciences USA, 79:4957-61 (1982)	Malcolm
1015	'415 patent reexamination, Owners' Resp. dated 11/25/05	Owners' Resp. (11/25/05)
1016	'415 patent reexamination, Owners' Resp. dated 10/30/06	Owners' Resp. (10/30/06)
1017	Harris, *Expression of Eukaryotic Genes in E. Coli*, in Genetic Engineering 4, 127-185 (1983)	Harris
1018	'415 patent reexamination, Declaration of Dr. Timothy John Roy Harris under 37 C.F.R. § 1.132	Harris Decl.
1019	'415 patent reexamination, Office Action dated 2/16/07	Office Action (2/16/07)
1020	'415 patent reexamination, Owners' Resp. dated 5/21/07	Owners' Resp. (5/21/07)
1021	U.S. Patent No. 4,399,216	Axel, or the Axel patent
1022	Colaianni and Cook-Deegan, *Columbia University's Axel Patents: Technology Transfer and Implications for the Bayh-Dole Act*, The Milbank Quarterly, 87:683-715 (2009)	Colaianni

1023	Rigby and Shenk, *Paul Berg, on His 65th Birthday*, Nucleic Acids Research, 19:7041 (1991)	Rigby
1024	Rice and Baltimore, *Regulated Expression of an Immunoglobulin K Gene Introduced into a Mouse Lymphoid Cell Line*, Proceedings of the National Academy of Sciences USA, 79:7862-65 (1982)	Rice
1025	Oi et al., *Immunoglobulin Gene Expression in Transformed Lymphoid Cells*, Proceedings of the National Academy of Sciences USA, 80:825-829 (1983)	Oi
1026	Kabat et al., Sequences of Proteins of Immunological Interest (1983) (excerpt)	Kabat
1027	'415 patent reexamination, Final Office Action dated 2/25/08	Final Office Action (2/25/08)
1028	'415 patent reexamination, Owners' Resp. dated 6/6/08	Owners' Resp. (6/6/08)
1029	U.S. Patent No. 4,237,224	Cohen & Boyer patent
1030	Cline, *Research on Gene Therapy*, in Basic Biology of New Developments in Biotechnology, 77-92 (1983)	Cline
1031	Alberts et al., *Molecular Biology of the Cell* (2002) (excerpts)	Alberts (2002)
1032	Efstratiadis et al., *The Structure and Evolution of the Human β-Globin Gene Family*, Cell, 21:653-68 (1980)	Efstratiadis
1033	Rogers et al., *Sequence Analysis of Cloned cDNA Encoding Part of an Immunoglobulin Heavy Chain*, Nucleic	Rogers

	Acids Research, 6:3305-21 (1979)	
1034	Strathearn et al., *Characterization of an Immunoglobin cDNA Clone Containing the Variable and Constant Regions for the MOPC 21 Kappa Light Chain*, Nucleic Acids Research, 5:3101-11 (1978)	Strathearn
1035	Ochi et al., *Functional Immunoglobulin M Production after Transfection of Cloned Immunoglobulin Heavy and Light Chain Genes into Lymphoid Cells*, Proceedings of the National Academy of Sciences USA, 80:6351-55 (1983)	Ochi (II)
1036	Cattaneo and Neuberger, *Polymeric Immunoglobulin M is Secreted by Transfectants of Nonlymphoid Cells in the Absence of Immunoglobulin J Chain*, The EMBO Journal, 6:2753-58 (1987)	Cattaneo
1037	Daugherty et al., *Polymerase Chain Reaction Facilitates the Cloning, CDR-Grafting, and Rapid Expression of a Murine Monoclonal Antibody Directed Against the CD18 Component of Leukocyte Integrins*, Nucleic Acids Research, 19:2471-76 (1991)	Daugherty
1038	Bruynck et al., *Characterisation of a Humanised Bispecific Monoclonal Antibody for Cancer Therapy*, British Journal of Cancer, 67:436-40 (1993)	Bruynck
1039	Reichart, *Marketed Therapeutic Antibodies Compendium*, mAbs, 4:413-15 (2012)	Reichert
1040	Beidler et al., *Cloning and High Level Expression of a Chimeric Antibody with Specificity for Human Carcinoembryonic*	Beidler

	Antigen, Journal of Immunology, 141:4053-60 (1988)	
1041	Sahagan et al., A Genetically Engineered Murine/Human Chimeric Antibody Retains Specificity for Human Tumor-Associated Antigen, Journal of Immunology, 137:1066-74 (1986)	Sahagan
1042	Nishimura et al., *Recombinant Human-Mouse Chimeric Monoclonal Antibody Specific for Common Acute Lymphocytic Leukemia Antigen*, Cancer Research, 47:999-1005 (1987)	Nishimura
1043	Komori et al., *Production of Heavy-Chain Class-Switch Variants of Human Monoclonal Antibody by Recombinant DNA Technology*, Clinical & Experimental Immunology, 71:508-16 (1988)	Komori
1044	Final Decision, Patent Interference 102,572, Paper No. 57 (Jul. 6, 1998)	Interference Final Decision
1045	*MedImmune, Inc. v. Genentech, Inc.*, No. 03-02567 (C.D. Cal. Aug. 17, 2007), Expert Report of E. Fintan Walton	Walton Expert Rep.
1046	Complaint in *MedImmune v. Genentech*, No. 03-02567 (C.D. Cal.)	-
1047	Stipulation and order of dismissal in *MedImmune v. Genentech*, No. 03-02567 (C.D. Cal.)	-
1048	Complaint in *Centocor v. Genentech*, No. 08-CV-3573 (C.D. Cal.)	-
1049	Order of dismissal in *Centocor v. Genentech*, No. 08-CV-3573 (C.D. Cal.)	-

1050	Complaint in *Glaxo Group Ltd. v. Genentech*, No. 10-02764 (C.D. Cal.)	-
1051	Order of dismissal in *Glaxo Group Ltd. v. Genentech,* No. 10-02764 (C.D. Cal.)	-
1052	Complaint in *Human Genome Sciences v. Genentech*, No. 11-CV-6519 (C.D. Cal.)	-
1053	Order of dismissal in *Human Genome Sciences v. Genentech*, No. 11-CV-6519 (C.D. Cal.)	-
1054	Complaint in *Eli Lilly and ImClone Systems LLC v. Genentech*, No. 13-CV-7248 (C.D. Cal.)	-
1055	Stipulation of dismissal in *Eli Lilly and ImClone Systems LLC v. Genentech*, No. 13-CV-7248 (C.D. Cal.)	-
1056	Complaint in *Bristol-Myers Squibb v. Genentech*, No. 13-CV-5400 (C.D. Cal.)	-
1057	Stipulation of dismissal in *Bristol-Myers Squibb v. Genentech*, No. 13-CV-5400 (C.D. Cal.)	-
1058	Declaration of Margaret H. Baron, M.D., Ph.D., in Support of Genzyme's Petition for Inter Partes Review of U.S. Patent No. 6,331,415	Baron Decl.

I. INTRODUCTION

Petitioner Genzyme Corporation requests *inter partes* review of claims 1-4, 9, 11, 12, 14-20 and 33 ("the challenged claims") of U.S. Patent No. 6,331,415 (the '415 patent, Ex. 1001) in accordance with 35 U.S.C. §§ 311–19.

The '415 patent claims well-known recombinant DNA ("rDNA") techniques to genetically engineer bacteria and other cells to produce immunoglobulins by introducing into a single cell the two DNA gene sequences necessary to make the two constituent polypeptides of an immunoglobulin. The groundwork for the inventors' purported contribution to the field was laid years before the '415 patent's 1983 filing date, by renowned scientists who had conceived of and developed prior art methodologies and molecular tools to create a series of platform technologies to produce proteins in genetically engineered cells.

Certain of these prior art platform technologies were submitted to the U.S. Patent Office during the reexamination of the '415 patent, including the Axel patent (Ex. 1021). The Owners of the '415 patent were able to successfully argue the validity of the claims over the Axel patent. This is not unexpected, as the Axel patent does not contain crucial anticipatory disclosures that would be required to demonstrate the invalidity of the '415 patent claims. Those very disclosures, however, are contained in the prior art relied upon by Petitioners herein, namely

the Salser patent (Ex. 1002). For this reason, the present Petition is not simply the '415 patent reexamination redux.

According to Owners, Axel failed to disclose multiple (two or more) different genes of interest in a single genetically engineered host cell. (Axel disclosed only multiple copies of the same gene.) Such a disclosure would be

> necessary to support the Office's assertions that the Axel process specifically teaches production of intact antibodies, because only that interpretation leads to the possibility that two different polypeptides (i.e., the heavy and light chains of the immunoglobulin) would be produced by the Axel process.

Ex. 1016, Owners' Resp. (10/30/06), at 44, n. 26 (emphasis added).

The Salser patent does not suffer from the infirmities of Axel. Salser expressly discloses the introduction of "two or more" genes into a single genetically engineered mammalian cell; and it makes it clear (including by way of example) that these can be multiple different genes of interest—e.g., a "plurality of unrelated genes." Salser also teaches that immunoglobulins are among the wide variety of proteins that can be produced by the inventors' disclosed methods. Taken together, those teachings would have been understood by a person of ordinary skill in the art (POSITA) as an unambiguous instruction to introduce into a single mammalian cell the two DNA sequences needed to make an immunoglobulin. The Salser patent therefore anticipates the challenged claims or makes them obvious in

view of the prior art Ochi (I) and Southern references.

II. REQUIREMENTS FOR INTER PARTES REVIEW

A. Grounds for Standing

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '415 patent is available for *inter partes* review and that the Petitioner is not barred or estopped from requesting an *inter partes* review challenging the claims of the '415 Patent on the grounds identified in this petition.

B. Identification of Challenge

Pursuant to 37 C.F.R. § 42.104(b), Petitioner provides the following statements of the precise relief requested for each claim challenged:

Ground 1. Claims 1-4, 9, 11, 12, 15-20 and 33 are anticipated under § 102(e) by the Salser patent (Ex. 1002).

Ground 2. In the alternative to Ground 1, claims 1-4, 9, 11, 12, 15-20 and 33 are obvious under § 103 in view of Salser in combination with Ochi (I) (Ex. 1003); and claim 14 is obvious under § 103 in view of Salser plus Ochi (I).

Ground 3. In the alternative to Ground 1 with respect to claims 2, 18 and 20, these claims are obvious under § 103 in view of Salser in combination with Southern (Ex. 1004).

For ease of reference, Petitioner provides the following table setting forth each challenged claim and the corresponding ground(s) of invalidity, with the shaded boxes representing alternative bases for invalidity to Ground 1:

	Challenged Claims														
Grounds	**1**	**2**	**3**	**4**	**9**	**11**	**12**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**33**
Ground 1: Salser	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
Ground 2: Salser + Ochi (I)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ground 3: Salser + Southern		✓										✓		✓	

There is no redundancy between any of the grounds of the Petition. Ground 2 with respect to claims 1-4, 9, 11, 12, 15-20 (i.e., all of the challenged claims except claim 14) is argued in the alternative to Ground 1 should the Board find that the Salser patent's disclosure of the small genus of "globulins" would not permit a POSITA to at once envisage the species of "immunoglobulins" that is the subject of the '415 patent claims. Likewise, Ground 3 is presented as an alternative to Ground 1 should the Board find that the Salser patent does not teach the use of two separate vectors to transform a single mammalian host cell.

Pursuant to 37 C.F.R. § 42.204(b), a detailed explanation of the relief requested for each challenged claim, including where each element is found in the prior art and the relevance of the prior art reference, is provided in Section VII below. Additional explanation and support for each ground of rejection is set forth in the accompanying Declaration of Margaret H. Baron, M.D., Ph.D. (Ex. 1058).

III. OVERVIEW OF THE '415 PATENT

The application that issued on December 18, 2001, as the '415 patent was

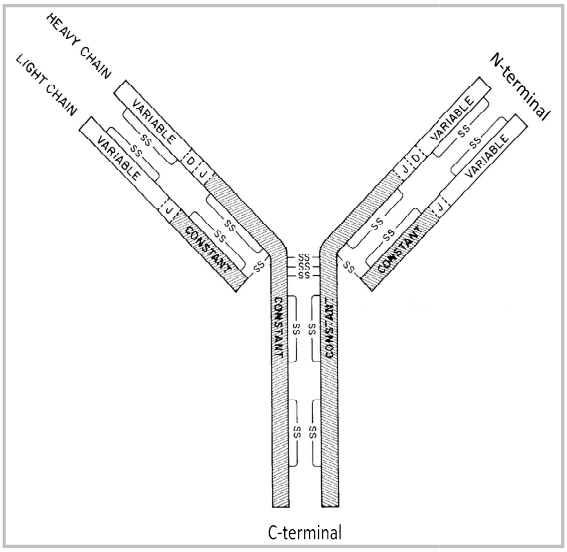
filed on June 10, 1988, and claimed the benefit of U.S. Patent Application Serial No. 06/483,457 ("the '457 application"), which was filed on April 8, 1983. The '457 application issued as U.S. Patent No. 4,816,567 (Ex. 1005, Cabilly I patent). The '415 patent is assigned to Genentech, Inc. and City of Hope ("Owners") and was the subject of two separate reexamination requests filed on May 13 and December 23, 2005; a reexamination certificate issued on May 19, 2009. Ex. 1006, Reexam Cert. The '415 patent was also involved in an interference proceeding for nearly ten years with U.S. Patent No. 4,816,397 (Ex. 1007, Boss patent). *See generally* Ex. 1008, Interference Final Order. Priority of invention was ultimately awarded to the inventors of the '415 patent, following settlement of a § 146 district court action. *Id.* at 5-6.

A. Technology Background of the '415 Patent

The '415 patent is titled "Methods of Producing Immunoglobulins, Vectors and Transformed Host Cells for Use Therein." The disclosed and claimed methods" of producing immunoglobulins referred to in the title utilize recombinant DNA ("rDNA") techniques to "genetically engineer" cells to "host" foreign DNA sequences and make the associated proteins—here, immunoglobulins—that the cells do not ordinarily make. Ex. 1001, 1:12-21, 4:52-55, 8:26-32; Ex. 1009, Reexam Appeal Br. at 23, 34; Ex. 1058, Baron Decl., ¶33. The '415 patent specification provides an overview of the claimed rDNA production of

immunoglobulins and compares it to the production of immunoglobulins that occurs in nature in certain types of B lymphocytes (and derivative cell lines, such as hybridomas[1]), which naturally contain immunoglobulin DNA sequences. Ex. 1001, 1:43-3:15, 4:6-5:39; Ex. 1058, Baron Decl., ¶33.

Immunoglobulins (depicted below, modified from Figure 1 of the '415 patent), and antibodies in particular, are proteins produced by the mammalian immune system in response to an infection by foreign cells or other "antigenic" (i.e., antibody generating) substances. Ex. 1001, 1:23-26; Ex. 1058, Baron Decl., ¶34. Antibodies specifically bind to the antigen to eliminate the foreign cell or substance from the body by recruiting other components of the immune system, such as phagocytic cells that envelop and ingest invading microorganisms. Ex. 1001, 1:26-35; Ex. 1010, Alberts (1983) at 966; Ex. 1058, Baron Decl., ¶34. Plasma cells (a type of B lymphocyte) are the primary cells of the immune system that make and secrete antibodies. Ex. 1001, 1:43-48; Ex. 1010, Alberts (1983) at 964; Ex. 1058,



[1] A hybridoma cell is a fusion of an antibody-producing B lymphocyte or spleen cell and an "immortal" cancer cell line. Ex. 1001, 1:64-2:11; Ex. 1058, Baron Decl., ¶34, n. 1.

Baron Decl., ¶34. The basic structure of immunoglobulins was "well understood" by April 1983. Ex. 1001, 3:16-19; Ex. 1058, Baron Decl., ¶35. Two identical heavy chain and two identical light chain polypeptides are connected together by disulfide bonds (–SS–) inside of plasma cells to form a tetrameric protein that is typically depicted as a Y-shaped molecule. Ex. 1001, Figure 1, 1:48-51, 3:16-59; Ex. 1058, Baron Decl., ¶35. As suggested by the name, immunoglobulins have globular shaped domains in each chain when they are properly folded as part of the tetramer. Ex. 1011, Huber at 1217; Ex. 1058, Baron Decl., ¶35.[2]

The amino acid sequence of the heavy and light chain polypeptides begins at the "N-terminal" position at the top of the Y and ends at the "C-terminal" position at the bottom of each chain. Ex. 1001, 3:42-44; Ex. 1058, Baron Decl., ¶36. At the N-terminal position is the variable region, which is the segment of the antibody

[2] The largest member of the globulin family of mammalian proteins are the "serum globulins," found in the plasma fraction of blood, which are comprised of alpha-, beta- and gamma-globulins. The most abundant and important member of the serum globulins are the gamma-globulins, more commonly referred to today as immunoglobulins. Aside from serum globulins, there were two other categories of mammalian proteins identified as globulins before April 1983 (lactoglobulins and thyroglobulins). Ex. 1012, MeSH at 256-57; Ex. 1013, Kuby at 84-85; Ex. 1058, Baron Decl., ¶61, n. 3.

responsible for specifically binding to the antigen that elicited it. Ex. 1001, 3:44-45; Ex. 1058, Baron Decl., ¶36. The variable region is linked in each chain to a constant region which extends the remaining length of the chain. Ex. 1001, 3:48-50; Ex. 1058, Baron Decl., ¶36.

The heavy and light polypeptide chains are produced in plasma cells according to the genetic instructions found in separate DNA sequences: one gene coding for the heavy chain, and one for the light chain. Ex. 1001, 1:48-51; Ex. 1014, Malcolm at 4957 (human light and heavy chain genes located on different chromosomes); Ex. 1058, Baron Decl., ¶37. Antibody-producing plasma cells "express"[3] each encoding DNA sequence to produce separate heavy and light chain polypeptides, which are joined together through disulfide bonds inside of the plasma cell ("*in vivo* assembly") into an immunoglobulin tetramer and secreted from the cell. Ex. 1001, 1:51-55, 3:33-38; Ex. 1013, Kuby at 130, 133-134; Ex. 1058, Baron Decl., ¶37.

[3] Expression of the heavy and light chain polypeptides from their respective genes is a two-step process: transcription and translation. In short, the DNA is first transcribed to a corresponding RNA molecule; then, the RNA transcript is translated into a sequence of amino acids linked by peptide bonds to form the heavy and light chain polypeptides. Ex. 1013, Kuby at 130; Ex. 1009, Reexam Appeal Br. at 35; Ex. 1058, Baron Decl., ¶37, n. 3.

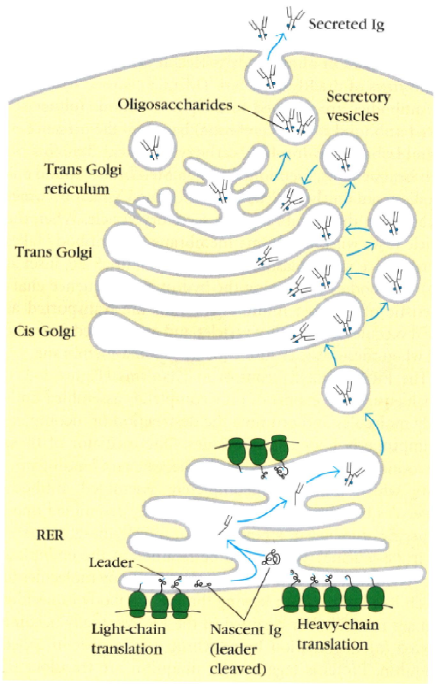


FIGURE 5-20 Synthesis, assembly, and secretion of the immunoglobulin molecule. The heavy and light chains are synthesized on separate polyribosomes (polysomes). The assembly of the chains, the formation of intrachain and interchain disulfide linkages, and the addition of carbohydrate all take place in the rough endoplasmic reticulum (RER). Vesicular transport brings the Ig to the Golgi, which it transits, departing in vesicles that fuse with the cell membrane. The main figure depicts the assembly of a secreted antibody. The inset depicts a membrane-bound antibody, which contains the carboxyl-terminal transmembrane segment. This form becomes anchored in the membrane of secretory vesicles and is retained in the cell membrane when the vesicles fuse with the cell membrane.

The process by which the heavy and light chains are assembled *in vivo* in plasma cells and secreted as an immunoglobulin tetramer is facilitated by an amino acid "leader" (or "signal") sequence attached at the N-terminal end of each chain and which is encoded by a corresponding DNA sequence that is part of the heavy and light chain genes. Ex. 1013, Kuby at 133-134; Ex. 1058, Baron Decl., ¶38. Each chain's respective leader sequence guides the chain to the endoplasmic reticulum compartment inside of the plasma cell. Ex. 1013, Kuby at 133-134; Ex. 1058, Baron Decl., ¶38. There, the leader sequences are cleaved from the heavy and light chains, and the chains are assembled stepwise into an immunoglobulin, which is then transported to the plasma cell membrane and secreted. Ex. 1013, Kuby at 134, Fig. 5-20 (above, modified); Ex. 1058, Baron Decl., ¶38.

B. The Purported Invention of the '415 Patent and the Challenged Claims

By April of 1983, the rDNA technology described in the '415 patent had already reached "sufficient sophistication" and embraced a "repertoire of techniques" and molecular tools to permit the kinds of genetic manipulations

utilized in the patent, including the isolation, introduction into and expression in cells of foreign DNA sequences. Ex. 1001, 4:6-41; Ex. 1058, Baron Decl., ¶39.[4] The challenged claims of the '415 patent are directed to various aspects and components of these techniques and tools to produce immunoglobulins by rDNA means. All of the challenged claims require two DNA sequences: the heavy chain gene and the light chain gene. The process claims also require that both genes be "independently expressed,"[5] which results in the production of the heavy and light chain polypeptides as "separate molecules." Ex. 1001, claims 1 and 33; Ex. 1015, Owners' Resp. (11/25/05), at 46; Ex.1016, Owners' Resp. (10/30/06), at 30. The process claims further require assembly of the separate heavy and light chains into an "immunoglobulin molecule," i.e., a tetramer. Ex. 1015, Owners' Resp.

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[4] By April 1983, using the prior art rDNA technologies discussed in the '415 patent, scientists had already produced a few dozen mammalian proteins in genetically engineered bacteria, as Genentech's expert in the reexamination, Dr. Timothy Harris, attested. Ex. 1017, Harris, at 163-169 (identifying insulin, interferon, growth hormone, ovalbumin, and β-globin, among other proteins); Ex. 1018, Harris Decl., ¶ 16; Ex. 1058, Baron Decl., ¶39, n. 4.

[5] This is referred to as "co-expression" in the '415 patent and during the reexamination. Ex. 1001, 12:50-51; Ex. 1019, Office Action (2/16/07), at 19.

(11/25/05), at 46. This can occur inside of host cells (*in vivo* assembly, as described above), or outside of the cells after they are lysed ("*in vitro* assembly"). Ex. 1020, Owners' Resp. (5/21/07), at 29, n. 8 ("[T]he claims of the '415 patent require, inter alia, assembly of an immunoglobulin molecule…. Dependent claims illustrate that this can also include the requirement that the immunoglobulin molecule… be produced within the cell and be secreted therefrom, or that this occur outside the cell.")

Claims 1, 15, 17 and 18 are representative of the claimed methods and compositions (bolded terms are defined below):

1. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell, comprising the steps of:

(i) **transforming** said single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain, and

(ii) independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell.

15. A **vector** comprising a first DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain and a second DNA sequence encoding at least a variable domain of an immunoglobulin light chain

wherein said first DNA sequence and said second DNA sequence are located in said vector at different insertion sites.

17. A **host cell transformed** with a vector according to claim 15.

18. A **transformed host cell** comprising at least two **vectors**, at least one of said vectors comprising a DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain and at least another one of said vectors comprising a DNA sequence encoding at least the variable domain of an immunoglobulin light chain.

Among the fundamental tools and techniques of rDNA technology claimed by the '415 patent is the process of "transforming" "host cells" through the construction of "vectors" capable of expressing the heavy and light chain DNA. The act of transformation is the process by which foreign DNA—here, the heavy and light chain genes—is introduced into a host cell. Ex. 1001, 4:21-24; Ex. 1058, Baron Decl., ¶40. Transformation may be carried out by calcium phosphate precipitation, protoplast fusion of DNA donor cells with receptor cells, or microinjection of the DNA into the cell. Ex. 1001, 10:31-37; Ex. 1058, Baron Decl., ¶40. These transformation techniques were well "in hand" at the time of filing of the '415 patent. Ex. 1001, 4:12-16; Ex. 1058, Baron Decl., ¶40.

A "vector"—referred to in the '415 patent interchangeably as an "expression vector" or "plasmid"—is typically a small, circular DNA sequence that can exist separately from a cell's genome and that is capable of replicating in the cell. Ex. 1001, 8:3-22; Ex. 1058, Baron Decl., ¶41. The vectors of the '415 patent claims

serve two functions: (1) to act as a vehicle to introduce the foreign DNA into the host cell, i.e., transformation (Ex. 1001, 12:9-30; Ex. 1058, Baron Decl., ¶41); and (2) to facilitate expression of the genes in the host cell (Ex. 1001, 4:21-29, 8:3-6; Ex. 1058, Baron Decl., ¶41). As with transformation, the techniques to construct these vectors by April 1983 were "standard" and well known among persons of ordinary skill in the art. Ex. 1001, 10:43-46, 4:12-16; Ex. 1058, Baron Decl., ¶41. Importantly, the methods employed for making the vectors "are not dependent on the DNA source, or intended host." Ex. 1001, 10:44-49; Ex. 1058, Baron Decl., ¶41.

"Host cells" are defined in the '415 patent as "cells which have been transformed with vectors constructed using recombinant DNA techniques." Ex. 1001, 8:26-28; Ex. 1058, Baron Decl., ¶42. By virtue of the transformation, the host cell can produce the antibody in amounts greater than those found in untransformed host cells, which commonly would produce the antibody in "less than detectable amounts," if at all. Ex. 1001, 8:28-32; Ex. 1058, Baron Decl., ¶42. Mammalian cells may be used as host cells. Ex. 1001, 9:63-66; Ex. 1058, Baron Decl., ¶42. The art of maintaining these cells was "well established" by April 1983. Ex. 1001, 4:42-50; Ex. 1058, Baron Decl., ¶42.

The basic process for making immunoglobulins using these tools and techniques according to the '415 patent and the challenged claims is as follows, and

is additionally depicted in Dr. Baron's declaration with figures. Heavy and light genes are isolated from a hybridoma producing the desired antibody and both chains are inserted into a single vector or the chains are inserted into separate vectors. Ex. 1001, 11:28-12:22; Ex. 1058, Baron Decl., ¶44. The single vector with both chains is then used to transform a mammalian cell. Ex. 1001, 12:23-30 ; Ex. 1058, Baron Decl., ¶44. Alternatively, the separate heavy and light chain vectors are used to "co-transform" a single cell. Ex. 1001, 12:23-30; Ex. 1058, Baron Decl., ¶44.

In either instance, the transformed and co-transformed mammalian host cells will co-express the heavy and light chain polypeptides. Ex. 1001, 12:31-33, 4:24-29; Ex. 1058, Baron Decl., ¶45. During reexamination, Owners characterized claim 9 of the '415 patent to require both the *in vivo* assembly of co-expressed heavy and light chains and their secretion from the cell as an assembled immunoglobulin (Ex. 1015, Owners' Resp. (11/25/05), at 47). Ex. 1058, Baron Decl., ¶45.[6]

[6] The inherent result of co-expressing the full-length heavy and light chain genes in a mammalian host cell that does not ordinarily make immunoglobulins (i.e., a cell other than a competent B lymphocyte or plasma cell) is the *in vivo* assembly and secretion of an immunoglobulin tetramer. *Infra* at pp. 43-44. Owners argued during the reexamination that *in vivo* assembly and secretion of chains co-expressed in a single host cell would not have been recognized by a POSITA in April 1983, and

IV. PERSON OF ORDINARY SKILL IN THE ART

A POSITA at the time of the earliest effective filing date of the '415 patent would have had a Ph.D. in molecular biology (or a related discipline, such as biochemistry) with 1 or 2 years of post-doctoral experience, or an equivalent amount of combined education and laboratory experience. The POSITA would also have experience using recombinant DNA techniques to express proteins and familiarity with protein chemistry, immunology, and antibody production, structure, and function. Ex. 1058, Baron Decl., ¶30. The person of ordinary skill in the art of the '415 patent—like all POSITAs—is "not an automaton," but rather would bring to bear the "ordinary creativity" and "common sense" of someone

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was in fact unpredictable at that time in the absence of experimental evidence (Ex. 1016, Owners' Resp. (10/30/06), at 34-36; Ex. 1020, Owners' Resp. (5/21/07), at 60), which the '415 patent did not provide. It was only in the months and years following the filing of the '415 patent that it became apparent that mammalian cells that do not ordinarily make immunoglobulins nevertheless have the correct cellular "machinery" to properly process the co-expressed heavy and light chain polypeptides to facilitate their assembly *in vivo* into a tetramer and the secretion of the assembled immunoglobulin, as depicted in the figure above at page 9, *supra*. Ex. 1058, Baron Decl., ¶45, n. 1; *see also infra* at pp. 43-44 (discussing the pertinent references published after April 1983).

knowledgeable in the field of rDNA technology as it relates to protein production, and antibodies in particular. *See KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). And, of course, the knowledge of a POSITA is specialized insofar as it is known to him or her while being outside the ken of a lay factfinder. *See Continental Can Co. USA v. Monsanto*, 948 F. 2d 1264, 1268-69 (Fed. Cir. 1991).

V. CLAIM CONSTRUCTION

The Board applies "the broadest reasonable interpretation" of patent claims in an *inter partes* petition, viewed in light of the specification. *In re Cuozzo Speed Techs.*, *LLC*, No. 2014-1301, 2015 WL 4097949, at *5-8 (Fed. Cir. Jul. 8, 2015); 37 C.F.R. § 42.100(b). Petitioner accepts, for purposes of this IPR only, that the claim terms of the '415 patent are presumed to take on the ordinary and customary meaning that they would have had to a POSITA in April 1983.

VI. THE STATE OF PRIOR ART rDNA ANTIBODY EXPRESSION IN APRIL 1983 AND OWNERS' ARGUMENTS DURING REEXAM

Before the earliest effective filing date of the '415 patent, there were numerous advances in rDNA technology known to those of ordinary skill in the art that facilitated the production of recombinant proteins, including immunoglobulin chains, in "heterologous"[7] mammalian host cell systems. Ex. 1058, Baron Decl.,

[7] "Heterologous" refers to the production of a protein in cells that do not ordinarily make that protein. Ex. 1001, 4:9-12, 33-41; Ex. 1058, Baron Decl., ¶46, n. 7.

¶46. The '415 patent itself acknowledges that by April 1983 the technology was already "sophisticated" and "include[d] a repertoire of techniques" to this end. Ex. 1001, 4:7-9.[8] Among the well-known technologies and rDNA resources readily available to a POSITA in April 1983 are those disclosed in the references discussed below: the Axel patent; the Southern publication; and the Rice, Ochi (I), and Oi publications.

A. Prior Art Platform Technologies for Expressing Foreign Genes in Mammalian Cells

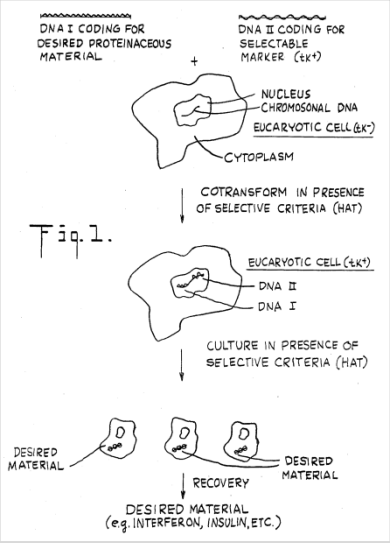
1. The Axel Patent

The Axel patent (Ex. 1021) was filed on February 25, 1980, and issued August 16, 1983, to Columbia University inventors Richard Axel, Saul Silverstein and Michael Wigler. The work of Drs. Axel, Silverstein and Wigler was important and foundational rDNA research aimed at achieving sustained and stable expression of heterologous proteins in mammalian cells; the related scientific

[8] These statements, as well as others—that techniques were "in hand," "standard" and "well established" for transformations, vector constructions and host cell maintenance (*supra* at pp. 12-13)—should be construed as admissions by the '415 patent inventors that these methodologies were known by persons of ordinary skill for purposes of establishing enablement of Petitioner's primary prior art reference, the Salser patent. *See In re Morsa*, 803 F.3d 1374, 1377-78 (Fed. Cir. 2015).

publications of the inventors were some of the most highly-cited papers of their day. Ex. 1022, Colaianni at 685-89; Ex. 1058, Baron Decl., ¶48. The methods disclosed in the Axel patent became "immensely useful in both university laboratories and pharmaceutical labs," and the Axel patent and related family members were widely licensed to the industry. Ex. 1022, Colaianni at 688, 699.

Specifically, the Axel patent discloses "the introduction and expression of genetic informational material, i.e., DNA which includes genes coding for



proteinaceous materials… into eucaryotic cells…. Such genetic intervention is commonly referred to as genetic engineering and in certain aspects involves the use of recombinant DNA technology." Ex. 1021, Axel, 1:12-21. Axel disclosed the transformation of mammalian host cells with two foreign DNA sequences. "DNA I" codes for a "desired proteinaceous material"[9] that is heterologous to the host cell. *Id.* at Figure 1 (above), 3:20-26, 8:56-62. "DNA II"

[9] A "desired proteinaceous material," or "protein of interest," is "the polypeptide that is sought to be isolated from the transformed cells." Ex. 1020, Owners' Response (5/21/07), at 49; Ex. 1058, Baron Decl., ¶ 49, n. 8.

codes for a protein that acts as a "selectable marker."[10] *Id.* at Figure 1, 3:20-26, 8:56-62. The Axel patent discloses mammalian host cell transformation using the calcium phosphate precipitation technique (among the transformation techniques disclosed in the '415 patent, discussed *supra* at p. 12), with or without the use of a plasmid/vector as a vehicle. *E.g., id.* at 7:34-42, 5:51-54; Ex. 1058, Baron Decl., ¶49. DNA I and DNA II are present in the transformed cell "physically unlinked" to each other. Ex. 1021, Axel at 1:61-67, 9:61-10:1, Figure 1. The respective proteins encoded by DNA I and II are therefore independently expressed as separate molecules. Ex. 1058, Baron Decl., ¶49. The method of the Axel patent "is particularly suited for the insertion into eucaryotic cells of DNA which codes for proteinaceous materials which are not associated with a selectable phenotype such as interferon protein, insulin, growth hormones, clotting factors, viral antigens, antibodies and certain enzymes." Ex. 1021, Axel at 3:31-36, 2:61-66.

2. The Southern Reference

The Southern reference (Ex. 1004) published in July 1982 (and one of

[10] A "selectable marker" is a protein whose expression permits the cells to be "readily identified and differentiated from those in which the introduced DNA II sequence is not expressed." It functions as "a genetic tag" that is "not itself isolated from the transformed host cell." Ex. 1015, Owners' Response (11/25/05), at 34; Ex. 1016, Owners' Resp. (10/30/06), at 42; Ex. 1058, Baron Decl., ¶ 49, n. 8.

Petitioner's refereneces underlying its grounds for rejection, *infra* at pp. 51-54) is another important and highly cited publication in the field of rDNA technology for the expression of proteins in mammalian cells. Ex. 1058, Baron Decl., ¶51. Paul Berg is considered to be the father of recombinant DNA technology (in which field he won the Nobel Prize in Chemistry in 1980) and is a towering figure in the conception and development of the field. Ex. 1023, Rigby at 7041. Titled "Transformation of Mammalian Cells to Antibiotic Resistance with a Bacterial Gene Under Control of the SV40 Early Region Promoter," Southern teaches a two-plasmid system for "cotransforming" (or "co-transducing"/"cotransfecting") a mammalian cell to express both "selectable markers" and "nonselectable genes," that is, "genes of interest" (so called because they do not confer a selective advantage to the cell.) Ex. 1004, Southern at 336-339; Ex. 1058, Baron Decl., ¶51. Southern describes two vectors derived from viral sequences: pSV2neo and pSV2gpt, each containing a different selectable marker gene (neo and gpt, respectively) that permits mammalian cells transformed with either plasmid to grow in the antibiotics G418 or MPA, respectively. Ex. 1004, Southern at 336-337, Table 3; Ex. 1058, Baron Decl., ¶51.

Southern experimentally demonstrated the important finding that the two vectors are compatible with each other when they are both co-transformed in a single mammalian cell, and that such a cell can survive "double selection" in the

presence of both antibiotics. Ex. 1004, Southern at 336-337, Table 3; Ex. 1058, Baron Decl., ¶52. Southern concludes with the observation that the system they describe was then being used in experiments in their lab to coexpress two "genes of interest," one on each vector: "[c]otransformation with nonselectable genes can be accomplished by inserting genes of interest into vector DNAs designed to express neo or gpt. The schemes used to select for the expression of gpt and neo are complementary and experiments that exploit the possibilities of a double and dominant selection are now in progress." Ex. 1004, Southern at 339, Table 3; Ex. 1058, Baron Decl., ¶52.

B. The Prior Art Taught Expression of Single Immunoglobulin Chains in Transformed Mammalian Host Cells

Employing basic rDNA tools and techniques (including those described in Axel and Southern), scientists before April 1983 had already succeeded in isolating the gene sequences encoding for both immunoglobulin heavy and light chains. Ex. 1058, Baron Decl., ¶53. A series of publications (Rice (Ex. 1024), Ochi (I) (Ex. 1003), and Oi (Ex. 1025)) reported the successful isolation of DNA for three different immunoglobulin light chains; a few dozen more heavy and light chain DNA sequences containing at least a variable region had been isolated, sequenced and published before April 1983 as well (Ex. 1026, Kabat at 246, 248, 249). Ex. 1058, Baron Decl., ¶53. Rice, Ochi (I) and Oi also report that the light chain DNA

sequences were inserted into expression vectors,[11] which were then transformed into mammalian host cells. Ex. 1024, Rice at 7862-63; Ex. 1003, Ochi (I) at 340; Ex. 1025, Oi at 825-26; Ex. 1058, Baron Decl., ¶53. The transformed cells of Rice, Ochi (I) and Oi successfully expressed the foreign light chain genes to make the respective light chain polypeptides. Ex. 1024, Rice at 7863-65; Ex. 1003, Ochi (I) at 341-42; Ex. 1025, Oi at 827; Ex. 1058, Baron Decl., ¶53.

C. Owners' Arguments During Reexamination Regarding Axel

The Axel patent and the Rice, Ochi (I) and Oi publications were the subject of a number of rejections during reexamination of the '415 patent. *E.g.,* Ex. 1027, Final Office Action (2/25/08), at 28-29; Ex. 1019, Office Action (2/16/07), at 26-42, 50-51. In response to the rejections, Owners conceded that the Axel patent—like Rice, Ochi (I) and Oi—"describe[d]… the production of one desired polypeptide (e.g., a heavy or a light immunoglobulin chain polypeptide) in one transformed host cell." Ex. 1009, Appeal Brief, at 47. But Axel, according to Owners, did not disclose the transformation of a single mammalian host cell with "more than one desired gene" or "multiple DNA sequences" encoding "different polypeptides of interest." Ex. 1009, Appeal Br. at 49; Ex. 1016, Owners' Resp.

[11] Rice and Oi used Southern's pSV2gpt vector; Ochi (I) used the pSV2neo vector. Ex. 1024, Rice at 7862; Ex. 1003, Ochi (I) at 340; Ex. 1025, Oi at 825-26; Ex. 1058, Baron Decl., ¶53, n. 10.

(10/30/06), at 44. Such a disclosure—of multiple genes, encoding different proteins in a single transformed host cell—would have been

> necessary to support the Office's assertions that the Axel process specifically teaches production of intact antibodies, because only that interpretation leads to the possibility that two different polypeptides (i.e., the heavy and light chains of the immunoglobulin) would be produced by the Axel process.

Ex. 1016, Owners' Resp. (10/30/06), at 44, n. 26 (emphasis added).

In Owners' view, the Axel patent merely reflected a so-called "prevailing mindset" in April 1983 that "only one eukaryotic polypeptide of interest should be produced in a recombinant host cell." Ex. 1028, Owners' Resp. (6/6/08), at 6, 24-27; *see also, e.g.,* Ex. 1009, Appeal Br. at 33, 46 ("conventional 'one polypeptide at a time' approach" and "prevailing 'one polypeptide in a host cell' mindset"). Owners argued that Axel's disclosure of DNA I and II did not satisfy the requirement of "more than one desired gene" because although DNA I encoded a protein of interest, DNA II encoded only a "selectable marker" protein and not a second protein "of interest." Ex. 1020, Owners Resp. (5/21/07), at 21. Moreover, the Axel patent's disclosure of "multiple" gene sequences was a reference only to copies of the same gene, as the Axel specification makes clear:

> By inserting multiple copies of genes coding for desired materials into eucaryotic cells according to either of these approaches it is possible to produce eukaryotic cells which yield desired materials in high concentrations.

> Another aspect of the invention involves processes for inserting multiple copies of genes into eucaryotic cells in order to increase the amount of gene product formed within the cell. One process for inserting a multiplicity of foreign DNA I molecules into a eukaryotic cell comprises cotransforming the cell with multiple DNA I molecules….
>
> Cotransformed eucaryotic cells which have acquired multiple copies of DNA I may then be used to produce increased amounts of the gene product for which DNA I codes in the same manner as described hereinabove.

Ex. 1021, Axel at 3:62-66; 6:44-50; 6:67-7:2; *see also* Ex. 1028, Owners Resp. (6/6/08), at 26-27; Ex. 1009, Appeal Br. at 52. At most, according to Owners, Axel disclosed no more than producing either the heavy chain or light chain (or their fragments) in a single host cell—but not both chains in single host cell. Ex. 1009, Appeal Br. at 47.

As argued by Owners, the contributions of the Axel inventors were in contrast to those of the '415 patent inventors, whose work was purported to be "the first report of a host cell that had been genetically engineered to produce <u>two different</u> desired eukaryotic polypeptides in a single host cell [and] the first report of the successful recombinant production of a functional multimeric protein having the structural complexity of an immunoglobulin." Ex. 1009, Appeal Br. at 23-24 (emphasis added).

* * * *

As discussed below in Petitioner's Grounds for Unpatentability, the

inventors of the '415 patent were hardly the first to envision expressing "two different desired eukaryotic polypeptides in a single host cell." That contribution was made at least four years earlier, in the seminal Cohen & Boyer patent (Ex. 1029) directed to rDNA methods for expressing foreign mammalian (eukaryotic) proteins in bacterial cells transformed with "one or more genes" (or "at least one foreign gene"). Ex. 1029, 5:59-65, 1:56-59, 6:43-47, claim 1; Ex. 1058, Baron Decl., ¶57. Paul Berg's laboratory suggested doing the same in transformed mammalian host cells. *Supra* at pp. 20-21. The inventors of the Salser patent (Ex. 1002, Petitioner's anticipatory prior art reference) were among those who advanced the methods of the Cohen & Boyer patent and built upon the work of others (including the Axel patent inventors and Southern) to conceive the production of multiple *different* desired mammalian polypeptides—and immunoglobulins[12] in particular—in a single mammalian host cell. Petitioner's grounds for invalidity, all of which rely on Salser, are therefore not redundant of the '415 patent reexamination proceedings concerning Axel. Simply put, as explained by Dr. Baron, who was working in the field in the relevant time period, there was no "prevailing mindset" in April 1983 that only one eukaryotic polypeptide of interest should be produced in a recombinant host cell. Ex. 1058, Baron Decl., ¶¶55-56.

[12] The Salser patent discloses the defined and limited genus of "globulins," which includes immunoglobulins. *See infra* at pp. 33-36.

VII. STATEMENT OF GROUNDS FOR THE UNPATENTABILITY OF THE CHALLENGED CLAIMS

A. Ground 1: The Salser Patent Anticipates Claims 1-4, 9, 11, 12, 15-20 and 33 Under 35 U.S.C. § 102(e)

1. Overview of the Salser Patent Disclosures

The Salser patent (Ex. 1002) was filed on March 26, 1980, and issued August 2, 1983, to inventors Winston Salser, Martin Cline and Howard Stang. Salser is prior art to the '415 patent under §102(e). The Salser patent was not cited by Owners or identified or relied upon by the PTO during prosecution or reexamination of the '415 patent.

The Salser patent reflects early work done in the field of gene replacement therapy, in which a defective gene in an animal is replaced with a competent version of the gene, thus restoring the animal's ability to make the "wild type" (correct, or non-defective) protein encoded by the gene. Ex. 1002, Salser at 1:16-28, 5:44-6:1; Ex. 1058, Baron Decl., ¶59. The "genetic deficiencies" addressed by the Salser patent "are usually either failure to produce a gene product or production of an abnormal product." Ex. 1002, Salser at 1:16-19; Ex. 1058, Baron Decl., ¶59. In these instances, the Salser patent inventors sought to provide the subject with either the "missing capability" to produce the desired protein; or, if the protein was

abnormal, the "normal capability" to do so. Ex. 1002, Salser at 1:21-22[13]; Ex. 1058, Baron Decl., ¶59. Fundamentally, the Salser inventors implemented their goal of treating genetic deficiencies through gene replacement by utilizing the very same rDNA tools and techniques required by the '415 patent claims: the "transformation" of "host cells" with two (or more) foreign genes of interest, facilitated by the use of "vectors" (or plasmids). Ex. 1058, Baron Decl., ¶59.The transformed host cell of the Salser patent is the same host cell required by the challenged claims of the '415 patent. *See infra* at pp. 36-40; Ex. 1058, Baron Decl., ¶59. In essence, Salser creates a host cell *ex vivo* to produce the proteins encoded by the foreign genes of interest introduced therein. These host cells, when returned to the subject with a genetic deficiency, produces the desired protein—in other words, Salser creates a "cell factory" to produce the missing or defective proteins. In a parallel manner, the '415 patent is also directed at creating a host cell to produce proteins coded by the foreign genes of interest. The sole conceptual difference is that Salser's cell factory is returned to a host whereas the '415 patent's cell factory remains *ex vivo*. Both host cells, however, function to produce recombinant proteins encoded by the foreign genes inserted. Ex. 1058, Baron Decl., ¶59.

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[13] *See also* Ex. 1002, Salser at 2:28-34 ("[T]reatment of genetic deficiencies… includes providing a genetic capability which the host lacks or production of a normal product where the host produces an abnormal one….")

The prior art rDNA technology for transferring foreign genes into mammalian cells "open[ed] up wide avenues in the treatment of genetic deficiencies and disease" and was the groundwork the inventors built upon in conceiving their method of modifying an animal's "genetic structure to provide for either additional genetic capabilities or reparation of a defective capability on a temporary or permanent basis." Ex. 1002, Salser at 1:6-15, 1:24-28; Ex. 1058, Baron Decl., ¶60. Specifically, the Salser patent discloses

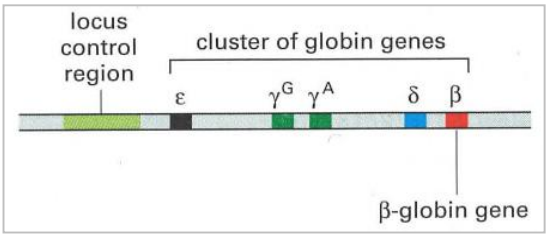
> methods and compositions… for gene transfer to intact mammals with expression of the exogenous genetic material in the host. Mammalian host cells… are transformed… with DNA capable of replication and expression in the host cell, wherein the DNA becomes incorporated into the cell. The modified cells are found to regenerate in the host with expression of the introduced DNA.

Ex. 1002, Salser, at Abstract (emphasis added); Ex. 1058, Baron Decl., ¶60. The mammalian host cells are either taken directly from the mammal or from a source that is "syngeneic" (genetically identical) with the mammal. Ex. 1002, Salser at 2:7-10; Ex. 1058, Baron Decl., ¶60.

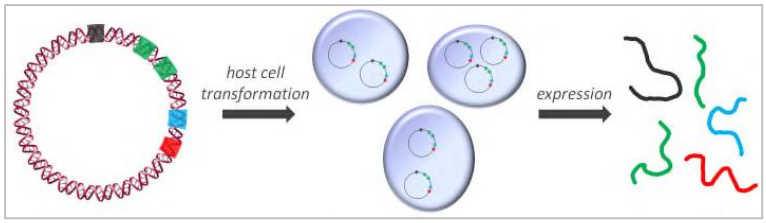
The DNA introduced into the mammalian host cell will also contain "genetic material"—including "two or more genes," "a single set of genes" or "a plurality of unrelated genes"—to provide "genetic functions… for a variety of purposes including… production of a wide variety of proteins." Ex. 1002, Salser at 2:15-18,

1:29-36, 3:46-53, 5:26-29; Ex. 1058, Baron Decl., ¶61. Among the "wide variety of proteins" that can be produced by the method disclosed in the Salser patent are "globulins" (Ex. 1002, Salser at 2:29-36), a small family of mammalian proteins that includes most prominently the immunoglobulins. *Infra* at pp. 33-36.

The Salser patent inventors specifically focused on treatments for hemoglobin-based genetic deficiencies, among them sickle cell anemia, a genetic disease caused by a mutation in the beta-globin gene, which results in a structural defect in the beta chain of the hemoglobin protein. Ex. 1002, Salser at 5:44-6:5; Ex. 1030, Cline at 88-89; Ex. 1058, Baron Decl., ¶62. The Salser patent describes treating sickle cell disease with gene replacement therapy designed to provide patients with a "structurally normal beta-globin gene." Ex. 1002, Salser at 17:23-27; Ex. 1058, Baron Decl., ¶62. The patent discloses that a "single set of genes, e.g., beta-globin gene cluster" can be transformed into a mammalian host cell using the calcium phosphate precipitation method. Ex. 1002, Salser at 5:26-29; Ex. 1058, Baron Decl., ¶62. The beta-globin gene cluster in humans is located on chromosome 11 and is comprised of five separate genes encoding five different polypeptides, all related to hemoglobin: epsilon globin, gamma-G globin, gamma-A globin, delta globin and beta globin, whose expression is under the control of a dominant regulatory element called the locus control



region. Ex. 1031, Alberts (2002) at 412, Fig 7-60 (above); Ex. 1058, Baron Decl., ¶62. Because each gene is separated by non-coding DNA (Ex. 1032, Efstratiadis at 654, Fig. 1), if the entire cluster is inserted into a vector and transformed into a mammalian host cell, the five genes will be expressed as five separate polypeptide molecules. Ex. 1058, Baron Decl., ¶62.



2. Applicable Law of Anticipation

A patent claim is anticipated if a single reference either expressly or inherently discloses every limitation of the claim. *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). "Even if a piece of prior art does not expressly disclose a limitation, it anticipates if a [POSITA] would understand the prior art to disclose the limitation and could combine the prior art description with his own knowledge to make the claimed invention." *Arthrocare Corp. v. Smith & Nephew, Inc.*, 406 F. 3d 1365, 1373-74 (Fed. Cir. 2005). For example, a POSITA may employ "common sense" or "simple logic" in considering a prior art reference to conclude that it contains a claim limitation that is not disclosed verbatim. *King Pharms. v. Eon Labs*, 616 F.3d 1267, 1276 (Fed. Cir. 2010); *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995); *see also Standard Haven Prods. v. Gencor Indus.*, 953 F.2d 1360, 1369 (Fed. Cir. 1991) ("An anticipatory reference...

need not duplicate word for word what is in the claims."); *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (anticipation not an "*ipsissimis verbis* test").

A claim limitation is inherent in a prior art reference if it is "necessarily present" in the reference. *Schering Corp. v. Geneva Pharms.*, 339 F. 3d 1373, 1377 (Fed. Cir. 2003). For example, where the "common knowledge of technologists is not recorded in the reference," such as where "technological facts are known to those in the field of the invention" but not to lay persons, *Continental Can Co. USA*, 948 F. 2d at 1268-69, the rule of inherency accommodates this common knowledge—"knowledge that judges might not know but that would be known to practitioners in the field," *Elan Pharm. v. Mayo Found.*, 304 F.3d 1221, 1229 (Fed. Cir.), *vacated on other grounds*, 314 F.3d 1299 (Fed. Cir. 2002).

Inherency can also be shown when the "natural result flowing" from an express disclosure in a prior art reference is the performance of a claimed feature that is not expressly disclosed in the reference. *Schering*, 339 F. 3d at 1379. "[W]hen the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence." *Continental Can Co. v. Monsanto*, 948 F. 2d 1264, 1268-69 (Fed. Cir. 1991). Recognition of the inherent characteristic in the prior art may be shown by evidence published after the filing date of the patent at issue because "recognition by a person of

ordinary skill in the art before the critical date . . . is not required to show anticipation by inherency." *Schering*, 339 F.3d at 1377.

When a prior art reference discloses a genus encompassing a claimed species, the species is anticipated if the genus is comprised of "a definite and limited class of compounds that enable[s] a person of ordinary skill in the art to at once envisage each member" of the genus. *Eli Lilly and Co. v. Zenith Goldline Pharms., Inc.*, 471 F. 3d 1369, 1376 (Fed. Cir. 2006); *see also In re Petering*, 301 F.2d 676, 682 (C.C.P.A. 1962) (genus comprised of "some twenty [chemical] compounds" anticipates a later-claimed species within the genus). "It is of no moment that each compound is not specifically named or shown" in the prior art publication. *Petering*, 301 F.2d at 682.

Furthermore, "[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter." *Schering*, 339 F.3d at 1380. If the suggestion in the prior art is enabling to a POSITA, that is sufficient to meet the claimed limitation and anticipate the claims. *Bristol-Myers Squibb v. Ben Venue Labs.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001). Importantly, U.S. patents and non-patent prior art publications are entitled to a presumption of enablement for all that they disclose. *Amgen v. Hoechst Marion Roussel*, 314 F.3d 1313, 1355 (Fed. Cir. 2003); *In re Antor Media Corp.*, 689 F. 3d 1282, 1287-88 (Fed. Cir. 2012).

3. The Salser Patent Anticipates Independent Claims 1, 15, 17, 18 and 33

The Salser patent anticipates independent claims 1, 15, 17, 18 and 33 of the '415 patent by disclosing each and every limitation of the claims. Petitioner sets forth immediately below a representative anticipation analysis for claim 1, broken down into three constituent sets of limitations, followed by an analysis of the remaining independent claims (15, 17, 18 and 33).

a. Independent Process Claim 1

i. "A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell…"

The Salser patent discloses a process for producing an immunoglobulin molecule in a single host cell. The Salser patent provides a method for producing a "wide variety of proteins" using rDNA technology in a transformed mammalian host cell, among which are "globulins." Ex. 1002, Salser at 2:29-36; Ex. 1058, Baron Decl., ¶63; *see also supra* at p. 29.

A POSITA considering the family of globulin proteins in April 1983 would have immediately and primarily envisioned the species of immunoglobulins within the genus of globulins for two reasons. First, a POSITA would have understood that the family of mammalian globulins of medical importance (i.e., the globulins a POSITA would have considered as potential targets for the gene replacement therapy in mammals described in Salser) was "defined and limited," numbering no

more than eight. Ex. 1058, Baron Decl., ¶64; *see Eli Lilly*, 471 F. 3d at 1376; *Petering*, 301 F.2d at 682. The Medical Subject Headings index, the controlled vocabulary for indexing articles and cataloging books and other holdings in the National Library of Medicine, identifies three distinct sub-genus members of the globulin family: lactoglobulins (lactoferrin), serum globulins, and thyroglobulin. Ex. 1012, MeSH at 256-57; Ex. 1058, Baron Decl., ¶64; *see also supra* at p. 7, n. 2. Serum globulins are further broken down into six species: immunoglobulins (gamma globulins), alpha-globulins, beta-globulins, fibronectins, macroglobulins and transcobalamins:

GLOBULINS
- LACTOGLOBULINS
  - LACTOFERRIN •
- SERUM GLOBULINS
  - ALPHA GLOBULINS
    - ALPHA 1-ANTITRYPSIN
    - ALPHA MACROGLOBULINS
    - ANTIPLASMIN
    - ANTITHROMBIN III
    - CERULOPLASMIN
    - HAPTOGLOBINS
    - OROSOMUCOID
    - PROGESTERONE BINDING GLOBULIN •
    - RETINOL BINDING PROTEINS
    - THYROXINE BINDING PROTEIN
    - TRANSCORTIN
  - BETA GLOBULINS
    - BETA 2 MICROGLOBULIN
    - BETA-THROMBOGLOBULIN •
    - BETA TRACE PROTEIN •
    - HEMOPEXIN
    - PROPERDIN
    - SEX HORMONE BINDING GLOBULIN
    - TRANSFERRIN
  - FIBRONECTINS
  - GAMMA GLOBULINS
  - IMMUNOGLOBULINS
    - IGA
      - IGA, SECRETORY
    - IGD
    - IGE
    - IGG
    - IGM
    - IMMUNOGLOBULIN FRAGMENTS
      - IMMUNOGLOBULINS, ALPHA CHAIN •
      - IMMUNOGLOBULINS, DELTA CHAIN •
      - IMMUNOGLOBULINS, EPSILON CHAIN •
      - IMMUNOGLOBULINS, FAB
      - IMMUNOGLOBULINS, FC •
      - IMMUNOGLOBULINS, FD •
      - IMMUNOGLOBULINS, GAMMA CHAIN •
      - IMMUNOGLOBULINS, HEAVY CHAIN
      - IMMUNOGLOBULINS, J CHAIN
      - IMMUNOGLOBULINS, KAPPA CHAIN •
      - IMMUNOGLOBULINS, LAMBDA CHAIN •
      - IMMUNOGLOBULINS, LIGHT CHAIN
      - IMMUNOGLOBULINS, MU CHAIN •
      - SECRETORY COMPONENT •
    - PARAPROTEINS
      - BENCE JONES PROTEIN
      - CRYOGLOBULINS
      - MYELOMA PROTEINS
      - PYROGLOBULINS •
  - MACROGLOBULINS
    - ALPHA MACROGLOBULINS
  - TRANSCOBALAMINS
- THYROGLOBULIN

Ex. 1012, MeSH at 256-57 (modified for clarity); Ex. 1058, Baron Decl., ¶64. For purposes of anticipation, a POSITA may rely on the MeSH reference as extrinsic evidence to understand the meaning of the Salser patent term "globulin." *See In re*

Baxter Travenol Labs., 952 F.2d 388, 390 (Fed. Cir. 1991) ("[E]xtrinsic evidence may be considered when it is used to explain, but not expand, the meaning of [an anticipatory] reference."); *see also Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 871-72 (Fed. Cir. 2015) (relying on extrinsic evidence (e.g., expert declaration) of the scope of a prior art genus in holding that it anticipated the claimed species); *Gnosis S.p.A. v. Merck & Cie*, IPR2013-00117, Paper 71 at 11-17 (PTAB 2014) (finding anticipation under *Petering* relying on a separate prior art reference as extrinsic evidence to establish the limited number of genus members).

Second, among the globulins identified in the Medical Subject Headings at the time, immunoglobulins were inarguably the most important of the globulins from a medical and therapeutic standpoint. Ex. 1058, Baron Decl., ¶65. Certainly immunoglobulins, and specifically antibodies, are an important and necessary component of a properly functioning immune system. Ex. 1058, Baron Decl., ¶65. And immunoglobulins were the subject of intense research and experimental focus before 1983 and remain so to this day. Ex. 1058, Baron Decl., ¶65. Dr. Salser himself published contemporaneously with the Salser patent filing his work on the cloning of immunoglobulin heavy and light chain genes. Ex. 1033, Rogers; Ex. 1034, Strathearn; Ex. 1058, Baron Decl., ¶65. The other globulin family members identified in the Medical Subject Headings index, while important in their own

right, did not attract the same kind of attention as immunoglobulins did from the medical and research community. Ex. 1058, Baron Decl., ¶65. This is reflected by their respective frequency of citation in the indexed literature from the inception of cataloging until April 1983. Ex. 1058, Baron Decl., ¶65 (comparing the number of PubMed search results for the globulin family members identified above).

Globulins therefore comprise "a definite and limited class of compounds," enabling a POSITA to "at once envisage" immunoglobulins as a member of the genus. *See Eli Lilly*, 471 F. 3d at 1376; *Petering*, 301 F.2d at 682. For this reason, Salser discloses a "process for producing an immunoglobulin" for purposes of anticipation. *See Eli Lilly*, 471 F. 3d at 1376; *Petering*, 301 F.2d at 682.

ii. "…comprising the steps of: (i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain…"

The Salser patent discloses transforming a single host cell with two DNA sequences, encoding the immunoglobulin heavy and light chains. As described in the Abstract, "mammalian host cells… are transformed or modified in vitro with DNA capable of replication and expression in the host cell, wherein the DNA becomes incorporated into the cell." Ex. 1058, Baron Decl., ¶67; *see also* Ex. 1002, Salser at 1:49-52 ("Host cells [are] treated with genetic material under conditions whereby the genetic material is introduced into the host cells and becomes capable

of replication and expression."). The process of transformation may be facilitated by using a vector or plasmid as a vehicle to introduce the exogenous DNA. Ex. 1002, Salser at 5:9-20 ("A number of ways have been developed for insertion of genetic materials into cells. Included among these techniques are viral vectors…. [and] fusion with bacterial protoplasts containing plasmid DNA."); *id.* at 13:9-30 (describing experiments transforming mouse fibroblast cells ("L cells") with "the plasmid vector pBR322"); Ex. 1058, Baron Decl., ¶67. The calcium phosphate precipitation method of transformation is also disclosed. Ex. 1002, Salser at 1:35-40; Ex. 1058, Baron Decl., ¶67. These are among the transformation techniques disclosed in the '415 patent. Ex. 1001, 10:31-37 ("If cells without formidable cell wall barriers are used as host cells, transfection is carried out by the calcium phosphate precipitation method…. However, other methods for introducing DNA into cells such as by… protoplast fusion."); Ex. 1058, Baron Decl., ¶67.

The DNA introduced into the transformed mammalian host cell will include "at least one marker which allows for selective advantage for the host cells"—a selectable marker. Ex. 1002, Salser at 1:52-56, 2:18-20; Ex. 1058, Baron Decl., ¶68. The DNA can also contain "other genetic material" to provide "genetic functions… for a variety of purposes including… production of a wide variety of proteins." Ex. 1002, Salser at 2:15-18, 1:29-36; Ex. 1058, Baron Decl., ¶68. The full complement of genetic material to be incorporated into the host cell by

transformation can therefore include "two or more genes," "a single set of genes" or "a plurality of unrelated genes" in addition to the selectable marker, and they can be "carried on a single chain, a plurality of chains, or combinations thereof." Ex. 1002, Salser at 3:46-53, 5:26-29; Ex. 1058, Baron Decl., ¶68; *see also* claim 6 (in addition to the selectable marker, the DNA introduced into the cell also "includes at least one additional gene which expresses a wild type protein" (emphasis added)) and claim 10 ("A method according to any of claims 1 or 6, wherein said host has a genetic deficiency, and said DNA includes at least one wild type gene which expresses the normal protein for said host deficiency" (emphasis added)).

These are all unmistakable references to multiple *different* genes of interest[14]—at once distinguishing the Salser patent from Axel (which contemplated only multiple copies of the same gene of interest) and demonstrating that there was no dogmatic "prevailing mindset" before April 1983 of producing only one polypeptide of interest in a host cell. Ex. 100.5, Baron Decl., ¶¶57, 68. Moreover, the Salser patent disclosure of multiple different genes of interest is the very

[14] A plurality of "unrelated" genes alone would prove the point, but the example of the beta-globin cluster as a "single set" of five different genes (*supra* at p. 30) drives it home.

teaching that Owners' argued would be "necessary" to support an assertion that a prior art reference "specifically teaches production of intact antibodies, because only that interpretation leads to the possibility that two different polypeptides (i.e., the heavy and light chains of the immunoglobulin) would be produced." *See* Ex. 1016, Owners' Resp. (10/30/06), at 44, n. 26; *supra* at 23.

Salser's disclosure of "two or more genes," "a single set of genes" or "a plurality of unrelated genes" introduced into a mammalian host cell therefore clearly accommodates the insertion into the cell of the two (heavy and light chain) DNA sequences that were known to a POSITA in 1983 to be required to make an immunoglobulin. Ex. 1058, Baron Decl., ¶69; *supra* at p. 8. This suggestion is made all the more clear by Salser's identification of globulins—which, as established above (pages 33-36), would be immediately understood by a POSITA to include immunoglobulins— as a protein that could be produced in the transformed mammalian host cells of the invention. *Id.* at ¶69. The heavy and light chain genes are certainly "two or more genes"; furthermore, they would also be considered by a POSITA to be a "single set of genes" (insofar as they encode two polypeptides that naturally associate into a single, tetrameric protein) and/or a "plurality of unrelated genes" (insofar as the heavy and light chain genes are located on different chromosomes and are therefore not physically linked or related). *Id.* at ¶69.

Whether considered as the rote application of common knowledge by a POSITA, or merely the employment of his or her common sense, it takes no more than a POSITA's ordinary creativity to understand as a matter of simple logic that producing an immunoglobulin in a single host cell transformed with a vector having "two or more genes" (or "a single set of genes" or a "plurality of unrelated genes") requires that both heavy and light chain DNA sequences be present in the single transformed host cell. *Id.* at ¶70; *see also Arthrocare Corp.*, 406 F. 3d at 1373-74 (reference anticipates in the absence of an express disclosure of a claim limitation if a POSITA "would understand the prior art to disclose the limitation and could combine the prior art description with his own knowledge to make the claimed invention"). This is how immunoglobulins are made in nature in plasma cells (*supra* at pp.8-9); the Salser patent inventors simply articulated a straightforward extension of the single chain expression work in Ochi (I), Oi and Rice (*supra* at pp. 21-22). Ex. 1058, Baron Decl., ¶70. Furthermore, the Salser patent's teaching to co-express heavy and light chains in a single host cell—from the disclosure of producing "globulins" by transforming a host cell with "two or more genes," "a single set of genes" or a "plurality of unrelated genes"—is in line with the inventors' goal of creating a gene-based treatment for subjects who cannot make, or make an incorrect version of, an immunoglobulin with therapeutic value; to produce the chains in separate cells and remove them from a common

environment where they can assemble *in vivo* into a functional (antigen-binding) immunoglobulin would completely vitiate the intended goals of the Salser invention. *Id.* at ¶70.

iii. "… and (ii) independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell."

The Salser patent discloses that the transformed single mammalian host cell described above will independently express the heavy chain and light chain DNA sequences to produce the heavy chain and light chain polypeptides as separate molecules. The Salser Abstract notes generally that the "modified cells are found to regenerate in the host with expression of the introduced DNA," and elsewhere the patent explains that the "genetic material is introduced into the host cells and becomes capable of replication and expression." Ex. 1002, Salser at 1:49-52; Ex. 1058, Baron Decl., ¶71; *see also* Ex. 1002, Salser at 1:60-62, 5:44-6:1. When a mammalian host cell is transformed with both immunoglobulin genes as described above (pages 36-40), the cell will express both of the heavy and light chain polypeptides by virtue of the particular genetic instructions present in the heavy and light chain DNA. Ex. 1058, Baron Decl., ¶71.

A POSITA would further understand without verbatim instruction in the Salser patent that "independent expression" of the heavy and light chains as

"separate molecules" would be necessary based on the identification of an immunoglobulin ("globulin," in the Salser patent) tetramer as an exemplary protein that could be produced by the Salser method.[15] *Id.* at ¶72. Were they not produced as "separate" polypeptide chains, the expressed protein would be a heavy-chain/light-chain fusion—that is, a single, continuous polypeptide consisting of both the heavy and light chain amino acid sequences. *Id.* at ¶72. Such a fusion product of expression is not disclosed in the Salser patent, nor would it be one that a POSITA in 1983 would call an immunoglobulin or that could form an immunoglobulin tetramer. *Id.* at ¶72.

A POSITA would therefore know that when producing an immunoglobulin, the heavy and light polypeptide chains must be expressed as separate molecules, as there is no other way for their assemblage to result in an immunoglobulin tetramer. *Id.* at ¶73. This could be accomplished by introducing the heavy and light chain genes into the host cell by either (1) carrying both genes on a "single [DNA] chain" that is inserted into a single vector or plasmid, or (2) carrying each gene on separate ("a plurality," i.e., two) DNA chains, which would require their insertion

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[15] Ex. 1016, Owners' Resp. (10/30/06), at 30 ("[T]he '415 patent requires that the transformed cell produce the immunoglobulin heavy and light chain polypeptides encoded by the two DNA sequences as separate molecules. This result stems from the requirement for independent expression of the introduced DNA sequences...")

into separate vectors or plasmids. Ex. 1002, Salser at 3:50-53; Ex. 1058, Baron Decl., ¶73. Either way, the two genes would necessarily have to be expressed in the same transformed host cell as separate polypeptide molecules.[16] Ex. 1058, Baron Decl., ¶73.

The expressed separate and heavy and light chain polypeptides will assemble *in vivo* to form an antibody tetramer, which is the inherent result of expressing the full length genes for each chain (including leader sequences) in a mammalian host cell. Ex. 1058, Baron Decl., ¶74; *supra* at p. 15, n. 6; *see also Schering Corp.*, 339 F. 3d at 1377-79 ("natural flowing result" of practicing the prior art can inherently anticipate, regardless of whether a POSITA would have appreciated it at the time of filing). While this was not recognized by a POSITA in April 1983 (*supra* at 15, n. 6), in publications subsequent to that date, scientists demonstrated that transformed mammalian cells that do not normally make antibodies are nevertheless able to assemble the heavy and light chains *in vivo* and

[16] The independent expression of separate proteins in a single host cell transformed with a vector containing two or more genes is exactly what the Salser patent inventors taught when they disclosed the insertion of the entire beta-globin gene cluster into a single mammalian host cell, which, as discussed above (*supra* at p. 30) would necessarily express all five genes independently to produce five separate globin polypeptides (beta, delta, gamma A, gamma G and epsilon).

secrete them as an assembled tetrameric immunoglobulin. Ex. 1058, Baron Decl., ¶74; *see e.g.,* Ex. 1035, Ochi (II) (Sp2/0 cells); Ex. 1036, Cattaneo (C6 glioma, CHO and HeLa cells); Ex. 1037, Daugherty (COS and CV1P cells); Ex. 1038, Bruynck (BHK cells); *see also* Ex. 1039, Reichert at 414, Table 1 (identifying the mammalian cell lines used to make FDA-approved therapeutic antibodies).

b. Independent Process Claim 33

The Salser patent anticipates claim 33 for the same reasons that it anticipates claim 1 of the '415 patent. Ex. 1058, Baron Decl., ¶75. Claims 1 and 33 are nearly identical process claims, except that claim 1 recites a discrete step of host cell transformation, while claim 33 presupposes a transformation step by reciting a "single host cell transformed with said first and second DNA sequences."

c. Independent Composition Claims 15 and 17

The Salser patent anticipates claim 15 of the '415 patent. Ex. 1058, Baron Decl., ¶76. Claim 15 is directed to "[a] vector comprising a first DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain and a second DNA sequence encoding at least a variable domain of an immunoglobulin light chain wherein said first DNA sequence and said second DNA sequence are located in said vector at different insertion sites." The use of vectors generally in the transformation process is disclosed in the Salser patent (Ex. 1002, Salser at 5:9-20; 13:9-30), and the specific vector of claim 15 is disclosed in the Salser patent as

discussed above (page 42, where both the heavy and light chain genes are carried on a "single [DNA] chain"). Ex. 1058, Baron Decl., ¶76. As explained there, a POSITA would know that the heavy and light chain DNA sequences must necessarily be arranged non-contiguously in the vector "at different insertion sites," separated from each other by sufficient non-coding DNA sequences, so that they are expressed as separate polypeptide molecules. Ex. 1058, Baron Decl., ¶76.

The Salser patent also anticipates claim 17. Ex. 1058, Baron Decl., ¶77. Claim 17 requires "[a] host cell transformed with a vector according to claim 15." Such a transformed host cell is also disclosed in the Salser patent. Ex. 1058, Baron Decl., ¶77.

d. Independent Composition Claim 18

The Salser patent anticipates claim 18 of the '415 patent. Ex. 1058, Baron Decl., ¶28. Claim 18 is directed to "[a] transformed host cell comprising at least two vectors, at least one of said vectors comprising a DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain and at least another one of said vectors comprising a DNA sequence encoding at least the variable domain of an immunoglobulin light chain." These vectors and the associated transformed host cell are disclosed in the Salser patent as discussed above (page 42, where the heavy and light chain genes are carried on separate chains, each inserted into separate vectors, and at pages 36-40). Ex. 1058, Baron Decl., ¶78.

4. The Salser Patent Anticipates Dependent Claims 2, 3, 4, 9, 11, 12, 16, 19 and 20

The limitations in dependent claims 2,-4, 9, 11, 12, 16, 19 and 20 are also disclosed in and therefore anticipated by Salser (Ex. 1058, Baron Decl., ¶79):

'415 Patent Claims	Disclosures of Salser
2. The process according to claim 1 wherein said first and second DNA sequences are present in different vectors.	Salser teaches two vectors, each containing a separate DNA gene sequence, and discloses immunoglobulins as one of the wide variety of proteins that can be made by the invention. *Supra* at pp. 36-40, 42, 45 (citing Salser at 5:9-20, 13:9-30, 3:46-53, 5:26-29, 3:50-53).
3. The process according to claim 1 wherein said first and second DNA sequences are present in a single vector.	Salser teaches a single vector containing two separate DNA gene sequences, and discloses immunoglobulins as one of the wide variety of proteins that can be made by the invention. *Supra* at pp. 36-40, 42, 45 (citing Salser at 5:9-20, 13:9-30, 3:46-53, 5:26-29, 3:50-53).
4. A process according to claim 3 wherein the vector is a plasmid.	Salser discloses plasmid vectors. *Supra* at pages 36-37 (citing Salser at 5:9-20, 13:9-30, 3:46-53, 5:26-29, 3:50-53).
9. A process according to claim 1 wherein the immunoglobulin heavy and light chains are expressed in the host cell and secreted therefrom as an immunologically functional immunoglobulin molecule or immunoglobulin fragment.[17]	Salser inherently discloses the *in vivo* assembly and secretion of an immunoglobulin. *Supra* at pp. 43-44.
11. A process according to claim 1 wherein the DNA sequences	Salser discloses immunoglobulins (*supra* at pp. 33-36, (citing Salser at 2:29-36)), not

[17] Production "in the host cell" of "heavy and light chains" that are "secreted" as an "immunoglobulin molecule" requires *in vivo* assembly of the chains. Ex. 1015, Owners' Resp. (11/25/05), at 47-48 (describing claim 9).

code for the complete immunoglobulin heavy and light chains.	fragments thereof, and therefore would be understood by a POSITA to disclose the DNA sequences for the complete (full length) heavy and light chains.
12. The process according to claim 1 wherein said first or said second DNA sequence further encodes at least one constant domain, wherein the constant domain is derived from the same source as the variable domain to which it is attached.	Salser discloses immunoglobulins (*supra* at pp. 33-36, (citing Salser at 2:29-36)) without further describing the source, e.g., animal species, of the constant and variable domains, and therefore would be understood by a POSITA to disclose an immunoglobulin whose constant and variable domains are from the same source (species).
16. A vector according to claim 15 which is a plasmid.	Salser discloses plasmid vectors. *Supra* at pp. 36-40 (citing Salser at 5:9-20, 13:9-30, 3:46-53, 5:26-29, 3:50-53).
19. The process of claim 1 wherein the host cell is a mammalian cell.	Salser teaches that the host cell is a mammalian cell. *Supra* at p. 36 (citing Salser at Abstract; *see also id.* at 1:46-49 ("Methods and compositions are provided for providing mammalian hosts with additional genetic capability, either a novel capability or enhancement of an existing one.")).
20. The transformed host cell of claim 18 wherein the host cell is a mammalian cell.	Salser teaches that the host cell is a mammalian cell. *Supra* at p. 36 (citing Salser at Abstract; *see also id.* at 1:46-49 ("Methods and compositions are provided for providing mammalian hosts with additional genetic capability, either a novel capability or enhancement of an existing one.")).

B. Ground 2: All of the Challenged Claims Are Obvious Over Salser in View of Ochi (I)

1. Claims 1-4, 9, 11, 12, 15-20 and 33

In the alternative to Ground 1, claims 1-4, 9, 11, 12, 15-20 and 33 are obvious over the Salser patent in combination with Ochi (I). Ex. 1058, Baron Decl., ¶80. Should the Board find that the Salser patent's teaching of the genus of

"globulins" is not a sufficient disclosure for purposes of anticipation of the immunoglobulin species of claims 1-4, 9, 11, 12, 15-20 and 33, the specific teaching of immunoglobulins may be found in Ochi (I). Ex. 1003, Ochi (I) at 340-42; Ex. 1058, Baron Decl., ¶80. The Ochi (I) reference (discussed *supra* at p. 22) published in March 1983 and is therefore prior art to the '415 patent under 35 U.S.C. § 102(a). Ochi (I) teaches that a foreign light chain immunoglobulin DNA sequence can be inserted into an expression vector and transformed into a mammalian host cell that will successfully express the light chain polypeptide. Ex. 1003, Ochi (I) at 340-42; Ex. 1020, Owners' Resp. (5/21/07) at 73 ("Ochi… does not provide any information beyond what is implicit in the [Cabilly I] patent claims (i.e., expression of one exogenous DNA sequence encoding one immunoglobulin light chain polypeptide in a transformed host cell)."); Ex. 1058, Baron Decl., ¶80. Ochi (I) also demonstrated that the expressed foreign light chain polypeptide could assemble *in vivo* with the host cell's endogenous heavy chain polypeptide to form an immunoglobulin capable of binding antigen. Ex. 1003, Ochi (I) at 340-41; Ex. 1058, Baron Decl., ¶80. The disclosure in Ochi (I) of the immunoglobulin species, when considered in view of the "globulin" genus in Salser, would render claims 1-4, 9, 11, 12, 15-20 and 33 obvious. Ex. 1058, Baron Decl., ¶80.

A POSITA would have been motivated to combine the Salser patent with the disclosure in Ochi (I) with a reasonable expectation of success in achieving the

purported invention of the claims. Ex. 1058, Baron Decl., ¶81. Both the Salser and Ochi (I) references are directed to the use of rDNA techniques to make heterologous proteins, and in particular, the same type of heterologous protein (globulins/immunoglobulins, or a chain or chains thereof). *Id.* at ¶81. Furthermore, Salser instructs the use of plasmid vectors containing viral components and protoplast fusion transformation to this end, and Ochi (I) employs such a vector construct and transformation technique in expressing the foreign light chain. Ex. 1002, Salser at 1:35-40, 5:9-20,13:9-30; Ex. 1003, Ochi (I) at 340-41; Ex. 1058, Baron Decl., ¶81. The Salser patent disclosure would have invited a POSITA to investigate publications to find instances of expressing specific globulins using rDNA technology facilitated by similar techniques (vectors and protoplast fusion), thus leading the POSITA to the Ochi (I) reference. Ex. 1058, Baron Decl., ¶81. A POSITA would therefore find motivation in both Salser itself as well as in the state of the art of rDNA technology to modify Salser by substituting the Salser genus of "globulin" with the Ochi (I) disclosure of the "immunoglobulin" species. *Id.* at ¶81.

Moreover, a POSITA would have been motivated to select immunoglobulins from the genus of globulins in Salser based on the demonstrated success in expressing an immunoglobulin light chain in Ochi (I). Ex. 1003, Ochi (I) at 341-42; Ex. 1058, Baron Decl., ¶82. A POSITA would have had no reason to believe that of all the members of mammalian globulin genus, immunoglobulins uniquely

would not be amenable to production by rDNA means. Ex. 1058, Baron Decl., ¶82. Indeed, in Ochi (I) the single (light) chain expression and subsequent assembly *in vivo* with the endogenous heavy chain would have given a POSITA a reasonable expectation of success that the Salser patent's teaching of co-expression of two genes of interest would be effective, and all the more so when the two genes of interest were the heavy and light chain genes. Ex. 1058, Baron Decl., ¶82.

2. Claim 14

Claim 14 is obvious over the Salser patent in combination with Ochi (I). Ex. 1058, Baron Decl., ¶83. Dependent claim 14 requires that the heavy and light chain DNA sequences "are derived from one or more monoclonal antibody producing hybridomas." The light chain gene in Ochi (I) was derived from an antibody-producing hybridoma. Ex. 1003, Ochi (I) at 340; Ex. 1058, Baron Decl., ¶83.

A POSITA would be motivated to combine Salser and Ochi (I) for the same reasons as discussed above for claims 1-4, 9, 11, 12, 15-20 and 33. Furthermore, a POSITA would have reasonably predicted that doing so would result in the successful expression of heavy and light chains genes that have been derived from a hybridoma. *Id.* at ¶84. There would be no doubt in a POSITA's mind that immunoglobulin genes derived from a hybridoma would work in the Salser method, and Ochi (I) itself teaches that mammalian host cells could be used to successfully make the light chain from these genes and that the light chain will

assemble *in vivo* with the host cell's natural heavy chain polypeptide. Ex. 1003, Ochi (I) at 340-42; Ex. 1058, Baron Decl., ¶84.[18]

C. Explanation of Ground 3 for Unpatentability: Claims 2, 18 and 20 Are Obvious Over Salser in View of Southern

In the alternative to Ground 1 with respect to claims 2, 18 and 20, these claims are obvious over Salser in view of Southern (Ex. 1004, discussed *supra* at pages 20-21). Dependent claim 2 requires that the heavy and light chain DNA sequences of independent claim 1 "are present in different vectors." Independent claim 18 requires a host cell transformed with two separate vectors—one containing the heavy chain gene, and one containing the light chain gene. Claim 20 (dependent on claim 18) require that the host cell is a mammalian host cell. Should the Board find that the Salser patent does not disclose the co-transformation of a single host cell with the two vectors of claims 2, 18 and 20, Southern supplies that teaching. Ex. 1058, Baron Decl., ¶85.

A POSITA would have had a number of reasons to combine (1) Salser's disclosure of a mammalian host cell transformed with two genes—which as

[18] As with claims 1-4, 9, 11, 12, 15-20 and 33, should the Board find that Salser's disclosure of the genus of "globulins" does not anticipate the immunoglobulin species of claim 14, the combination of the Salser patent and Ochi (I) would render claim 14 obvious.

discussed above include the species of the heavy and light chain immunoglobulin genes—in a single vector with (2) the two-vector teaching in Southern (*supra* at pp. 20-21) of the co-transformation of a mammalian host cell two genes of interest. Ex. 1058, Baron Decl., ¶86. Both references disclose the use of rDNA technology to express heterologous proteins in host cells transformed with one or more foreign genes of interest. *Id.* at ¶86. And both references specifically teach that this can be accomplished using plasmid vectors with viral components and transformation by calcium phosphate precipitation. Ex. 1002, Salser at 5:9-20; 13:9-30; Ex. 1004, Southern at 327, 329, 332 (Fig. 2), 336 (Fig. 7); Ex. 1058, Baron Decl., ¶86. Moreover, Salser itself suggests that transformation with two or more genes may be accomplished using two (or more) separate DNA sequences: "when two or more genes are to be introduced they may be carried on a single chain, a plurality of chains, or combinations thereof" (Ex. 1002, Salser at 3:50-53 (emphasis added)), thereby accommodating the two-vector approach in Southern. Ex. 1058, Baron Decl., ¶86. The Salser patent disclosure would have invited a POSITA to investigate publications to find specific instances of expressing two genes introduced into a single mammalian host cell on separate chains using rDNA technology facilitated by similar techniques (vectors and calcium phosphate precipitated DNA), which would have led a POSITA to the Southern reference. Ex. 1058, Baron Decl., ¶86. A POSITA would therefore find the motivation in Salser

as well as in the state of the art of rDNA technology to combine Salser with Southern and to modify Salser accordingly by putting the heavy and light chain DNA sequences into separate vectors to be co-transformed into a single mammalian host cell. Ex. 1058, Baron Decl., ¶86.

A POSITA would have also had a reasonable expectation that such a modification of Salser would have resulted in the subject matter of claims 2, 18 and 20. *Id.* at ¶87. Southern taught the feasibility of co-expression (transcription and translation) of two proteins of interest in a single mammalian host cell when the respective genes are present on separate vectors. *Id.* at ¶87. The Salser patent taught that heavy and light chain genes can be successfully co-expressed when they are present in a single transformed mammalian host cell, whether or not they are contained on the same vector or on separate DNA chains. *Id.* at ¶87. A POSITA therefore would have been confident that the specific application of the Southern approach using heavy and light chains on separate vectors would result in the successful co-expression in a single mammalian host cell of heavy and light chain genes when present on separate vectors. *Id.* at ¶87. A POSITA would have no reason to doubt that the protein synthesizing apparatus of the host cell would work just as well for immunoglobulin chains as it would for any other two genes, regardless of the fact that the genes are on separate vectors. *Id.* at ¶87. Furthermore, because the heavy and light chain genes are on separate vectors in the

same host cell, they would necessarily be "independently expressed" and produced as "separate molecules," as required by claim 2. *Id.* at ¶87. A POSITA would therefore have had a reasonable expectation of success in combining Salser with Southern to result in the subject matter of challenged claims 2, 18 and 20. *Id.* at ¶87.[19]

D. The Immunoglobulin Co-Expression rDNA Work Reflected in the Boss Patent and Ochi (II) Supports a Finding of Obviousness

When the alleged invention claimed by a patentee is also "independently made" by another, "near[ly] simultaneous" with the patentee's work, that is "strong evidence of what constitutes the level of ordinary skill in the art" and is "persuasive evidence that the [patented invention] 'was the product only of ordinary… skill.'" *George M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed.

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[19] After the '415 patent was filed, several research groups expressed heavy and light chain in the same mammalian cell to produce immunoglobulins using the exact approach and the same vectors suggested by Southern: the gene for one immunoglobulin chain was inserted into the pSV2neo vector, the gene for the other chain was inserted into the pSV2gpt vector, and both vectors were co-transformed into a single mammalian host cell. Ex. 1040, Beidler at 4054; Ex. 1041, Sahagan at 1067; Ex. 1042, Nishimura 1000; Ex. 1043, Komori at 511; Ex. 1058, Baron Decl., ¶87, n. 16.

Cir. 2010) (quoting *Concrete Appliances Co. v. Gomery*, 269 U.S. 177, 184 (1925); *Ecolochem v. S. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000); *see also Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1335 (Fed. Cir. 2015) ("express teaching to prove sufficient motivation to modify the prior art to arrive at the claimed invention" not necessary when other workers were pursuing the same research around the same time as the patentees). Here, the work of the inventors of the Boss patent (Ex. 1007) and of the co-authors of the Ochi (II) publication (Ex. 1035) is strong evidence of the obviousness of the challenged claims of the '415 patent.

The Boss patent, which was the subject of a decade-long interference proceeding with the '415 patent (*supra* at p. 5), was filed in the United States in November 1984 and claimed priority to a British patent application filed on March 23, 1983. Ex. 1044, Interference Final Decision at 3. The Boss patent disclosed experiments demonstrating heavy and light chain co-expression in transformed bacteria and yeast cells (and suggested the same in mammalian cells). Ex. 1007, Boss patent, 5:43-56, 6:1-17, 17:31-20:3, 22:1-23:29; Ex. 1058, Baron Decl., ¶58, n. 11. Similarly, the Ochi (II) reference—submitted to the journal Proceedings of the National Academy of Sciences USA in July 1983 (which would have reflected work done in the months previous to that) and published that October—

experimentally demonstrated co-expression of heavy and light chains in mammalian host cells. Ex. 1035, Ochi (II) at 6351-52; Ex. 1058, Baron Decl., ¶58.

That two additional research groups independent from the '415 patent inventors were pursuing immunoglobulin co-expression using rDNA technology in transformed host cells and had actually performed experiments achieving co-expression nearly simultaneously with the filing of the '415 patent gives the lie to the supposed "one polypeptide per host cell" postulate advocated by Owners during the reexamination. The work of the Boss patent inventors and of the Ochi (II) co-authors, as well as the inventors of the Salser patent, demonstrates that there was no such "prevailing mindset" and that the purported invention of the '415 patent was merely the product of ordinary skill. *See George M. Martin Co.*, 618 F.3d at 1305; *Ecolochem v.*, 227 F.3d at 1379; *Spectrum Pharms., Inc.*, 802 F.3d at 1335.

E. The Publicly Available Licensing Record of the '415 Patent Does Not Rescue the Challenged Claims from Obviousness

In a Preliminary Response filed by Owners in a Related Matter concerning the '415 patent, IPR2015-01624 (identified in additional detail below), Owners point to the "extensive" licensing of the '415 patent by the biotechnology industry, relying on 70 licenses under the '415 patent. *See* Preliminary Response, IPR2015-01624, Paper No. 14, at 6-7. The Walton Expert Report (Ex. 1045 hereto, and Exhibit 2009 in IPR2015-01624) that Owners cite for this purpose only identifies

58 licenses (at page 22). Importantly, neither the Walton Expert Report nor the Owners' Preliminary Response show any nexus between the merits of the invention and the alleged acquiescence by the industry that the licenses purport to demonstrate. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1324 (Fed. Cir. 2004). Owners and Dr. Walton appear to be content simply to assume there is a nexus, rather than considering alternative explanations. *See id.* (It is often "cheaper to take licenses than to defend infringement suits.") In the absence of any such evidence, the licenses are entitled to little weight as secondary indicia of non-obviousness. *See id.* ("[L]icenses 'may constitute evidence of nonobviousness; however, only little weight can be attributed to such evidence if the patentee does not demonstrate a nexus between the merits of the invention and the licenses of record.'")

Furthermore, none of these licenses reflect the present state of the industry's "respect" for the '415 patent, as they were all entered into before 2008. Ex. 1045 , Walton Expert Report, at 22. Since the '415 patent issued, Owners have been involved in six patent infringement lawsuits challenging the validity of the '415 patent, five of which were filed after Dr. Walton's report was generated. Notably, Owners settled all of the cases before a decision on the merits on invalidity. (See the complaints and dismissals in the lawsuits filed by MedImmune (Exs. 1046, 1047), Centocor (Exs. 1048, 1049), Glaxo Group Ltd (Exs. 1050, 1051), Human

Genome Sciences (Exs. 1052, 1053), Eli Lilly (Exs. 1054, 1055) and Bristol-Myers Squibb (Exs. 1056, 1057) against Genentech and City of Hope.)

VIII. MANDATORY NOTICES

A. Real Party-In-Interest

Sanofi, the ultimate parent company of Genzyme, is the real party-in-interest for Petitioner.

B. Related Matters

Petitioner identifies IPR2015-01624 as a Related Matter under 37 C.F.R. § 42.8(b)(2). IPR2015-01624 challenged the '415 patent and was filed by sanofi-aventis U.S. LLC and Regeneron Pharmaceuticals on July 27, 2015. In IPR2015-01624, Sanofi (the ultimate parent company of sanofi-aventis U.S. LLC) was identified as a real party-in-interest for sanofi-aventis U.S. LLC.

Neither the prior art nor the arguments in the instant Petition are "the same or substantially the same" as those presented in IPR2015-01624. *See* 35 U.S.C. § 325(d). The Salser patent does not form the basis for any grounds of unpatentability in IPR2015-01624, nor does the Ochi (I) reference. The only overlapping prior art reference between the two IPRs is the Southern publication, which is relied on by Petitioners here only to the extent the Board finds that Salser alone does not disclose the two vectors required by claims 2, 18 and 20 of the '415 patent. (In IPR2015-01624, the Southern reference forms part of a ground for invalidity that is not in the alternative to another ground.)

Moreover, although Petitioner's arguments bear some similarity to those presented in IPR2015-01624—as they must, given that the same claims with the same limitations are at issue in both IPRs—the arguments are not "substantially the same." The Salser patent reflects work performed by scientists investigating the use of rDNA technology in the field of gene replacement therapy. The inventors were not merely interested in the production of proteins per se, but in the production of those proteins in living subjects in need of the protein to correct a genetic deficiency—a goal not considered in the prior art presently before the Board in IPR2015-01624. Accordingly, the Salser patent inventors addressed the problem they were trying to solve in a unique manner (not present in the prior art in IPR2015-01624) that dictates that the heavy and light chain genes must be co-expressed in the same cell if the fruits of their research were to have any therapeutic value at all. *Supra* at p. 40. The application of the Salser reference, in which a host cell is created that contains two foreign genes of interest for production of a protein in a gene therapy context, is novel in challenging the patentability of the '415 patent. For at least these reasons, the Salser patent should be considered and rejection of this Petition under § 325(d) is not warranted.

C. Lead and Back-up Counsel and Service Information

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(212) 262-1910, Rmccormick@mayerbrown.com. Backup counsel are Lisa M. Ferri and Brian W. Nolan (Reg. No. 45,821), also of Mayer Brown LLP in New York. Petitioner consents to email service at MB-Genzyme-Cabilly-IPR@mayerbrown.com. Ms. Ferri is an experienced attorney and has an established familiarity with the subject matter at issue in this proceeding. She has appeared as Backup Counsel previously in connection with the '415 patent in Related Matter IPR2015-01624. Petitioner will file a motion seeking the admission of Ms. Ferri to appear *pro hac vice* when authorized to do so.

IX. CONCLUSION

Petitioner submits that issues have been presented that demonstrate a reasonable likelihood that claims 1-4, 9, 11, 12, 14-20 and 33 of the '415 patent are unpatentable. Petitioner therefore requests that the Board grant *inter partes* review for each of those claims. Please charge any fees to Deposit Account number 130019.

Dated: December 30, 2015

Respectfully submitted,

By: _____

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CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing Petition for Inter Partes Review of U.S. Patent No. 6,331,415 and Exhibits 1001-1058 were served on December 30, 2015, via UPS OVERNIGHT service to the attorneys of record for U.S. Patent No. 6,331,415 as evidenced in Public PAIR on December 29, 2015, namely:

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