UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANOFI-AVENTIS U.S. LLC AND
REGENERON PHARMACEUTICALS, INC.,
Petitioners

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

IPR Trial No. IPR2015-01624

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,331,415 UNDER 35 U.S.C. § 311-319 AND 37 C.F.R. § 42.100 et seq.

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37 C.F.R. § 42.104(b) 2

37 C.F.R. § 42.204(b) 3

PETITION EXHIBIT LIST

Exhibit No.	Description	Abbreviation
1001	U.S. Patent No. 6,331,415	The '415 patent
1002	U.S. Patent No. 4,495,280	Bujard, or the Bujard Patent
1003	Riggs and Itakura, *Synthetic DNA and Medicine*, American Journal of Human Genetics, 31:531-538 (1979)	Riggs & Itakura
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, 1:327-341 (1982)	Southern
1005	U.S. Patent No. 4,237,224	Cohen & Boyer, or the Cohen & Boyer patent
1006	Declaration of Jefferson Foote, Ph.D., in Support of Sanofi And Regeneron's Petition for Inter Partes Review of U.S. Patent No. 6,331,415	Foote Decl.
1007	U.S. Patent No. 4,816,657	The Cabilly I patent
1008	'415 patent reexamination, Office Action dated 2/16/07	Office Action (2/16/07)
1009	'415 patent reexamination, Owners' Resp. dated 11/25/05	Owners' Resp. (11/25/05)
1010	'415 patent reexamination, Owners' Resp. (5/21/07)	Owners' Resp. (5/21/07)
1011	'415 patent reexamination, Office Action dated 9/13/05	Office Action (9/13/05)

1012	U.S. Patent No. 4,816,397	The Boss patent
1013	'415 patent file history, paper no. 17	-
1014	'415 patent file history, paper no. 14	-
1015	'415 patent file history, paper no. 18	-
1016	'415 patent reexamination, Office Action dated 8/16/06	Office Action (8/16/06)
1017	'415 patent reexamination, Office Action dated 2/25/08	Office Action (2/25/08)
1018	U.S. Patent No. 4,399,216	Axel, or the Axel patent
1019	U.S. Patent No. 5,840,545	Moore, or the Moore patent
1020	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, 79:7862-7865 (1982)	Rice & Baltimore
1021	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)
1022	'415 patent reexamination, Owners' Resp. dated 10/30/06	Owners' Resp. (10/30/06)
1023	'415 patent reexamination, Owners' Resp. dated 6/6/08	Owners' Resp. (6/6/08)
1024	'415 patent reexamination, Appeal Brief	Appeal Brief
1025	'415 patent reexamination, Notice of Intent to Issue Ex Parte Reexamination	NIRC

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1026	'415 reexamination, Ex Parte Reexamination Certificate	Reexam Cert.
1027	T.J.R. Harris, *Expression of Eukaryotic Genes in E. Coli*, in Genetic Engineering 4, 127-185 (1983)	Harris
1028	'415 patent reexamination, Declaration of Dr. Timothy John Roy Harris under 37 C.F.R. § 1.132	Harris Decl.
1029	Kabat et al., Sequences of Proteins of Immunological Interest (1983) (excerpt)	Kabat
1030	Cohen, *Recombinant DNA: Fact and Fiction*, Science, 195:654-657 (1977)	Cohen
1031	Oi et al., *Immunoglobulin Gene Expression in Transformed Lymphoid Cells*, Proceedings of the National Academy of Sciences USA, 80:825-829 (1983)	Oi
1032	European Patent Application Publication No. 0044722 A1, published 1/27/82	Kaplan
1033	U.S. Patent No. 4,487,835	-
1034	U.S. Patent No. 4,371,614	-
1035	U.S. Patent No. 4,762,785	-
1036	U.S. Patent No. 4,476,227	-
1037	U.S. Patent No. 4,362,867	-
1038	U.S. Patent No. 4,396,601	-
1039	Milstein, *Monoclonal Antibodies from Hybrid Myelomas*, Proceedings of the Royal Society of London, 211:393-412	Milstein

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1040	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, 80:6351-6355 (1983)	Ochi (II)
1041	*MedImmune, Inc. v. Genentech, Inc.*, No. 03-02567 (C.D. Cal. Aug. 17, 2007), Expert Report of E. Fintan Walton	Walton Expert Rep.
1042	'415 patent reexamination, Request for Reconsideration and/or Petition Under 37 C.F.R. § 1.183 dated 5/15/09	Request for Reconsideration
1043	Feldman et al., *Lessons from the Commercialization of the Cohen-Boyer Patents: The Stanford University Licensing Program*, in Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices, 1797-1807 (2007)	Feldman
1044	ReoPro® Prescribing Information	ReoPro® Prescribing Info.
1045	*Genentech v. Centocor*, No. 94-01379 (N.D. Cal.), Affidavit of John Ghrayeb, Ph.D.	Ghrayeb Aff.
1046	'415 patent reexamination, Declaration of Dr. E. Fintan Walton under 37 C.F.R. § 1.132	Walton Decl.
1047	Complaint in *MedImmune v. Genentech*, No. 03-02567 (C.D. Cal.)	-
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1052	Order of dismissal in *Glaxo Group Ltd. v. Genentech,* No. 10-02764 (C.D. Cal.)	-
1053	Complaint in *Human Genome Sciences v. Genentech*, No. 11-CV-6519 (C.D. Cal.)	-
1054	Order of dismissal in *Human Genome Sciences v. Genentech*, No. 11-CV-6519 (C.D. Cal.)	-
1055	Complaint in *Eli Lilly and ImClone Systems LLC v. Genentech*, No. 13-CV-7248 (C.D. Cal.)	-
1056	Stipulation of dismissal in *Eli Lilly and ImClone Systems LLC v. Genentech*, No. 13-CV-7248 (C.D. Cal.)	-
1057	Complaint in *Bristol-Myers Squibb v. Genentech*, No. 13-CV-5400 (C.D. Cal.)	-
1058	Stipulation of dismissal in *Bristol-Myers Squibb v. Genentech*, No. 13-CV-5400 (C.D. Cal.)	-

I. INTRODUCTION

Sanofi-aventis U.S. LLC and Regeneron Pharmaceuticals, Inc. (collectively, "Petitioners") request *inter partes* review under 35 U.S.C. § 311-319 of claims 1-4, 9, 11, 12, 14-20 and 33 of U.S. Patent No. 6,331,415 ("the '415 patent," Ex. 1001), which issued on Dec. 18, 2001 to inventors Cabilly et al. and is assigned to Genentech, Inc. and City of Hope ("Owners"). A petition for *inter partes* review must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition." 35 U.S.C. § 314(a). This petition meets this threshold for the reasons outlined below.

The challenged claims of the '415 patent purport to cover recombinant DNA processes and associated compositions for making immunoglobulins (or antibodies) in "host" cells that are genetically engineered to contain the two DNA sequences encoding the heavy and light chain polypeptides necessary for the cell to make an immunoglobulin. The generally applicable techniques employed by the '415 patent inventors were already disclosed and commonly used in the prior art, including Petitioners' prior art references: the Bujard patent, and the seminal Cohen & Boyer patent, one of the foundational platform technologies in the field of recombinant DNA. Neither of these references were substantively considered by the PTO during prosecution or reexamination of the '415 patent. Moreover, Bujard and Cohen & Boyer disclose the precise teachings that Owners have previously

argued were missing from the prior art: the introduction of "a plurality of" or "one or more" DNA sequences into a host cell—language which necessarily accommodates two DNA sequences, including the heavy and light chain sequences. Because Bujard and Cohen & Boyer also expressly identify immunoglobulins as being among the types of proteins that can be made in host cells by their respective methods, Bujard and Cohen & Boyer anticipate—or at least make obvious in view of the Riggs & Itakura and Southern prior art references—the challenged claims of the '415 patent.

II. REQUIREMENTS FOR INTER PARTES REVIEW

A. Grounds for Standing (37 C.F.R. § 42.104(a))

Petitioners certify that the '415 patent is available for *inter partes* review and that Petitioners are not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this petition.

B. Identification of Challenge (37 C.F.R. § 42.104(b))

Petitioners request that the Board cancel claims 1-4, 9, 11, 12, 14-20 and 33 ("the challenged claims") of the '415 patent on the following grounds:

Grounds Based on the Bujard Patent:
***All* of the Challenged Claims Are Covered by Grounds 1-3**

Ground 1. Claims 1, 3, 4, 9, 11, 12, 15, 16, 17, 19 and 33 are anticipated under § 102(e) by Bujard (Ex. 1002);

Ground 2. Claims 1, 3, 4, 11, 12, 14, 19 and 33 are obvious under § 103

over Bujard in view of Riggs & Itakura (Ex. 1003); and

Ground 3. Claims 1, 2, 18, 20 and 33 are obvious under § 103 over Bujard in view of Southern (Ex. 1004).

Grounds Based on the Cohen & Boyer Patent:
***A Subset* of the Challenged Claims Are Covered by Ground 4**

Ground 4. Claims 1, 3, 4, 11, 12, 14 and 33 are obvious under § 103 over Cohen & Boyer (Ex. 1005) in view of Riggs & Itakura.

Pursuant to 37 C.F.R. § 42.204(b), a detailed explanation of the precise 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 V below, including claim charts. Additional explanation and support for each ground of rejection is set forth in the accompanying Declaration of Jefferson Foote, Ph.D. (Ex. 1006).

III. RELEVANT INFORMATION REGARDING THE '415 PATENT

A. Brief Description of the Challenged Patent

The '415 patent issued on December 18, 2001, from Application No. 07/205,419 ("the '419 application"), filed on June 10, 1988. The '419 application has an earliest effective filing date under 35 U.S.C. § 120 of April 8, 1983, by virtue of a priority claim to Application No. 06/483,457, which issued as U.S. Patent No. 4,816,567 ("the Cabilly I patent," Ex. 1007). A reexamination certificate for the '415 patent issued on May 19, 2009, based on two separate

reexamination requests filed on May 13 and December 23, 2005.

The '415 patent is directed to processes and related compositions for making immunoglobulins[1] (or fragments thereof) in host cells using recombinant DNA technology. Ex. 1001, 1:14-21, 3:53-67. Immunoglobulins are proteins (or "polypeptides") having a globular conformation that are produced by and secreted from cells of the immune system of vertebrates in response to the presence in the body of a foreign substance, called an "antigen," often a foreign protein or a foreign cell (such as a bacterium). *Id.* at 1:23-37; 16:38-39; Ex. 1006, Foote Decl., ¶ 26. Immunoglobulins bind to antigens to rid the body of the foreign invader. Ex. 1001, 1:26-31; Ex. 1006, Foote Decl., ¶ 26. Most immunoglobulins are composed of two heavy chain polypeptides and two light chain polypeptides that are connected via disulfide bonds (represented above as –SS–) to form a four-chain "tetramer" with a highly specific and defined Y-shaped conformation that is required for antigen binding.

[1] For purposes of this Petition, the claim term "immunoglobulin" is interchangeable with "antibodies," which the '415 patent defines as "specific immunoglobulin polypeptides." Ex. 1001, 1:23-24.

Ex. 1001, Fig. 1 and 3:17-26; Ex. 1006, Foote Decl., ¶ 26. The heavy and light chains comprise segments referred to as the variable and constant regions. Ex. 1001, 3:42-59; Ex. 1006, Foote Decl., ¶ 27. The heavy chain and light chain are encoded by separate DNA sequences or "genes." Ex. 1001, 1:48-51; Ex. 1006, Foote Decl., ¶ 27. The nature of immunoglobulin structure and function as described above was well known in the prior art, as is evidenced by the discussion in the "Background of the Invention" in the '415 patent. Ex. 1001 at 1:22-4:5; Ex. 1006, Foote Decl., ¶ 27.

The patent identifies a prior art method of making antibodies in hybridoma cells, which results in the production of a homogeneous antibody population that specifically bind to a single antigen, so called "monoclonal" antibodies. Ex. 1001 at 1:64-2:19. According to the patent, the use of recombinant DNA technology to make antibodies avoids the drawbacks of hybridoma production. *Id.* at 2:40-3:2.

The recombinant DNA approach to making antibodies described in the patent, in short, proceeds as follows: (1) the genetic material encoding the heavy and light chains is identified and isolated (for example, from a hybridoma) (*id.* at 11:28-12:8; Ex. 1006, Foote Decl., ¶ 29); (2) the heavy and light chain DNA is introduced into suitable host cells by a process called "transformation," which may

be facilitated by first inserting the DNA into an expression vector[2] that acts as a vehicle to introduce the foreign DNA into the host cell (Ex. 1001, 12:9-30; Ex. 1006, Foote Decl., ¶ 29); and (3) the host cells transcribe and translate the heavy and light chain DNA, a process called "expression," to produce the heavy and light chain polypeptides (Ex. 1001, 12:31-33, 4:24-29; Ex. 1006, Foote Decl., ¶ 29). Host cells may either be microorganisms (for example, prokaryotic cells, such as bacteria) or cell lines from multicellular eukaryotic organisms, including mammalian cells. Ex. 1001 at 8:41-56, 9:56-10:18.

The challenged claims of the '415 patent cover various aspects and components of the above-described recombinant production of immunoglobulins. All of the challenged claims (whether process or composition) require <u>two</u> genes: a first DNA sequence encoding the heavy chain and a second DNA sequence encoding the light chain. All of the challenged process claims require that the host cell express <u>both</u> DNA sequences to produce both heavy chain and light chain polypeptides (referred to as "co-expression" in the '415 patent and during the reexamination[3]). Ex. 1009, Owners' Resp. (11/25/05), at 46. The heavy and light chain polypeptides are produced as "separate molecules" by virtue of their

[2] Vectors that express inserted DNA sequences are called "expression vectors" in the patent, a term that is used interchangeably with "plasmid." Ex. 1001, 8:16-22.

[3] Ex. 1001, 12:50-51; Ex. 1008, Office Action (2/16/07), at 19.

"independent expression." Ex. 1001, claims 1, 33; Ex. 1022, 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...")

Furthermore, the process claims also require assembly of the separate heavy and light chain polypeptides into an immunoglobulin tetramer. Ex. 1001, claim 1 ("A process for producing an immunoglobulin molecule…"); Ex. 1009, Owners' Resp. (11/25/05), at 46. This can occur inside of the host cell through its natural cellular machinery ("*in vivo*" assembly), which could then secrete the assembled immunoglobulin; or, if the host cell is unable to assemble the chains *in vivo*, the cell may be lysed and the separate chains assembled by chemical means ("*in vitro*" assembly). Ex. 1001, 12:50-55, claims 9 and 10; Ex. 1010, Owners' Resp. (5/21/07), at 29, n. 8.

B. Discussion of the File History and Related Proceedings in the PTO

The '415 patent and the '419 application have had an extended and extensive history in the PTO. The '415 patent issued nearly thirteen-and-a-half years after its filing date and more than eighteen years after its priority filing date. During prosecution, the '415 patent was involved in a decade-long interference proceeding (and related 35 U.S.C. § 146 action) with U.S. Patent No. 4,816,397, issued to

Boss et al. (Ex. 1012). After the interference was resolved, prosecution of the '415 patent continued until it issued. The '415 patent was later the subject of an *ex parte* reexamination for four years, from May 13, 2005 to May 19, 2009.

1. Prosecution of the '419 application

The prosecution of the '419 application consisted largely of a series of restriction requirements by the PTO and claim cancellations and elections by Owners. *See generally* Ex. 1009, Owners' Resp. (11/25/05), at 8-10, 12-13. There were no prior art rejections of the pending claims. However, in an Information Disclosure Statement filed on September 18, 1991, Genentech characterized the Rice & Baltimore (Ex. 1020) prior art reference as "distinguishable from the instant claims in that the cells are not transformed with exogenous DNA encoding both of the heavy and light chains." Ex. 1013, '415 patent file history, paper no. 17, at 2 (emphasis in original).

2. Interference with the Boss Patent

On February 28, 1991, the Board of Patent Appeals and Interferences declared an interference between claims 1-18 of the Boss patent and then-pending claims 101-120 in the '419 application, which were copied from the Boss patent. Ex. 1014, '415 patent file history, paper no. 14. The count was defined to be claim 1 of the Boss patent, which was identical to claim 101 of the' 419 application (and which issued as claim 1 of the '415 patent). *Id.* at 4. The BPAI decided priority in

favor of the senior party, Boss, holding that the inventors of the '415 patent had not established an actual reduction to practice before the Boss patent's British priority date. *Cabilly v. Boss*, 55 U.S.P.Q.2d 1238 (Bd. Pat. App. & Int. 1998). Priority of invention was ultimately awarded to the inventors of the '415 patent on March 16, 2001, following the settlement by the parties of an action instituted by Genentech under 35 U.S.C. § 146. Ex. 1015, '415 patent file history, paper no. 18.

3. Ex Parte Reexamination of the '415 Patent

a. Rejections Over the Axel Patent

Over the course of the reexamination, the PTO rejected the claims of the '415 patent in each of four office actions. *See* Exs. 1011, 1016, 1008 and 1017, '415 patent reexamination, Office Actions dated 9/13/2005, 8/16/2006, 2/16/2007, and 2/25/2008. Among the prior art relied upon by the PTO were U.S. Patent Nos. 4,399,216 ("Axel," Ex. 1018) and 5,840,545 ("Moore," Ex. 1019), Rice & Baltimore (Ex. 1020), and Ochi (I) (Ex. 1021). The PTO rejected the claims on a variety of grounds, including obviousness-type double patenting, anticipation and obviousness.

The ODP rejections were in part based on (1) the claims of the Cabilly I

patent, which were directed to chimeric[4] heavy or light chains produced using recombinant DNA technology, in combination with (2) Axel, Rice & Baltimore or Ochi (I), alone or in combination with Moore. *E.g.,* Ex. 1008, Office Action (2/16/07), at 26-42. The obviousness rejections were based in part on the Moore patent either alone or in combination with the Axel patent. *Id.* at 12-14.

The PTO rejections relying on Axel were based on the Examiner's interpretation of Axel as disclosing the co-expression of heavy and light chains in a single host cell transformed with the respective DNA sequences. The invention of the Axel patent concerned "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. 1018, Axel, 1:12-21. Axel disclosed the transformation of eukaryotic (mammalian) host cells using a two-DNA system:

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[4] A "chimeric" chain has variable regions derived from one species of mammal, with constant portions derived from another species. *See* Ex. 1007, Cabilly I patent, 6:54-59 and claim 1.

"DNA I," which coded for a "desired proteinaceous material"[5] that is "heterologous" to the host cell;[6] and "DNA II," which coded for a protein that would act as a "selectable marker."[7] *Id.* at Figure 1, 3:20-26, 8:56-62. Because DNA I and DNA II are present in a single vector "physically unlinked" to each other (*id.* at 9:61-10:1; Figure 1), the respective proteins encoded by DNA I and II would be independently expressed as separate molecules. Ex. 1006, Foote Decl., ¶ 39. The Axel patent identified "antibodies" as one of the preferred "proteinaceous materials" that could be made by the disclosed methods. *Id.* at 3:31-36, 2:61-66. In the first Office Action, the PTO characterized Axel as "demonstrat[ing] the predictability of expression of multiple heterologous proteins in a single host cell

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[5] A "desired proteinaceous material," or "protein of interest," is the protein that is sought to be isolated from the host cell after its production by the cell. Ex. 1010, Owners' Response (5/21/07), at 49; Ex. 1006, Foote Decl., ¶ 39, n. 2.

[6] A "heterologous" protein is a protein produced in a cell that does not normally make that protein or that is foreign to the cell, e.g., by genetically engineering the cell. Ex. 1006, Foote Decl., ¶ 39, n. 3; Ex. 1001, 4:9-12, 4:33-41.

[7] The function of a "selectable marker" is to permit scientists to identify which host cells have been transformed. Because it is not intended to be isolated or studied, it is not, strictly speaking, a protein "of interest" or a "desired" protein. Ex. 1009, Owners' Response (11/25/05), at 34; Ex. 1006, Foote Decl., ¶ 39, n. 4.

[and the] desirability of expressing immunoglobulins in mammalian host cells, and as intact (assembled) proteins." Ex. 1011, Office Action (9/13/05), at 5.

The Examiner eventually entered a Final Office Action rejecting the claims in part over Axel, stating that the "Axel Abstract and definitions suggest co-transforming <u>more than one desired gene</u> for making proteinaceous materials which include multimeric proteins."[8] Ex. 1017, Office Action (2/25/08), at 29; *see also id.* at 30 ("The Axel reference clearly encompasses <u>one or more genes</u> which encode one or more proteins."). Moreover, the Examiner also found that Axel "teaches <u>co-expression</u> of two different proteins encoded by foreign DNA I and foreign DNA II in a single eukaryotic host cell." *Id.* at 28 (emphasis added). Because the proteins disclosed in the Axel patent included "multimeric proteins particularly '...interferon protein, <u>antibodies</u>, insulin, and the like,'" the Examiner concluded that "the Axel reference suggests expressing two immunoglobulin chains in a single eukaryotic host cell, since Axel discloses and claims encoding an antibody that necessarily possesses both light and heavy immunoglobulin chains."

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[8] A "multimeric" protein is a protein that is composed of more than one distinct polypeptide constituents or subunits. Ex. 1009, Owners' Response (11/25/05), at 37. An immunoglobulin is a multimeric protein because it is composed of four distinct polypeptide subunits: two heavy chains and two light chains. Ex. 1022, Owners' Response (10/30/06), at 33; Ex. 1006, Foote Decl., ¶ 67-69.

Ex. 1008, Office Action (2/16/07), at 51.

Based on these rejections and others, all thirty-six of the '415 patent claims stood finally rejected by the PTO over the prior art in the Office Action dated Feb. 25, 2008. Ex. 1017, Office Action (2/25/08), at 1.

b. Owners' Arguments in Response to the Rejections

i. Owners Contrive a So-Called "Prevailing Mindset" before April 1983 that Only One Eukaryotic Protein of Interest Should Be Produced in a Transformed Host Cell

In response to the rejections, Owners argued over the course of four responses and an appeal brief[9] (relying on no fewer than seven Rule 132 declarations from technical experts) that none of the prior art disclosed the co-expression of both immunoglobulin heavy and light chains in a single host cell transformed with the genes encoding for both the heavy and light chains. Owners framed their specific arguments about the teachings of Axel with the general proposition that before April 1983, the so-called "prevailing mind-set" among persons of ordinary skill in the art (POSITA) was "that only one eukaryotic polypeptide of interest should be produced in a recombinant host cell." Ex. 1023, Owners' Resp. (6/6/08), at 6; *see also, e.g.,* Ex. 1024, Appeal Brief, at 33, 46 ("conventional 'one polypeptide at a time' approach" and "prevailing 'one

[9] Exs. 1009, 1022, 1010, 1023, 1024, Owners' Responses, dated 11/25/05, 10/30/06, 5/21/07, and 6/6/08, and Appeal Brief, respectively.

polypeptide in a host cell' mindset"). This "prevailing mindset" would have led a POSITA "to break down a complex project, such as production of a multimeric eukaryotic protein, into more manageable steps (e.g., produce each constituent polypeptide of the multimer in a separate host cell)." Ex. 1023, Owners' Resp. (6/6/08), at 6-7. (As discussed below (at pages 21-25), this was decidedly <u>not</u> the prevailing mindset before April 1983: there were multiple prior art references teaching the expression of one or more genes in a single transformed host cell.)

This mindset, Owners argued, was reflected specifically in Axel. Ex. 1023, Owners' Resp. (6/6/08), at 24-27. 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: "The evidence of record thus demonstrates that Axel describes nothing more than what is inherently required by the [Cabilly I patent]—production of <u>one</u> desired polypeptide (e.g., a heavy <u>or</u> a light immunoglobulin chain polypeptide) in <u>one</u> transformed host cell." Ex. 1024, Appeal Brief, at 47.

ii. Owners Argue that the Axel Patent Does Not Disclose the Co-Expression of "One or More" Genes of Interest

Owners also argued that neither Axel nor any other piece of prior art taught or suggested the transformation of a single host cell with <u>any two</u> different genes of interest encoding two different "proteins of interest"—and specifically failed to do so for immunoglobulin heavy and light chains. In Owners' view, Axel in

particular did not disclose the introduction of "more than one desired gene" or "multiple DNA sequences" encoding "different polypeptides of interest" into a single host cell. Ex. 1024, Appeal Brief, at 49; Ex. 1022, Owners' Resp. (10/30/06), at 44. Such a disclosure of more than one gene in Axel 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. 1022, Owners' Resp. (10/30/06), at 44, n. 26 (emphasis added). According to Owners, the Axel patent's specific disclosure of a two DNA system (DNAs I and II) did not fill in this alleged gap in the prior art because although DNA I encoded a single protein of interest, DNA II encoded only a "selectable marker" protein and not a second protein "of interest." Ex. 1010, Owners Response (5/21/07), at 21. A POSITA reading the entire disclosure of Axel would therefore "not read the passing references in Axel to 'antibodies' to mean that an antibody tetramer is to be produced by co-expressing the heavy and light chains in one host cell." *Id.*

Owners eventually successfully convinced the PTO that Axel failed to disclose the "co-expression" requirement of the '415 patent claims, (notwithstanding that the host cells in Axel produced two separate proteins). Ex. 1025, NIRC, at 4 ("Axel et al taught a process for inserting foreign DNA into eukaryotic cell by cotransformation with the disclosed foreign DNA I and DNA II

that encodes a selectable marker. Axel et al. did not teach a single host cell transformed with immunoglobulin heavy chain and light chain independently. Axel et al did not teach co-expression of two foreign DNA sequences."). A reexamination certificate issued on May 19, 2009. Ex. 1026, Reexam Cert.

C. Person of Ordinary Skill in the Art

A POSITA at the time of the earliest effective filing date of the '415 patent would have 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. 1006, Foote Decl., ¶ 23.

D. Claim Construction

The Board is charged with applying "the broadest reasonable interpretation consistent with the specification," reading the claim language in light of the specification as it would be understood by a POSITA. *In re Cuozzo Speed Techs., LLC*, No. 2014-1301, 2015 WL 4097949, at *5-8 (Fed. Cir. Jul. 8, 2015). The terms in the challenged claims of the '415 patent should therefore be given their broadest reasonable interpretation consistent with the specification. Petitioners do not believe that any special meanings apply to the claim terms in the '415 patent.

Petitioners' position regarding the scope of the challenged claims should not be taken as an assertion regarding the appropriate claim scope in other adjudicative forums where a different claim interpretation standard may apply.

IV. RELEVANT PRIOR ART

A. Technology Background

1. The Sophistication of Recombinant DNA Technology Was Advanced by April 8, 1983, and Mammalian Proteins Were Being Made in Host Cells Transformed with Foreign Genes

The technology and associated methodologies for creating, introducing, and expressing (i.e., transcribing and translating) foreign DNA in host cells was past its formative years by April 1983. Ex. 1006, Foote Decl., ¶ 42. The '415 patent notes that by then, "[r]ecombinant DNA technology [had] reached sufficient sophistication that it includes a repertoire of techniques for cloning and expression of gene sequences." Ex. 1001, 4:7-9. "Various DNA sequences can be recombined with some facility, creating new DNA entities capable of producing heterologous protein product in transformed microbes and cell cultures. The general means and methods… for producing expression vectors, and for transforming organisms are now in hand." *Id.* at 4:9-16. The "expression vector is useful to produce the polypeptide sequence for which the inserted gene codes, a process referred to as 'expression.' The resulting product may be obtained by lysis, if necessary, of the host cell and recovery of the product by appropriate purifications from other proteins." *Id.* at 4:27-32.

Before the priority filing date of the '415 patent, scientists had already produced a few dozen eukaryotic proteins in bacteria. Ex. 1006, Foote Decl., ¶ 44. Timothy Harris, one of Owners' experts who submitted declarations to the PTO during reexamination, authored a 1983 review article compiling all of the higher eukaryotic (including mammalian) proteins expressed in *E. coli* that had been reported to date. Ex. 1027, Harris, at 163-169; Ex. 1028, Harris Decl., ¶ 16. Among the proteins listed are human insulin and fibroblast interferon, human and bovine growth hormone, rat preproinsulin, chicken ovalbumin, and rabbit β-globin.

The Cohen & Boyer patent (discussed below in greater detail as a reference underlying Petitioners' grounds for rejection) was one of the foundational platform technologies available before April 1983 that utilized recombinant DNA to make mammalian proteins in bacterial host cells. The Axel patent was similarly a seminal platform technology that advanced the Cohen & Boyer bacterial host cell method by teaching the production of mammalian proteins in eukaryotic (including mammalian) host cells. Ex. 1006, Foote Decl., ¶ 45.

The recombinant production of heterologous proteins in host cells was so well developed by April 1983 that the '415 patent was able to make broad generalizations about the form in which such proteins are produced and how they may be recovered:

> [I]t is common for mature heterologous proteins expressed in E. coli to be deposited within the cells as insoluble particles which require cell lysis and solubilization in denaturant to permit recovery. On the other hand, proteins under proper synthesis circumstances, in yeast and bacterial strains, can be secreted into the medium (yeast and gram positive bacteria) or into the periplasmic space (gram negative bacteria) allowing recovery by less drastic procedures. Tissue culture cells as hosts also appear, in general, to permit reasonably facile recovery of heterologous proteins.

Ex. 1001, 12:39-49.

2. The Prior Art Taught Expression of Single Immunoglobulin Chains

Before April 1983, the technology existed to produce either heavy or light immunoglobulin chains in host cells.[10] During the '415 patent reexamination, for example, Owners argued that the Axel patent "describes nothing more than what is inherently required by the [Cabilly I patent]—production of one desired polypeptide (e.g., a heavy or a light immunoglobulin chain polypeptide) in one transformed host cell." Ex. 1024, Appeal Brief, at 47. Similarly, Owners

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[10] By April 1983, there were a dozen or so published sequences of isolated DNA encoding for at least the variable domains of immunoglobulin heavy and light chains. Ex. 1029, Kabat at 246, 248, 249 (selected pages from a compendium of "sequences of proteins of immunological interest"). A POSITA therefore would have had access to or have been able to isolate without undue experimentation these DNA sequences. Ex. 1006, Foote Decl., ¶ 43 & n. 5.

summarized Moore as calling for the "production of heavy and light immunoglobulin polypeptides in separate host cells, and propos[ing] assembly of the multimeric immunoglobulin complex by combining the individually produced chains in a test tube." Ex. 1023, Owners Response (6/6/08), at 25; Ex. 1006, Foote Decl., ¶ 47.

Even in 1977, before the Cohen & Boyer patent was filed, Stanley Cohen anticipated that bacteria could be engineered to make antibodies:

> [R]ecombinant DNA techniques potentially permit the construction of bacterial strains that can produce biologically important substances such as antibodies and hormones. Although the full expression of higher organism DNA that is necessary to accomplish such production has not yet been achieved in bacteria, the steps that need to be taken to reach this goal are defined, and we can reasonably expect that the introduction of appropriate "start" and "stop" control signals into recombinant DNA molecules will enable the expression of animal cell genes.

Ex. 1030, Cohen, at 655.

In 1979, Arthur Riggs (a co-inventor on the '415 patent) and Keiichi Itakura wrote that "[c]learly there is no fundamental barrier to prevent transcription and translation [i.e., expression] of eukaryotic genes in prokaryotes." Ex. 1003, Riggs & Itakura, at 537. "Techniques have developed rapidly, so that the genes necessary for altering the bacteria can be made and inserted with relatively modest expenditures of time and money." *Id.* at 533. The authors envisioned that "bacteria

may… be used for the production of the antibody peptide chains." *Id.* at 537.

Scientists subsequently employed these methods to produce single immunoglobulin chains in host cells. Rice & Baltimore (Ex. 1020), Ochi (I) (Ex. 1021) and Oi (Ex. 1031) reported experiments in which light chain DNA was successfully transformed into and expressed in mammalian host cells. Ex. 1006, Foote Decl., ¶ 50; Ex. 1016, Office Action (8/16/06), at 5, 23, 26.

The prior art reviewed in the '415 patent also taught that heavy and light chains produced in separate bacterial host cells may then be assembled *in vitro* using prior art protein denaturing (by reduction) and renaturing (by oxidation) chemical techniques. Ex. 1001, 12:58-13:52; Ex. 1006, Foote Decl., ¶ 51; *see also* Ex. 1003, Riggs & Itakura, at 537-38 ("Bacteria may then be used for the production of the antibody peptide chains, which could be assembled in vitro."); Ex. 1019, Moore, 11:1-6 (separately expressed single chains combined *in vitro*); Ex. 1032, Kaplan, 10:31-33 (same).

3. The Prevailing Mindset by April 1983 Was That One or More Proteins of Interest Could be Made in a Single Host Cell

In April of 1983, there was <u>not</u> a "prevailing mindset" in the prior art that only one protein of interest could be made per host cell. There were multiple references available before April 1983 teaching that <u>more than one mammalian gene</u> could be introduced into and expressed by a single host cell. Ex. 1006, Foote Decl., ¶¶ 52-58 (discussing the prior art summarized below).

For example, U.S. Patent No. 4,487,835 (Ex. 1033) summarizes the state of bacterial expression of eukaryotic (mammalian) proteins before April 1983:

> It is known to prepare useful polypeptides and proteins, for example enzymes, hormones… by cultivation of bacteria carrying plasmids with genes coding for the desired polypeptides or proteins. It is also known to construct plasmids containing desired genes by so-called recombinant DNA technique, which makes it possible to obtain, from the cultivated bacteria carrying such recombinant DNA plasmids, gene products which inherently are characteristic to other organisms than the bacteria used as host cells. In the preparation of recombinant DNA, a so-called cloning vector, that is, a plasmid which is able to replicate in the host bacterium, is combined with a DNA fragment containing a gene or genes coding for the desired product or products…. If the foreign DNA is transcribed and translated in the bacterial host, the gene products of the foreign DNA are produced in the bacterial host.

Ex. 1033, 1:17-31, 51-53; *see also* U.S. Patent No. 4,371,614 (Ex. 1034), 1:43-58 ("[O]ne or more genes from a donor organism, such as a… eukaryotic cell are introduced into a vector" that is transformed into "a host organism, usually a prokaryotic bacterial microorganism" to "produce corresponding enzymes using the available protein-synthesizing apparatus of the host."); U.S. Patent No. 4,762,785 (Ex. 1035), 2:66-3:5 (vector for transforming a prokaryotic host in which "[o]ne or more segments of alien DNA will be included in the plasmid, normally encoding one or more proteins of interest…. derived from any convenient

source, either prokaryotic or eukaryotic, including… mammals."); U.S. Patent No. 4,476,227 (Ex. 1036), 3:1-4 (vector comprising foreign DNA, wherein "the foreign DNA can be of eukaryotic or prokaryotic origin and might include… one or more genes for expression and production of commercially useful products"); U.S. Patent No. 4,362,867 (Ex. 1037), 8:48-52 (eukaryotic DNA inserted into a plasmid for transforming *E. coli* to produce a desired protein may include a "gene or genes coding for the cellular production of a desired [protein] product or products").

Similarly, U.S. Patent No. 4,396,601 (Ex. 1038) teaches introducing and co-expressing multiple independent eukaryotic genes in a single mammalian host cell. The patent teaches that "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. 1038, 3:51-53. "The DNA employed may provide for a single gene, a single set of genes, e.g., the beta-globin gene cluster, or a plurality of unrelated genes." *Id.* at 5:26-29 (emphasis added). The Southern prior art publication (Ex. 1004), one of Petitioners' references underlying their grounds for rejection, also teaches expressing multiple genes of interest in a mammalian host cell by using two vectors to co-transform the cell, with each vector containing a different gene of interest. *Infra* at 33-34, 47-50.

The expression of "one or more genes," "two or more genes," a "plurality of unrelated genes" or "a gene or genes" "encoding one or more proteins of interest"

in a single host cell—this was the prevailing mindset in April 1983, and not the "one polypeptide per host cell" postulate advocated by Owners during reexamination. Ex. 1006, Foote Decl., ¶ 59. And it was this prevailing mindset that is reflected around the time of filing of the '415 patent in the teachings of heavy and light chain co-expression in the Boss patent (Ex. 1012, 5:43-566:1-17) and in the work of scientists who published their heavy and light chain co-expression experiments shortly after April 1983 (Ex. 1040, Ochi (II)). Ex. 1006, Foote Decl., ¶ 59.

The state of the art of the co-expression of genes (eukaryotic and otherwise) in recombinant systems before April 1983 was advanced enough so that even as early as 1980, Dr. César Milstein—a Nobel Laureate (with Georges Köhler) for his work on monoclonal antibodies—suggested its application in antibody production. He anticipated bacterial and mammalian host cells transformed with heavy and light chain DNA, followed by expression of the respective polypeptides. Ex. 1039, Milstein, at 409-10. Dr. Milstein observed that if bacterial host cells are used, "we have to face the possibility that bacteria may not be able to handle properly the separated heavy and light chains so that correct assembly becomes possible." *Id.* at 410. This concern of Dr. Milstein's—that bacteria may not be able to correctly assemble the heavy and light chains—necessarily presumes a single bacterial cell

that has been transformed with the both heavy chain and light chain genes and was co-expressing both genes. Ex. 1006, Foote Decl., ¶ 60.

Thus, in the five years preceding the '415 patent's filing date: (1) there was an available set of platform technologies for making mammalian proteins in bacterial and mammalian host cells; (2) the ability to make single immunoglobulin (either heavy or light) chains in bacterial and mammalian host cells was known in the art; and (3) the art expressed multiple suggestions that more than one gene of interest can be introduced into a host cell to produce more than one protein of interest. All of these teachings are germane to Petitioners' grounds for rejection of the challenged claims in view of Bujard and Cohen & Boyer.

B. References Underlying the Grounds for Rejection

1. Bujard Teaches Introducing and Expressing a "Plurality of Genes" in Bacterial or Mammalian Host Cells and Identifies "Immunoglobulins" as a Protein of Interest

Bujard (Ex. 1002) issued on January 22, 1985, to inventors Hermann Bujard and Stanley Cohen based on an application filed May 20, 1981. Bujard qualifies as prior art under §102(e). Bujard was never cited by Genentech, or identified or relied upon by the PTO, during prosecution or reexamination of the '415 patent.

Bujard is directed to vectors made by recombinant DNA technology for expressing proteins of interest in transformed host cells. Ex. 1006, Foote Decl., ¶¶ 61-64. Bujard notes that the preexisting technology had already "established the

feasibility of producing a wide variety of naturally occurring and synthetic polypeptides by means of hybrid DNA technology," but acknowledges that "there are continuing and extensive efforts to provide for more efficient and economic methods for producing the polypeptides." Ex. 1002, 1:13-18. The vectors in Bujard are optimized over prior art vectors by increasing their efficiency in transcribing DNA to RNA and in expressing one or more genes of interest (referred to in the patent as "structural genes"[11]) in host cells to produce one or more proteins of interest. Ex. 1006, Foote Decl., ¶¶ 61-62, 64-66. Bujard identifies immunoglobulins among the proteins that can be made by the disclosed process, vectors and transformed host cells taught by Bujard. *Id.* at ¶ 69.

The vector of Bujard consists of four elements in this order: (1) a "strong promoter," (2) a "DNA sequence of interest" encoding for the desired protein(s) of interest, (3) a "balanced terminator," and (4) a DNA sequence encoding for a selectable marker. Ex. 1002, 2:3-20; Ex. 1006, Foote Decl., ¶ 63. The DNA sequence of interest, which "usually" consists of "structural genes," is inserted between the strong promoter and terminator to "provide for efficient transcription and/or expression of the sequence." Ex. 1002, 2:33-38; Ex. 1006, Foote Decl., ¶¶ 63-66. The DNA sequence of interest may contain "<u>more than one</u> gene, that is

[11] A "structural gene" is a gene that "provid[es] a poly(amino acid)," i.e., a protein. Ex. 1002, 3:9-14; Ex. 1006, Foote Decl., ¶ 65.

a plurality of genes, including multimers and operons."[12] Ex. 1002, 3:46-48; Ex. 1006, Foote Decl., ¶¶ 64-66; *see also* Ex. 1002, 7:61-63 ("[O]ne or more structural genes may be introduced between the promoter and terminator") and 8:7-11 ("Alternatively, the gene(s) of interest may be ligated to the appropriate regulatory signal sequences before insertion into the [plasmid] vehicle"). These are the exact teachings of multiple DNA sequences that Owners argued during the '415 patent reexamination were absent from the Axel patent. *Supra* at 14-15.

Further, the vector with the inserted DNA sequence of interest containing one or more structural genes "can be used with one or more hosts for gene expression" of a "wide variety of poly(amino acids)" by transforming the host cell (either a microorganism, *e.g.*, *E. coli*, or a mammalian cell) with the vector. Ex. 1002, 3:61-63, 6:23-37, 8:1-3, 11:28-31; Ex. 1006, Foote Decl., ¶ 64. Among the "wide variety" of genes and proteins of interest identified in the patent are

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[12] "Multimer" refers to a protein with more than one subunit. *Supra* at 12, n. 8. In the context of Bujard, a POSITA would therefore understand the use of the term "multimer" to mean "genes encoding multimeric proteins." Ex. 1006, Foote Decl., ¶¶ 67-68. When a multimeric protein is encoded by a "plurality of genes," with each gene making a different type of polypeptide, this can only be construed as a multimeric protein with chemically distinct (*i.e.*, non-identical) polypeptide subunits, for example, an immunoglobulin. *Id.* at ¶¶ 68-69.

"immunoglobulins e.g. IgA, IgD, IgE, IgG and IgM and fragments thereof," as well as "free light chains." Ex. 1002, 4:14-16, 4:30-36, 5:11-27. The Bujard patent makes clear the common knowledge at the time that antibodies are assembled from multiple, discrete polypeptides (four—two heavy and two light chains) encoded for by two different genes: it identifies the molecular formula of each type of immunoglobulin that can be produced according to the disclosed method—for example, the patent notes that IgG has the molecular formula of "$\gamma_2\kappa_2$ or $\gamma_2\lambda_2$" (two heavy chains (γ_2) and two light chains (κ_2 or λ_2)). Ex. 1002, 5:11-14; Ex. 1006, Foote Decl., ¶ 70.

The resultant proteins produced by the transformed host cells may be prepared either "as a single unit" or "as individual subunits and then joined together in appropriate ways." Ex. 1002, 4:19-21. The "single unit" is a reference that a POSITA would understand to include an *in vivo* assembled multimeric protein, such as an immunoglobulin; the joining together of "individual subunits" by appropriate is a reference that a POSITA would understand to include the *in vitro* assembly of the constituent polypeptide subunit chains of a multimeric protein, such as an immunoglobulin. Ex. 1006, Foote Decl., ¶ 73.

2. Cohen & Boyer Teaches Introducing and Expressing "One or More Genes" in Bacteria and Identifies "Antibodies" as a Protein of Interest

Cohen & Boyer (Ex. 1005) issued on December 2, 1980, to inventors

Stanley Cohen and Herbert Boyer based on an application filed January 4, 1979 (with a priority claim through a series of continuation-in-part applications dating back to 1974). Cohen & Boyer qualifies as prior art under §102(b). Although Cohen & Boyer appears under "References Cited" in the '415 patent, it was never the subject of a rejection by the PTO during prosecution or reexamination.

Cohen & Boyer teaches a process for creating vectors or plasmids to serve as a vehicle for introducing into a bacterial host cell a DNA sequence that contains one or more foreign (or exogenous) genes encoding for a protein that the bacterial host cell would not ordinarily make. Ex. 1006, Foote Decl., ¶¶ 75, 77. The bacterial host cell transformed with the vector containing the foreign gene or genes will express the protein or proteins of interest encoded by the foreign DNA. *Id.* at ¶¶ 77-78. Proteins of interest that can be made by the disclosed process and associated vectors and transformed host cells in Cohen & Boyer include antibodies. *Id.* at ¶ 80.

The starting point for the Cohen & Boyer process is a vector that is compatible with a microorganism host cell and which already contains a gene sequence encoding for a selectable marker. Ex. 1005, 2:30-34, 3:3-24; Ex. 1006, Foote Decl., ¶ 77. The patent teaches that into this vector is inserted (or "ligated") a foreign DNA fragment. Ex. 1005, 1:56-59, 4:29-38, 5:12-20; Ex. 1006, Foote Decl., ¶ 77. This foreign DNA fragment may include "one or more genes"

(alternatively, "at least one intact gene" or "at least one foreign gene"). Ex. 1005, 5:59-65, 1:56-59, 6:43-47, claim 1; Ex. 1006, Foote Decl., ¶¶ 78-79. The source of the foreign DNA can be eukaryotic, thus including vertebrates, for example mammals. Ex. 1005, 5:59-61, 8:64-68; 16:36-41. As with Bujard, these are the very teachings of multiple DNA sequences that Owners asserted were absent from the prior art (including the Axel patent) under consideration by the PTO during reexamination of the '415 patent. *Supra* at 14-15.

Cohen & Boyer's vector with the inserted foreign DNA fragment containing one or more foreign genes (referred to in the patent as the "plasmid chimera") is then used to transform a bacterial host cell. Ex. 1005, 7:31-33, 9:1-11; Ex. 1006, Foote Decl., ¶ 77. Isolating those cells that have been successfully transformed provides a source of cells for the "expression of the DNA molecules present in the modified plasmid," including "expression of [the] exogenous genes." Ex. 1005, Abstract; Ex. 1006, Foote Decl., ¶ 77. More specifically,

> [b]y introducing one or more exogeneous genes into a unicellular organism, the organism will be able to produce polypeptides and proteins ("poly(amino acids)") which the organism could not previously produce. In some instances the poly(amino acids) will have utility in themselves…. [P]oly(amino acids) of interest include… globulin e.g. gamma-globulins or antibodies.

Ex. 1005, 9:12-17, 9:28-32; Ex. 1006, Foote Decl., ¶ 80. Cohen & Boyer teaches that the protein or proteins of interest produced using the disclosed methods can be

produced by the cells as the "desired end product," *e.g.*, an "antibody," that is, an assembled tetramer of two heavy and two light chains. Ex. 1005, 1:64-67; Ex. 1006, Foote Decl., ¶ 81. On the other hand, the protein can be recovered by lysing the microorganism, which permits isolation of the protein(s) from the cell lysate. Ex. 1005, 1:67-68; Ex. 1006, Foote Decl., ¶ 81. When the recovered proteins are part of a multimeric protein, they can be subjected to chemical manipulation by known methods to assemble the polypeptide subunits *in vitro* to result in the multimeric protein of interest identified in the patent. Ex. 1006, Foote Decl., ¶ 81.

Cohen & Boyer constitutes a platform technology—that is, a process with broad applicability beyond the inventors' initial "proof of concept," minimizing any need to "reinvent the wheel" to support future developments in the field, Ex. 1006, Foote Decl., ¶¶ 83, 76, 82, as Cohen & Boyer itself acknowledges:

> The subject process provides a technique for introducing into a bacterial strain a foreign capability which is genetically mediated. <u>A wide variety of genes may be employed</u> as the foreign genes <u>from a wide variety of sources</u>. Any intact gene may be employed which can be bonded to the plasmid vehicle. The source of the gene can be other bacterial cells, mammalian cells, plant cells, etc. <u>The process is generally applicable to bacterial cells capable of transformation</u>.

Ex. 1005, 8:62-9:2 (emphasis added).

Unsurprisingly, the Cohen & Boyer patent family was widely licensed to the pharmaceutical industry for a variety of blockbuster therapeutic protein products

made by recombinant DNA technology, including antibodies. Ex.1043, Feldman, at 1805. Eli Lilly (partnered with Centocor) licensed the patents for its "abciximab" (ReoPro®) product, an FDA-approved antibody to prevent cardiac ischemia. *Id.*; Ex. 1044, ReoPro® Prescribing Info., at 1. Abciximab is a chimeric antibody fragment, with variable regions of mouse origin and partial constant regions of human origin. Ex. 1044, ReoPro® Prescribing Info., at 1. The heavy and light chain fragments are co-expressed in a single mammalian (mouse) host cell line. Ex. 1045, Ghrayeb Aff., ¶ 6-8; Ex. 1006, Foote Decl., ¶ 84.

3. Riggs & Itakura Teaches Hybridomas as a Source of Antibody Genes and the In Vitro Assembly of Heavy and Light Chains

Riggs & Itakura (Ex. 1003) published in 1979 and qualifies as prior art under §102(b). Riggs & Itakura was never cited by Genentech, or identified or relied upon by the PTO, during prosecution or reexamination of the '415 patent.

Arthur Riggs and Keiichi Itakura were among the first scientists to use recombinant DNA technology to express mammalian proteins in bacteria. Ex. 1006, Foote Decl., ¶ 85. In the article, they provide an overview of their work on making human insulin in bacteria: creating synthetic DNA encoding for the insulin A and B polypeptide chains, using recombinant DNA techniques to insert the genes into separate plasmids, separately transforming *E. coli* cells with plasmids containing the genes for the A and B chains, recovering the expressed chains from lysed bacterial cells, and *in vitro* assembly of the chains into an intact insulin

molecule. Ex. 1003, at 531-533; Ex. 1006, Foote Decl., ¶ 85. The authors saw the practical application for this technology as extending beyond insulin production. Ex. 1003, at 537-38; Ex. 1006, Foote Decl., ¶ 85.They taught that "[h]ybridomas will provide a source of mRNA for specific antibodies. Bacteria may then be used for the production of the antibody peptide chains, which could be assembled in vitro." Ex. 1003, at 537-38; Ex. 1006, Foote Decl., ¶ 85.

4. Southern Teaches One Host Cell Transformed with Two Vectors

Southern (Ex. 1004) published in July 1982 and qualifies as prior art under §102(a). Southern was never cited by Genentech, or identified or relied upon by the PTO, during prosecution or reexamination of the '415 patent.

Southern teaches a single mammalian host cell that is "cotransformed"[13] with two separate plasmids: the first (called "pSV2neo") containing the selectable marker gene "neo," which when expressed as a protein provides the cells with the ability to grow in the presence of the antibiotic G418; the second ("pSV2gpt") containing the selectable marker gene "gpt," which when expressed as a protein provides the cells with the ability to grow in the presence of the antibiotic MPA. Ex. 1004, at 336-337, Table 3; Ex. 1006, Foote Decl., ¶¶ 86-87. The cotransformed host cells successfully expressed both selectable marker proteins and were able to

[13] This is also referred to as "cotransduction" and "cotransfection" in the article. Ex 1004, at 336, 337; Ex. 1006, Foote Decl., ¶ 88, n. 8.

grow in the presence of both antibiotics, *i.e.*, they were "double selected." Ex. 1004, at 336-337, Table 3; Ex. 1006, Foote Decl., ¶¶ 88-89. Southern evinces a formal proof that the two expression vectors are compatible and can be used and selected for simultaneously in the same cell without interfering with each other. 1006, Foote Decl., ¶ 88.

While Southern's cotransformation experiments used the two vectors without "gene-of-interest" insertions, that was merely an experimental convenience. Ex. 1006, Foote Decl., ¶ 89. Both vectors are described repeatedly as expression vectors, and the intent to use them to coexpress multiple "genes of interest,"[14] one on each vector, with double selection is made explicit in the paper's concluding statement: "[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, at 339; Ex. 1006, Foote Decl., ¶ 89.

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[14] Also called "nonselectable genes" in Southern, that is, genes that do not confer a selective advantage to the host cell. Ex. 1004, at 336; Ex. 1006, Foote Decl., ¶ 90, n. 9.

V. FULL STATEMENT OF PRECISE RELIEF REQUESTED AND THE REASONS THEREFORE (37 C.F.R. § 42.22(a))

A. Explanation of Ground 1 for Unpatentability: Bujard Anticipates Claims 1, 3, 4, 9, 11, 12, 15-17, 19 and 33

Bujard (Ex. 1002) anticipates claims 1, 3, 4, 9, 11, 12, 15, 16, 17, 19 and 33 by disclosing each and every limitation of these challenged claims, either expressly or inherently. *See Allergan v. Apotex*, 754 F. 3d 952, 958 (Fed. Cir. 2014). Whether a claim limitation is present in a prior art reference must be determined from the perspective of a POSITA. *Dayco Prods. v. Total Containment*, 329 F.3d 1358, 1368-69 (Fed. Cir. 2003); *see also In re Donohue,* 632 F.2d 123, 125 (C.C.P.A. 1980) (reference must be "taken in conjunction with the knowledge of those skilled in the art" to anticipate).

A claim limitation is inherent in a prior art reference if it is "necessarily present" in the reference. *Schering Corp. v. Geneva Pharmaceuticals*, 339 F. 3d 1373, 1377 (Fed. Cir. 2003). This can occur, for example, (1) when the "natural result flowing" from an express disclosure in the reference is the performance of the inherent feature, *id.* at 1379; or (2) 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 v. Monsanto*, 948 F. 2d 1264, 1268-69 (Fed. Cir. 1991). A POSITA may therefore apply "simple logic" or "common sense" in interpreting a prior art

reference to find that it anticipates even when the reference does not disclose a claim limitation 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). Simply put, anticipation does not require a specific incantation in the prior art of the exact language in the claims. *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").

Moreover, anticipation also does not require "actual performance of suggestions in a disclosure." *Bristol-Myers Squibb v. Ben Venue Labs.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001); *see also Gleave*, 560 F.3d at 1334 ("actual creation or reduction to practice" not necessary to anticipate). Rather, "anticipation only requires that those suggestions be enabled to one of skill in the art." *Bristol-Myers Squibb*, 246 F.3d at 1379. "This is so despite the fact that the description provided in the anticipating reference might not otherwise entitle its author to a patent." *Gleave*, 560 F.3d at 1334 (citing *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991) (distinguishing claim supporting disclosures under § 112 from claim anticipating disclosures under § 102(b)).

Like all U.S. patents (as well as non-patent prior art publications), Bujard is presumed to be enabled for both its claimed and unclaimed subject matter. *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). Because "[e]very patent application and reference relies to some extent upon knowledge of persons skilled in the art to complement that disclosed in order that it be 'enabling' within the meaning of § 112 and to satisfy the requirements of a reference under § 102," *In re Wiggins*, 488 F.2d 538, 543 (C.C.P.A. 1973), "a patent need not teach, and preferably omits, what is well known in the art." *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

1. Bujard Anticipates Independent Claims 1, 15, 17 and 33

The Bujard patent teaches a process for producing proteins of interest—among which the patent expressly identifies immunoglobulins—in a transformed host cell using a plasmid vector that is optimized to increase the efficiency of expression. Ex. 1002, 2:1-20, 3:9-14, 3:61-62, 4:14-16, 4:30-36, 5:11-27; Ex. 1006, Foote Decl., ¶ 91; *see also supra* at 25-28. Producing such proteins as taught by Bujard occurs in a single host cell—either bacterial or mammalian—that is transformed with a single plasmid containing "more than one gene, that is a plurality of genes." Ex. 1002, 3:46-48, 3:61-62, 6:23-37; Ex. 1006, Foote Decl., ¶ 91; *see also supra* at 26-27. Bujard's identification of immunoglobulins—a tetrameric molecule well known at the time by technologists in the field to be composed of two different polypeptide chains, each encoded by a separate DNA

sequence—as a protein that can be produced in a host cell would have clearly disclosed to a POSITA that the plasmid necessarily must contain two foreign DNA sequences, one each for the heavy and light chains. Ex. 1006, Foote Decl., ¶ 91. This is made explicit in Bujard by its identification of the molecular formulas for immunoglobulins, e.g., $\gamma_2\kappa_2$ or $\gamma_2\lambda_2$ (two heavy and two light chains). Ex. 1002, 5:11-14; Ex. 1006, Foote Decl., ¶ 91; *see also supra* at 28. It would have been common knowledge to a POSITA, and he or she would have understood as a matter of simple logic and common sense, that there would simply be no other way to produce an "immunoglobulin" in a single host cell transformed with a plasmid having "more than one gene" unless both heavy and light chain DNA sequences were present in the plasmid. *Id.* at ¶ 91. These teachings in Bujard correspond directly and unambiguously to the limitations of the challenged independent process claims (Ex. 1001, claims 1, 33) that require "a process for producing an immunoglobulin" in a "single host cell" by "transforming" the host cell with "a first DNA sequence… and a second DNA sequence encoding" the "immunoglobulin heavy chain" and "immunoglobulin light chain." *Id.* at ¶ 91. These teachings in Bujard also read on the limitations of the independent composition claims (Ex. 1001, claims 15, 17) that require "a vector" with "a first DNA sequence… and a second DNA sequence encoding" the "immunoglobulin heavy chain" and "immunoglobulin light chain," and "a host cell transformed" with this vector. *Id.*

A host cell transformed with the plasmid containing the immunoglobulin (heavy and light chain) DNA sequences will "express" (Ex. 1001, claims 1, 33) both of the inserted genes in the plasmid. Ex. 1002, 2:28-32, 3:39-42, 7:64-68; Ex. 1006, Foote Decl., ¶ 92; *see also supra* at 26-27. A POSITA would have known that the heavy and light chain DNA sequences would necessarily be arranged non-contiguously in the plasmid "at different insertion sites" (Ex. 1001, claim 15), separated from each other by sufficient non-coding DNA sequences so that they are "independently expressed" to produce "separate molecules," *i.e.*, separate heavy and light chains (Ex. 1001, claims 1 and 33). Ex. 1006, Foote Decl., ¶ 92. The necessity of this particular arrangement of the heavy and light chain genes in the plasmid would have been within the common knowledge of, and clearly understood by, a POSITA based on the identification of antibodies as an exemplar protein that could be produced in a single host cell by the Bujard method. *Id.* at ¶ 92. If the heavy and light chain DNA sequences were not so arranged, the expressed protein would be a fusion of a heavy chain and a light chain as a single, continuous polypeptide—a product not contemplated by Bujard, and certainly not one that would be understood by a POSITA in 1983 to be an "antibody," or that could form an antibody tetramer.[15] *Id.* at ¶ 92. A POSITA would therefore know

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[15] Even the PTO recognized that such an interpretation of the prior art would make no sense: "[E]xpressing the light and heavy chains as a fusion protein as implied by

that when producing an "immunoglobulin" as a protein of interest, the heavy and light chains must be produced as separate polypeptide molecules, as there is no other way for their assemblage to result in an immunoglobulin tetramer. *Id.* at ¶ 92. Furthermore, the independent expression of separate proteins in a single host cell transformed with a vector containing two different genes would not have been a novelty or surprising process to employ by a POSITA in April 1983: it is exactly what Axel taught when it disclosed the expression of two DNA sequences in a mammalian host cell. *Id.* at ¶ 92; *supra* at 10-11.

Finally, Bujard teaches that when transformed as described above, a host cell can produce *in vivo* a "single unit" of the protein of interest, here an immunoglobulin, *i.e.*, an assembled tetrameric molecule, as required by the challenged process claims of the '415 patent. Ex. 1002, 4:19-21, 4:30-36, 5:11-27; Ex. 1006, Foote Decl., ¶ 93; *see also supra* at 28. However, if the heavy and light chains do not assemble into a immunoglobulin tetramer inside of the host cell, Bujard instructs POSITAs that the "individual subunits" may be "joined together in appropriate ways," Ex. 1002, 4:19-21, a reference that a POSITA would have readily understood to refer to *in vitro* assembly of the chains to create an immunoglobulin tetramer. Ex. 1006, Foote Decl., ¶ 93.

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the patentee… would make assembly of the light and heavy chains prohibitive." Ex. 1008, Office Action (2/16/07), at 53.

Summary of Bujard's Anticipation of Claims 1, 15, 17 and 33	
'415 Patent Claims	**Representative Disclosures of Bujard**
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.	**a.** "A wide variety of structural genes are of interest for production of proteins, including but not limited to proteins of physiological interest…. The following is a representative list of proteins of interest… immunoglobulins e.g. IgA, IgD, IgE, IgG and IgM and fragments thereof." 4:14-36 **b.** "A vector is constructed having a strong promoter, followed by a DNA sequence of interest, optionally followed by one or more translational stop codons in one or more reading frames, followed by a balanced terminator, followed by a marker allowing for selection of transformants." 2:8-13. **c.** "T5 phage promoters are isolated, cloned in conjunction with a strong terminator, and appropriate vectors developed for insertion of DNA sequences of interest, usually structural genes, to provide for high and efficient transcription and/or expression of the sequence." 2:33-38 **d.** "[T]he promoter and terminator may be separated by more than one gene, that is, a plurality of genes, including multimers and operons." 3:46-48 **e.** "The plasmids may then be used for transformation of an appropriate microorganism host." 3:61-62
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.	*See* **a-d** above for Claim 1
17. A host cell transformed with a vector according to	*See* **a-e** above for

claim 15.	Claim 1
33. 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: independently expressing 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 so that said immunoglobulin heavy and light chains are produced as separate molecules in said single host cell transformed with said first and second DNA sequences.	*See* **a-e** above for Claim 1

VI. Bujard Anticipates Dependent Claims 3, 4, 9, 11, 12, 16 and 19

The additional limitations in dependent claims 3, 4, 9, 11, 12, 16 and 19 are also disclosed in, and therefore anticipated by, Bujard. **Claim 3** requires that the heavy and light chain DNA sequences be "present in a single vector." Bujard teaches this vector as discussed *supra* at pages 37-39. Ex. 1006, Foote Decl., ¶ 94. **Claims 4** and **16** require that the "vector" of the claims that they depend upon is a "plasmid." Again, the teaching of a plasmid vector in Bujard is discussed above. Ex. 1006, Foote Decl., ¶ 94.

Claim 9 requires that the heavy and light chains of claim 1 "are expressed in the host cell and secreted therefrom as an immunologically functional immunoglobulin molecule or immunoglobulin fragment." Producing chains "in the host cell" as an immunoglobulin molecule is a reference to *in vivo* assembly of the

chains into an immunoglobulin,[16] which Bujard expressly teaches as discussed *supra* at 40; Ex. 1006, Foote Decl., ¶ 95. Moreover, heavy and light chains can only assemble *in vivo* in a mammalian host cell if their genes (as they would have been isolated by a POSITA and inserted into the vector) encode particular amino acid sequences that "signal" the cellular processing machinery to route the immunoglobulin polypeptide chains through the host cell's secretory pathway, as opposed to retaining the chains in the host cell's cytoplasm. Ex. 1006, Foote Decl., ¶ 95. (That is why immunoglobulins made by immune system cells (generally, B cells) are naturally secreted from these cells. *Id.*) These signal sequences, as an intermediate step in the secretory pathway, cause the localization of the chains to a compartment within the mammalian host cell that provides a chemically hospitable environment to permit the chains to assemble *in vivo* into an immunoglobulin. *Id.* The natural flowing result of the presence of these sequences is that they also therefore "signal" the host cell to secrete the assembled immunoglobulin from the cell and into the cell culture medium. *Id.* As in B cells, heavy and light chains in transformed mammalian host cells would also be localized to a compartment for their assembly into an immunoglobulin tetramer and secretion from the cell. *Id.*

Claim 11 requires that the DNA sequences encode the "complete" heavy

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[16] Ex. 1009, Owners' Response (11/25/05), at 47-48 (distinguishing claim 9 from the Axel patent).

and light chain polypeptides. Bujard teaches this claim limitation insofar as its disclosure of immunoglobulins is not qualified in any way to be limited to fragments. *Id.*, ¶ 96.[17] Indeed, a POSITA would have understood that, by definition, a reference to "immunoglobulins," without any additional qualifications, means a tetrameric assembly of complete heavy and light chains. *Id.*

Claim 12 requires that any "constant domain" encoded by the DNA sequences "is derived from the same source as the variable domain to which it is attached." Bujard teaches this claim limitation insofar as the disclosure of immunoglobulins in the patent is not qualified in any way as limited to chimeric antibodies. *Id.* at ¶ 97. Indeed, a POSITA would have understood that a reference to "immunoglobulins," without additional qualifications, would include immunoglobulins in which the constant and variable domains are derived from the same species. *Id.*

Claim 19 requires that the host cell of claim 1 is a "mammalian cell." Bujard teaches mammalian host cells. Ex. 1002, 6:34-37; Ex. 1006, Foote Decl., ¶ 98.

A. Explanation of <u>Ground 2</u> for Unpatentability: Claims 1, 3, 4, 11, 12, 14, 19 and 33 Are Obvious Over Bujard in View of Riggs & Itakura

Claims 1, 3, 4, 11, 12, 14, 19 and 33 are invalid as obvious over Bujard in view of Riggs & Itakura. These claims all require that an "immunoglobulin"—*i.e.*,

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[17] Bujard also discloses the production of antibody "fragments." Ex. 1002, 4:35-36.

a tetrameric molecule of two heavy and two light chains—be "produced" by following the claimed methods. Bujard teaches this limitation insofar as it expressly teaches the production of "immunoglobulins" in host cells, either through assembly by *in vivo* or *in vitro* means. *Supra* at 40. But even if a POSITA would not interpret Bujard to teach assembly of the chains into an immunoglobulin tetramer, a POSITA would nevertheless be motivated to combine Bujard with the *in vitro* assembly disclosures in Riggs & Itakura (Ex. 1003, at 537-38) with a reasonable expectation of success in achieving the purported invention of the challenged claims, thus rendering the claims obvious. Ex. 1006, Foote Decl., ¶ 99.

Bujard and Riggs & Itakura are publications in the same general field of research: the production of heterologous eukaryotic proteins in host cells. *Id.* at ¶ 100. Beyond that general motivation to combine the references, the particular motivation to combine the *in vitro* protein assembly techniques of Riggs & Itakura with the Bujard antibody production method is found in Bujard itself. *Id.* Bujard suggests at least two ways of obtaining the desired protein end product, one of which is that "individual [protein] subunits" can be "joined together in appropriate ways." Ex. 1002, at 4:20-21; Ex. 1006, Foote Decl., ¶ 100; *see also supra* at 28. When the desired end product is a multi-subunit protein such as an immunoglobulin, a POSITA would have understood that the individual subunits (heavy and light chains) may be recombined according to known methods,

including those referenced in Riggs & Itakura, which addresses the same problem of joining unassociated immunoglobulin (and insulin) chains separately produced in microorganism host cells. Ex. 1003, at 537-38; Ex. 1006, Foote Decl., ¶ 100. A POSITA would therefore have had a good reason to combine Bujard with Riggs & Itakura. Ex. 1006, Foote Decl., ¶ 100.

A POSITA would have also reasonably predicted that combining Bujard with the *in vitro* assembly techniques in Riggs & Itakura would result in an assembled immunoglobulin molecule. Ex. 1006, Foote Decl., ¶ 101. Riggs & Itakura themselves demonstrated that the separate chains of insulin could be joined *in vitro*, and taught that the same or similar techniques could be used successfully for immunoglobulin chains made by recombinant DNA means in microorganism host cells. Ex. 1003, at 531-32, 537-38; Ex. 1006, Foote Decl., ¶ 101. There would have been no reason for a POSITA to believe that these methods could not also be successfully used to assemble the heavy and light chains produced by Bujard's similar recombinant DNA methodologies. Ex. 1006, Foote Decl., ¶ 101. A POSITA would therefore have had a reasonable expectation of success in combining Bujard with Riggs & Itakura to result in the subject matter of the challenged claims. *Id.*

Dependent claim 14 also requires that the heavy and light chain DNA sequences "are derived from one or more monoclonal antibody producing

hybridomas." A POSITA would have been motivated to combine Bujard with the hybridoma teachings in Riggs & Itakura (Ex. 1003, at 537) with a reasonable expectation of success in achieving the purported invention of claim 14, thus rendering the claim obvious. Ex. 1006, Foote Decl., ¶ 102. Riggs & Itakura expressly teaches that hybridomas would be a source of genetic material for heavy and light chains, which could then be used for their production in bacteria. Ex. 1003, at 537; Ex. 1006, Foote Decl., ¶ 102. As discussed above, a POSITA would have been motivated to combine these references, and would have done so with the reasonable expectation that the hybridoma immunoglobulin genes could be successfully used in the Bujard system to result in the subject matter of claim 14. Ex. 1006, Foote Decl., ¶ 102. Indeed, a POSITA would not doubt that immunoglobulin genes derived from a hybridoma would work in the Bujard method, and Riggs & Itakura itself teaches that bacterial host cells could be used to successfully make the chains from these genes. Ex. 1003, at 537-38; Ex. 1006, Foote Decl., ¶ 102.

B. Explanation of <u>Ground 3</u> for Unpatentability: Claims 1, 2, 18, 20 and 33 Are Obvious Over Bujard in View of Southern

Claims 1, 2, 18, 20 and 33 are invalid as obvious over Bujard in view of Southern. Claim 2 requires that the two DNA sequences of claim 1 "are present in different vectors"; claims 18 and 20 require a host cell and mammalian host cell, respectively, transformed with both of these separate vectors. A POSITA would

have been motivated to combine (1) Bujard's teaching of a mammalian host cell transformed with two DNA sequences (for heavy and light chains), both in a single vector with (2) the co-transformation approach taught in Southern, *i.e.*, a mammalian host cell transformed with two vectors, each with a different selectable marker and gene of interest. Ex. 1006, Foote Decl., ¶ 103. Both Bujard and Southern are publications directed to the expression of heterologous proteins in cells by using recombinant DNA technology and the related tools (vectors, host cells) to accomplish this. *Id.* Beyond this general motivation to combine the references, a POSITA would have recognized that both references have as a goal the expression of <u>genes of interest</u> in a single transformed host cell, whether by using one (Bujard) or two (Southern) vectors. *Id.* A POSITA would therefore have had a reason to combine Bujard with Southern and to modify Bujard accordingly by splitting the heavy and light chain DNA sequences into two separate vectors to be transformed in a single mammalian host cell. *Id.*

A POSITA would have also reasonably predicted that this modification of Bujard in accordance with Southern would have resulted in the purported inventions of claims 2, 18 and 20. *Id.* at ¶ 104. A POSITA would have been confident that a host cell's expression (transcription and translation) machinery would successfully make heavy and light chains from DNA sequences in separate vectors based on Southern's teaching that multiple proteins (selectable markers and

proteins of interest) present on separate vectors could be expressed in a single host cell. *Id.* Once a POSITA knows that heavy and light chain genes could be successfully co-expressed in a single host cell when present on one vector (as taught by Bujard), and that two genes of interest could also be successfully expressed in a single host cell when present on two vectors (as taught by Southern), the POSITA would have been confident that heavy and light chains could be successfully co-expressed in a single host cell when present on separate vectors. *Id.* A POSITA would have known that the expression machinery in cells works universally, regardless of any difference in genes (heavy/light chain versus non-immunoglobulin polypeptides) or whether they are on separate vectors (instead of one). *Id.* Furthermore, because the heavy and light chain genes are on different vectors in the same host cell, they would necessarily be "independently expressed" and produced as "separate molecules," as required by claim 2. *Id.* A POSITA would therefore have had a reasonable expectation of success in combining Bujard with Southern to result in the subject matter of challenged claims 2, 18 and 20. *Id.*

Because claim 2 is obvious over Bujard in combination with Southern, independent claim 1 on which claim 2 depends is necessarily obvious as well. *Callaway Golf Co. v. Acushnet Co.*, 576 F. 3d 1331, 1344 (Fed. Cir. 2009) (broader independent claim cannot be nonobvious where a dependent claim

stemming from that independent claim is invalid for obviousness); Ex. 1006, Foote Decl., ¶ 105. Furthermore, because the scope of claim 33 is no different in any meaningful way than the scope of claim 1—*i.e.*, they are both directed to co-expression of heavy and light chains in a single host cell, and are broad enough to encompass this through either a single vector or two-vector transformation—claim 33 is similarly obvious (as explained above for claim 2) over Bujard in view of Southern. Ex. 1006, Foote Decl., ¶ 105.

C. Explanation of <u>Ground 4</u> for Unpatentability: Claims 1, 3, 4, 11, 12, 14 and 33 Are Obvious Over Cohen & Boyer in View of Riggs & Itakura

1. The Disclosures of Cohen & Boyer

Cohen & Boyer teaches a process for producing an immunoglobulin molecule in a transformed unicellular organism, for example, a bacterial cell: "[b]y introducing one or more exogenous genes into a unicellular organism, the organism will be able to produce polypeptides and proteins ('poly(amino acids)') which the organism could not previously produce…. [P]oly(amino acids) of interest include… globulin e.g. gamma-globulins or antibodies…." Ex. 1005, 9:12-15, 9:28-30; Ex. 1006, Foote Decl., ¶ 106. The production of a protein or proteins of interest taught by Cohen & Boyer occurs in a single host cell that is transformed with a single plasmid containing "<u>one or more</u> genes," "<u>at least one</u> intact gene" or "<u>at least one</u> foreign gene." Ex. 1005, 4:29-38, 5:59-65, 1:56-59, 6:43-47, claim 1; Ex. 1006, Foote Decl., ¶ 106; *see also supra* at 29-30. Cohen & Boyer's

identification of "antibodies," which were known in April 1983 to be a tetrameric assemblage of heavy and light chains encoded by different genes, as a protein that could be produced in a unicellular organism would have clearly taught a POSITA that the plasmid necessarily must contain two foreign DNA sequences—one each for the heavy and light chains. Ex. 1006, Foote Decl., ¶ 106. A POSITA would have understood that there would simply be no other way to make an "antibody" in a single host cell transformed with a single plasmid having "at least one foreign gene" unless both heavy and light chain DNA sequences were present in the plasmid. *Id.* These teachings in Cohen & Boyer are identical to the limitations of the challenged independent process claims (Ex. 1001, claims 1, 33) that require "a process for producing an immunoglobulin" in a "single host cell" by "transforming" the host cell with "a first DNA sequence… and a second DNA sequence encoding" the "immunoglobulin heavy chain" and "immunoglobulin light chain." *Id.*

A bacterial host cell transformed with the plasmid containing the two immunoglobulin (heavy and light chain) DNA sequences will "express" (Ex. 1001, claims 1 and 33) both of the inserted genes in the plasmid. Ex. 1005, Abstract, 16:42-47; Ex. 1006, Foote Decl., ¶ 107. For the same reasons discussed above with respect to the Bujard patent (*supra* 39-40), the heavy and light chain DNA sequences would necessarily be arranged non-contiguously in the Cohen & Boyer

plasmid so that they are "independently expressed" to produce "separate molecules," *i.e.*, separate heavy and light chains (Ex. 1001, claims 1 and 33). Ex. 1006, Foote Decl., ¶ 107. Furthermore, a POSITA would understand that when producing an "antibody" as a protein of interest, as Cohen & Boyer plainly instructs is within its "generally applicable" process (Ex. 1005, 8:62-9:2), the heavy and light chains must be produced as separate polypeptide molecules. *Id.*

Summary of Cohen & Boyer's Disclosures with Respect to Claims 1 and 33	
'415 Patent Claims	**Representative Disclosures of Cohen & Boyer**
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	**a.** "By introducing one or more exogeneous genes into a unicellular organism, the organism will be able to produce polypeptides and proteins ("poly(amino acids)") which the organism could not previously produce…. Other poly(amino acids) of interest include… globulin e.g. gamma-globulins or antibodies…." 9:12-30 **b.** "A plasmid or viral DNA is modified to form a linear segment having ligatable termini which is joined to [foreign] DNA having at least one intact gene and complementary ligatable termini." 1:56-59 **c.** "[T]he DNA containing the foreign gene(s) to be bound to the plasmid vehicle will be cleaved in the same manner as the plasmid vehicle…. In this way, the foreign gene(s) will have ligatable termini, so as to be able to covalently bonded to the termini of the plasmid vehicle." 4:29-38 **d.** "The foreign DNA can be derived from a wide variety of sources. The DNA may be derived from eukaryotic or prokaryotic cells.... The DNA fragment may include one or more genes or one or more operons." 5:59-65 **e.** "The termini are then bound together to form a 'hybrid' plasmid molecule which is used to

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molecules in said transformed single host cell.	transform susceptible and compatible microorganisms." 1:60-67 **f.** "The plasmid vehicle… is capable of transforming a bacterial cell, so as to be capable of replication, transcription, and translation." 16:42-47 **g.** "The newly functionalized microorganisms may then be employed to carry out their new function; for example, by producing proteins which are the desired end product." 1:60-67 **h.** "[T]he subject method provides means for preparing enzymes and enzymic products from bacteria where the natural host is not as convenient or efficient a source of such product. Besides enzymes, other proteins can be produced such as antibodies, antigens, albumins, globulins, glycoproteins, and the like." 16:54-65
33. 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: independently expressing 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 so that said immunoglobulin heavy and light chains are produced as separate molecules in said single host cell transformed with said first and second DNA sequences.	*See* **a-h** above for Claim 1.

The additional limitations in dependent claims 3, 4, 11 and 12 are also disclosed in Cohen & Boyer. **Claim 3** requires that the heavy and light chain DNA sequences be "present in a single vector." Cohen & Boyer's teaching of such a vector is discussed above at pages 50-51; Ex. 1006, Foote Decl., ¶ 108. **Claim 4** further requires that the "vector" is a "plasmid." The teaching of a plasmid in

Cohen & Boyer is also discussed above. Ex. 1006, Foote Decl., ¶ 108.

Claim 11 requires that the DNA sequences encode the "complete" heavy and light chain polypeptides, *i.e.*, not a fragment of either chain. Cohen & Boyer teaches this limitation insofar as the disclosure of "antibodies" in the patent is not qualified in any way to be limited to antibody fragments. Ex. 1006, Foote Decl., ¶ 109. Indeed, a POSITA would have understood that, by definition, a reference to "antibodies," without any additional qualifications, means a tetrameric assembly of complete heavy and light chains. *Id.*

Claim 12 requires that any "constant domain" encoded by the DNA sequences "is derived from the same source as the variable domain to which it is attached." Cohen & Boyer teaches this claim limitation insofar as the disclosure of "antibodies" in the patent is not qualified in any way to be limited to chimeric antibodies, where, for example, the constant and variable domains are derived from different species. *Id.* at ¶ 110. Indeed, a POSITA would have understood that a reference to "antibodies," without any additional qualifications, would include antibodies in which the constant and variable domains are derived from the same source—species or otherwise. *Id.*

2. Cohen & Boyer in Combination with Riggs & Itakura's Teachings of In Vitro Assembly of Heavy and Light Chains Renders Obvious Claims 1, 3, 4, 11, 12, 14 and 33

Claims 1, 3, 4, 11, 12, 14 and 33 require that an "immunoglobulin"—an

assembled tetramer of heavy and light chains—be "produced" by following the claimed methods. Insofar as Cohen & Boyer may not teach this limitation, a POSITA would nevertheless be motivated to combine Cohen & Boyer with the *in vitro* assembly disclosures in Riggs & Itakura (Ex. 1003, at 537-38) with a reasonable expectation of success in achieving the purported invention of the challenged claims, thus rendering the claims obvious. Ex. 1006, Foote Decl., ¶ 111.

Cohen & Boyer and Riggs & Itakura are both publications in the same general field of research: the production of eukaryotic proteins in heterologous host cell systems, specifically microorganisms. *Id.* at ¶ 112. Beyond that general motivation to combine the references, the particular motivation to combine *in vitro* protein assembly techniques, such as those in Riggs & Itakura, with the Cohen & Boyer antibody production method is found in Cohen & Boyer itself. *Id*. The patent suggests at least two ways of obtaining the desired end product protein of the method. *Id.* The host cells may produce the protein in a form that is already the "desired end product" (Ex. 1005, at 1:64-67), for example, an *in vivo* assembled antibody. *Id.* If the host cells do not produce the protein in the desired end product form, the patent teaches that this problem may be solved by lysing the cells and recovering the protein from the cell lysate. Ex. 1005, at 1:67-68; Ex. 1006, Foote Decl., ¶ 112. In this instance, when the desired end product is a multi-subunit protein like an immunoglobulin, a POSITA would have understood that the

individual, unassociated subunit polypeptides (heavy and light chains) in the cell lysate may be recombined according to known methods, including those referenced in Riggs & Itakura, which addresses the same problem of combining unassociated immunoglobulin (and insulin) chains produced in microorganism host cells. Ex. 1003, at 537-38; Ex. 1006, Foote Decl., ¶ 112. A POSITA therefore have had a good reason to combine Cohen & Boyer with Riggs & Itakura. Ex. 1006, Foote Decl., ¶ 112.

A POSITA would have also reasonably predicted that combining Cohen & Boyer with the *in vitro* assembly techniques in Riggs & Itakura would have resulted in an assembled immunoglobulin molecule from its separate constitutive chains in the cell lysate. *Id.* at ¶ 113. The bases for a POSITA's reasonable expectation of success are no different than the bases discussed above (at page 46) with respect to combining Bujard and Riggs & Itakura. *Id.*

Dependent claim 14 also requires that the heavy and light chain "DNA sequences are derived from one or more monoclonal antibody producing hybridomas." A POSITA would have been motivated to combine Cohen & Boyer with the hybridoma teachings in Riggs & Itakura (Ex. 1003, at 537) with a reasonable expectation of success in achieving the purported invention of claim 14, thus rendering the claim obvious. *Id.* at ¶ 114. The bases for this motivation to combine with a reasonable expectation of success are no different than the bases

discussed above (at pages 46-47) with respect to combining Bujard and Riggs & Itakura. *Id.*

D. Secondary Indicia of Non-Obviousness in the Public Record Do Not Rebut Petitioners' Prima Facie Case of Obviousness

During the reexamination of the '415 patent, Owners relied upon the "licensing record and commercial success" of the patent, asserting that it provided evidence of non-obviousness of the claims. Ex. 1023, Owners' Resp. (6/6/08), at 40-42; Ex. 1046, Walton Decl., at 4-9. Neither Owners nor Dr. Walton provided any "explanation or evidence to establish a nexus between the merits of the invention and the licenses themselves" or to the licensing royalties received by Owners. *See CBS Interactive Inc. v. Helferich Patent Licensing, LLC*, IPR2013-00033, Decision to Institute, at 22 (Mar. 25, 2013) (citing *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1324 (Fed. Cir. 2004); *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1358 (Fed. Cir. 2000)). There is no explanation of "the terms of the licenses and the circumstances under which they were granted," for example, whether "they were entered into as business decisions to avoid litigation or other economic reasons." *See id.* For these reasons alone, any reliance here by Owners on evidence from the reexamination of alleged licensing acquiescence and commercial success should be given no weight. *See id.*

Moreover, the history of licensing and licensing revenues relied on in the reexamination is now stale (there is no information beyond 2007 in Dr. Walton's

declaration) and does not reflect the pharmaceutical and biotech industry's recent collective opinion of the value of the '415 patent or its validity. Since the '415 patent issued, Owners have been involved in six patent infringement lawsuits challenging the validity of the '415 patent, only one of which was filed before 2007, and all of which settled after 2007.[18] Many of these challenges covered antibody licenses that Owners highlighted during the reexamination proceeding as evidencing acquiescence by the industry. Ex. 1046, Walton Decl., at ¶ 29, n. 6; Ex. 1041, Walton Expert Rep., at 23 (exhibit to Request for Reconsideration (Ex. 1042)). Owners' assurances of the industry's acquiescence to the '415 patent before 2007 cannot be squared with the subsequent challenges brought by the very types of "large, sophisticated, patent-savvy companies" (Ex. 1023, Owners' Resp. (6/6/08), at 41) who Owners claim demonstrate their respect for the '415 patent. Owners' decisions to settle with each of these challengers before a court could render a decision on the invalidity arguments presented paints a different picture

[18] See the complaints and dismissals concerning the '415 patent in the lawsuits filed by MedImmune (Exs. 1047, 1048), Centocor (Exs. 1049, 1050), Glaxo Group Ltd (Exs. 1051, 1052), Human Genome Sciences (Exs. 1053, 1054), Eli Lilly (Exs. 1055, 1056) and Bristol-Myers Squibb (Exs. 1057, 1058) against Genentech and City of Hope.

than the speculation put forth by Dr. Walton as to why these companies entered into licenses in the first place.

VII. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(a)(1)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Sanofi (the ultimate parent company of sanofi-aventis U.S. LLC), sanofi-aventis U.S. LLC, and Regeneron Pharmaceuticals, Inc. are the real parties-in-interest for Petitioners.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioners are not aware of any related matters at this time.

C. Lead and Back-up Counsel and Service Information Under 37 C.F.R. § 42.8(b)(3), (4)

Petitioners provide the following designation of counsel and service information:

Lead Counsel	Backup Counsel
Richard McCormick (Reg. No. 55,902) Rmccormick@mayerbrown.com <u>Postal and hand Delivery Address</u> Mayer Brown LLP 1221 Avenue of the Americas New York, NY 10020-1001 Tel: (212) 506-2500 Fax: (212) 262-1910 ***Petitioners consent to email service at: MB-Cabilly-IPR@mayerbrown.com***	Lisa M. Ferri (*pro hac vice* to be filed) LFerri@mayerbrown.com Brian W. Nolan (Reg. No. 45,821) BNolan@mayerbrown.com <u>Postal and hand Delivery Address</u> Mayer Brown LLP 1221 Avenue of the Americas New York, NY 10020-1001 Tel: (212) 506-2500 Fax: (212) 262-1910

Petitioners will request authorization to file a motion for Lisa M. Ferri to appear *pro hac vice*. 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, including on behalf of Vertex Pharmaceuticals Inc. in IPR2013-00024 and IPR2015-00405. Petitioners intend to file a motion seeking the admission of Lisa M. Ferri to appear *pro hac vice* when authorized to do so.

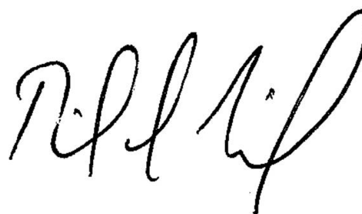
VIII. CONCLUSION

Petitioners submit 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 in view of the prior art. Petitioners therefore request that the Board grant *inter partes* review for each of those claims.

Please charge any fees or credit overpayment to Deposit Account number 130019.

Dated: July 27, 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 July 27, 2015, via UPS OVERNIGHT service to the attorneys of record for U.S. Patent No. 6,331,415 as evidenced in Public PAIR on July 27, 2015, namely:

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