UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

GENENTECH, INC. AND CITY OF HOPE,
Patent Owners

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U.S. Patent No. 6,331,415
Appl. No. 07/205,419, filed June 10, 1998
Issued: Dec. 18, 2001

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

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*Inter Partes* Review No.: IPR2016-00710

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**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.**

# TABLE OF CONTENTS

## TABLE OF AUTHORITIES

### Cases



### Statutes



### Regulations

## LIST OF EXHIBITS

| 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) |

| **Exhibit No.** | **Description** | **Abbreviation** |
|---|---|---|
| **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) |

| **Exhibit No.** | **Description** | **Abbreviation** |
|---|---|---|
| **1024** | '415 patent reexamination, Appeal Brief | Appeal Brief |
| **1025** | '415 patent reexamination, Notice of Intent to Issue Ex Parte Reexamination | NIRC |
| **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 | - |

| **Exhibit No.** | **Description** | **Abbreviation** |
|---|---|---|
| **1039** | Milstein, *Monoclonal Antibodies from Hybrid Myelomas*, Proceedings of the Royal Society of London, 211:393-412 (1981) | |
| **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.) | - |

| **Exhibit No.** | **Description** | **Abbreviation** |
|---|---|---|
| **1048** | Stipulation and order of dismissal in *MedImmune v. Genentech*, No. 03-02567 (C.D. Cal.) | - |
| **1049** | Complaint in *Centocor v. Genentech*, No. 08-CV-3573 (C.D. Cal.) | - |
| **1050** | Order of dismissal in *Centocor v. Genentech*, No. 08-CV-3573 (C.D. Cal.) | - |
| **1051** | Complaint in Glaxo *Group Ltd. v. Genentech*, No. 10-02764 (C.D. Cal.) | - |
| **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.) | - |
| **1059** | Declaration of Kathryn Calame, Ph.D., in Support of Mylan Pharmaceuticals Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 6,331,415 | Calame Decl. |
| **1060** | Curriculum Vitae of Kathryn Calame, Ph.D. | - |

## I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Mylan") requests *inter partes* review under 35 U.S.C. §§ 311-319 of claims 1-4, 11, 12, 14, 18-20, and 33 ("the challenged claims") of U.S. Patent No. 6,331,415 ("the '415 patent," Ex. 1001), which issued on December 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.

In this Petition, Mylan asserts the same grounds of unpatentability upon which the Board has already instituted review of the challenged claims of the '415 patent in IPR2015-01624 (the "Sanofi IPR"). For the exact same reasons previously considered by the Board, on the exact same trial schedule, Mylan respectfully seeks to join the Sanofi IPR. This Petition does not add to or alter any arguments that have already been considered by the Board, and this Petition does not seek to expand the grounds of unpatentability that the Board has already instituted. Accordingly, and as explained below, there exists a reasonable likelihood that Mylan will prevail in demonstrating unpatentability of at least one of the challenged claims based on teachings set forth in the references presented in this Petition.

Because this Petition is filed within one month of the institution of IPR2015-01624, and because this Petition is accompanied by a Motion for Joinder, this Petition is timely and proper under 35 U.S.C. § 315(c).

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 the Bujard patent. This reference was not substantively considered by the PTO during prosecution or reexamination of the '415 patent. Moreover, Bujard discloses 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 also expressly identifies immunoglobulins as being among the types of proteins that can be made in host cells by their respective methods, Bujard, in view of the Riggs & Itakura and Southern prior art references, makes obvious the challenged claims of the '415 patent.

## II. REQUIREMENTS FOR INTER PARTES REVIEW

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

Petitioner certifies that the '415 patent is available for *inter partes* review and that Petitioner is 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))

Petitioner requests that the Board cancel claims 1-4, 11, 12, 14, 18-20, and 33 of the '415 patent on the following grounds:

**Ground 1.** Claims 1, 3, 4, 11, 12, 14, 19, and 33 are obvious under § 103 over Bujard (Ex. 1002) in view of Riggs & Itakura (Ex. 1003); and

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

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. Additional explanation and support for each ground of unpatentability is set forth in the accompanying Declaration of Jefferson Foote, Ph.D. (Ex. 1006). Solely to preserve its right to rely on expert testimony in the event that joinder is not granted or in the case that the Sanofi IPR is settled, Mylan further relies on the accompanying Declaration of Kathryn Calame, Ph.D. (Ex. 1059), in which Dr. Calame adopts the opinions set forth by Dr. Foote in connection with the Sanofi IPR.

Importantly, the Calame Declaration does not alter or otherwise seek to supplement the opinions offered by Dr. Foote, and Dr. Calame does not intend to offer opinions beyond those in support of the grounds of unpatentability instituted in connection with the Sanofi IPR. For at least the reasons set forth in Mylan's Motion for Joinder, filed concurrently herewith, Mylan respectfully requests institution of trial on the unpatentability grounds detailed below and joinder with the Sanofi IPR.

## III. RELEVANT INFORMATION REGARDING THE '415 PATENT

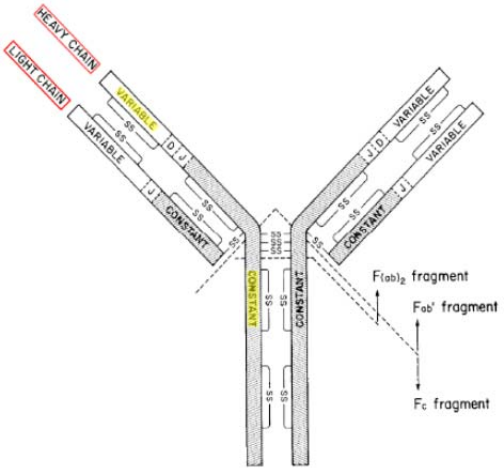
### A. Brief Description of the Challenged Patent

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

[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.

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; Ex. 1059, Calame Decl., ¶ 16. Immunoglobulins bind to antigens to rid the body of the foreign invader. Ex. 1001, 1:26-31; Ex. 1006, Foote Decl., ¶ 26; Ex. 1059, Calame Decl., ¶ 16.




Ex. 1001, Fig. 1; Ex. 1006, Foote Decl., ¶ 26; Ex. 1059, Calame Decl., ¶ 16.

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. Ex. 1001, Fig. 1 and

3:17-26; Ex. 1006, Foote Decl., ¶ 26; Ex. 1059, Calame Decl., ¶ 16. 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; Ex. 1059, Calame Decl., ¶ 16. The heavy chain and light chain are encoded by separate DNA sequences or "genes." Ex. 1001, 1:48-51; Ex. 1006, Foote Decl., ¶ 27; Ex. 1059, Calame Decl., ¶ 16. 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; Ex. 1059, Calame Decl., ¶ 16.

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; Ex. 1059, Calame Decl., ¶ 16); (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; Ex. 1059, Calame Decl., ¶ 16); 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; Ex. 1059, Calame Decl., ¶ 16). 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, 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 two 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 both DNA sequences to produce both heavy chain and light chain polypeptides (referred to as "co-expression" in the '415 patent and during reexamination[3]). Ex. 1009, Owners' Resp. (11/25/05), at 46. The heavy and light

[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.

chain polypeptides are produced as "separate molecules" by virtue of their "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 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 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 OTDP 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

[4] A "chimeric" chain has variable regions derived from one species of mammal,

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: "DNA I," which coded for a "desired proteinaceous material"[5] that is

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with constant portions derived from another species. *See* Ex. 1007, Cabilly I patent, 6:54-59 and claim 1.

[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,

"heterologous" to the host cell;[6] and "DNA II," which coded for a protein that would act as a "selectable marker."[7] *Id.* at Fig. 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; Fig. 1), the respective proteins encoded by DNA I and II would be independently expressed as separate molecules. Ex. 1006, Foote Decl., ¶ 39; Ex. 1059, Calame Decl., ¶ 16. The Axel patent identified "antibodies" as one of the preferred "proteinaceous materials" that could be made by the disclosed methods. Ex. 1018, Axel, 3:31-36, 2:61-66. In the first Office Action, the PTO

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Owners' Response (5/21/07), at 49; Ex. 1006, Foote Decl., ¶ 39, n.2; Ex. 1059, Calame Decl., ¶ 16.

[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. 1059, Calame Decl., ¶ 16; 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; Ex. 1059, Calame Decl., ¶ 16.

characterized Axel as "demonstrat[ing] the predictability of expression of multiple heterologous proteins in a single host cell [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 cotransforming more than one desired gene 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 one or more genes which encode one or more proteins."). Moreover, the Examiner also found that Axel "teaches co-expression 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

[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. 1059, Calame Decl., ¶ 16.

particularly '. . . interferon protein, antibodies, 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." 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 coexpression 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

[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.

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 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 not 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 any two 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' Resp. (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; Ex. 1059, Calame Decl., ¶ 16.

### 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*, 793 F.3d 1268, 1275-79 (Fed. Cir. 2015). The terms in the challenged claims of the '415 patent should therefore be given their broadest reasonable interpretation consistent with the specification. Petitioner does not believe that any special meanings apply to the claim terms in the '415 patent. Petitioner's 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; Ex. 1059, Calame Decl., ¶ 16. 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; Ex. 1059, Calame Decl., ¶ 16. 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 163-69; 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 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; Ex. 1059, Calame Decl., ¶ 16.

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 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' Resp. (6/6/08), at 25; Ex. 1006, Foote Decl., ¶ 47; Ex. 1059, Calame Decl., ¶ 16.

[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; Ex. 1059, Calame Decl., ¶ 16.

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; Ex. 1059, Calame Decl., ¶ 16.

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; Ex. 1059, Calame Decl., ¶ 16; *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 not 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 more than one mammalian gene could be introduced into and expressed by a single host cell. Ex. 1006, Foote

Decl., ¶¶ 52-58 (discussing the prior art summarized below); Ex. 1059, Calame Decl., ¶ 16.

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 coexpressing 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 Petitioner's references underlying its 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 32-34, 38-41.

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; Ex. 1059, Calame Decl., ¶ 16. 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, 5:43-56, 6:1-17) 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; Ex. 1059, Calame Decl., ¶ 16.

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—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; Ex. 1059, Calame Decl., ¶ 16.

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 Petitioner's grounds for rejection of the challenged claims.

### 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 Owners, 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; Ex. 1059, Calame Decl., ¶ 16. 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-

[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; Ex. 1059, Calame Decl., ¶ 16.

66; Ex. 1059, Calame Decl., ¶ 16. Bujard identifies immunoglobulins among the proteins that can be made by the disclosed process, vectors, and transformed host cells taught by Bujard. Ex. 1006, Foote Decl., ¶ 69; Ex. 1059, Calame Decl., ¶ 16.

The vector of Bujard consists of 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." Ex. 1002, 2:3-20; Ex. 1006, Foote Decl., ¶ 63; Ex. 1059, Calame Decl., ¶ 16. 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; Ex. 1059, Calame Decl., ¶ 16. The DNA sequence of interest may contain "more than one gene, that is, a plurality of genes, including multimers and operons."[12] Ex. 1002,

[12] "Multimer" refers to a protein with more than one subunit. *Supra* at 13, 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; Ex. 1059, Calame Decl., ¶ 16. 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-

3:46-48; Ex. 1006, Foote Decl., ¶¶ 64-66; Ex. 1059, Calame Decl., ¶ 16; *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 16-17.

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; Ex. 1059, Calame Decl., ¶ 16. Among the "wide variety" of genes and proteins of interest identified in the patent are "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

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identical) polypeptide subunits, for example, an immunoglobulin. Ex. 1006, Foote Decl., ¶¶ 68-69; Ex. 1059, Calame Decl., ¶ 16.

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 "γ2κ2 or γ2λ2" (two heavy chains (γ2) and two light chains (κ2 or λ2)). Ex. 1002, 5:11-14; Ex. 1006, Foote Decl., ¶ 70; Ex. 1059, Calame Decl., ¶ 16.

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 ways" 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; Ex. 1059, Calame Decl., ¶ 16.

### 2. 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 Owners, 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; Ex. 1059, Calame Decl., ¶ 16. 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 531-33; Ex. 1006, Foote Decl., ¶ 85; Ex. 1059, Calame Decl., ¶ 16. The authors saw the practical application for this technology as extending beyond insulin production. Ex. 1003, at 537-38; Ex. 1006, Foote Decl., ¶ 85; Ex. 1059, Calame Decl., ¶ 16. 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 and used for passive immunization." Ex. 1003, at 537-38; Ex. 1006, Foote Decl., ¶ 85; Ex. 1059, Calame Decl., ¶ 16.

### 3. 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 Owners, 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 336-37, Table 3; Ex. 1006, Foote Decl., ¶¶ 86-87; Ex. 1059, Calame Decl., ¶ 16. The cotransformed host cells successfully expressed both selectable marker proteins and were able to grow in the presence of both antibiotics, i.e., they were "double selected." Ex. 1004, at 336-37, Table 3; Ex. 1006, Foote Decl., ¶¶ 88-89; Ex. 1059, Calame Decl., ¶ 16. 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. Ex. 1006, Foote Decl., ¶ 88; Ex. 1059, Calame Decl., ¶ 16.

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; Ex. 1059, Calame Decl., ¶ 16. Both

[13] This is also referred to as "cotransduction" and "cotransfection" in the article. Ex. 1004, at 336-37; Ex. 1006, Foote Decl., ¶ 88, n.8; Ex. 1059, Calame Decl., ¶ 16.

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; Ex. 1059, Calame Decl., ¶ 16.

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

### A. Explanation of Ground 1 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. Independent claims 1 and 33 require the recombinant production of an immunoglobulin molecule (i.e., an antibody) or immunologically functional fragment by "independently expressing" DNA sequences encoding at least the variable domains of the immunoglobulin heavy and light chains within a

[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; Ex. 1059, Calame Decl., ¶ 16.

"single host cell." Dependent claim 3 requires that the heavy and light chain DNA sequences be "present in a single vector" and dependent claim 4 requires that the "vector" of the claims from which it depends be a "plasmid." Dependent claim 11 requires that the DNA sequences encode the "complete" heavy and light chain polypeptides and dependent claim 12 requires that any "constant domain" encoded by the DNA sequences be "derived from the same source as the variable domain to which it is attached." Dependent claim 14 also requires that the heavy and light chain DNA sequences be "derived from one or more monoclonal antibody producing hybridomas" and dependent claim 19 requires that the host cell of claim 1 is a "mammalian cell."

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; Ex. 1059, Calame Decl., ¶ 16; *see also supra* at 27-31. 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; Ex. 1059, Calame Decl., ¶ 16; *see also supra* at 28-30.

A POSITA would have been 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; Ex. 1059, Calame Decl., ¶ 16.

Bujard and Riggs & Itakura are publications in the same general field of research: the production of heterologous eukaryotic proteins in host cells. Ex. 1006, Foote Decl., ¶ 100; Ex. 1059, Calame Decl., ¶ 16. 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. Ex. 1006, Foote Decl., ¶ 100; Ex. 1059, Calame Decl., ¶ 16. 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, 4:20-21; Ex. 1006, Foote Decl., ¶ 100; Ex. 1059, Calame Decl., ¶ 16; *see also supra* at 31. 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; Ex. 1059, Calame Decl., ¶ 16. A POSITA would therefore have had a good reason to combine Bujard with Riggs & Itakura. Ex. 1006, Foote Decl., ¶ 100; Ex. 1059, Calame Decl., ¶ 16.

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; Ex. 1059, Calame Decl., ¶ 16. 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; Ex. 1059, Calame Decl., ¶ 16. 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; Ex. 1059, Calame Decl., ¶ 16. 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. Ex. 1006, Foote Decl., ¶ 101; Ex. 1059, Calame Decl., ¶ 16. In sum, a POSITA would have found it obvious to insert the genes encoding for the heavy and light chains, separated by a stop codon, between the promoter and terminator sequences of the vector, which would permit the independent

expression of those genes as separate molecules in the transformed host cell. *See* Ex. 1006, Foote Decl., ¶ 92; Ex. 1059, Calame Decl., ¶ 16.

As noted above, dependent claim 14 requires that the heavy and light chain DNA sequences be "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; Ex. 1059, Calame Decl., ¶ 16. 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; Ex. 1059, Calame Decl., ¶ 16. 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; Ex. 1059, Calame Decl., ¶ 16. 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; Ex. 1059, Calame Decl., ¶ 16.

### B. Explanation of Ground 2 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; Ex. 1059, Calame Decl., ¶ 16. 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. Ex. 1006, Foote Decl., ¶ 103; Ex. 1059, Calame Decl., ¶ 16. Beyond this general motivation to combine the references, a POSITA would have recognized that both references have as a goal the expression of genes of interest in a single transformed host cell, whether by using one (Bujard) or two (Southern) vectors. Ex. 1006, Foote Decl., ¶ 103; Ex. 1059, Calame Decl., ¶ 16. 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. Ex. 1006, Foote Decl., ¶ 103; Ex. 1059, Calame Decl., ¶ 16.

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. Ex. 1006, Foote Decl., ¶ 104; Ex. 1059, Calame Decl., ¶ 16. 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. Ex. 1006, Foote Decl., ¶ 104; Ex. 1059, Calame Decl., ¶ 16. 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. Ex. 1006, Foote Decl., ¶ 104; Ex. 1059, Calame Decl., ¶ 16. 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). Ex. 1006, Foote Decl., ¶ 104; Ex. 1059, Calame Decl., ¶ 16. 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. Ex. 1006, Foote Decl., ¶ 104; Ex. 1059, Calame Decl., ¶ 16. 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. Ex. 1006, Foote Decl., ¶ 104; Ex. 1059, Calame Decl., ¶ 16.

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) ("A broader independent claim cannot be nonobvious where a dependent claim stemming from that independent claim is invalid for obviousness."); Ex. 1006, Foote Decl., ¶ 105; Ex. 1059, Calame Decl., ¶ 16. 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 coexpression 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; Ex. 1059, Calame Decl., ¶ 16.

### C. Secondary Indicia of Non-Obviousness in the Public Record Do Not Rebut Petitioner's 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 CBS Interactive*, IPR2013-00033, Decision to Institute, at 22. 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.[15] 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

[15] See complaints and dismissals for the '415 patent in lawsuits involving 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) filed 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.

## VI. 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)

For purposes of the present Petition only, the real parties-in-interest designated for Petitioner are Mylan Pharmaceuticals Inc., Mylan Inc., Mylan GmbH, Mylan N.V., Mylan Institutional LLC, Biocon Ltd, and Biocon Research Ltd. Mylan N.V. has been asserted to be a real party in interest in other proceedings (which Mylan has disputed); nevertheless, Mylan N.V. is identified out of an abundance of caution, but this in no way constitutes an admission that it is or was a real party-in-interest in any other IPR proceeding.

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

Petitioner identifies IPR2015-01624, IPR2016-00383, and IPR2016-00460 as Related Matters under 37 C.F.R. § 42.8(b)(2). IPR2015-01624 challenged the '415 patent, was filed by Sanofi-Aventis U.S. LLC and Regeneron Pharmaceuticals on July 27, 2015, and identified Sanofi (the ultimate parent company of Sanofi-Aventis U.S. LLC) as a real party-in-interest for Sanofi-Aventis U.S. LLC. IPR2016-00383 challenged the '415 patent, was filed by Genzyme Corporation on December 30, 2015, and identified Sanofi (the ultimate parent company of Genzyme) as the real party-in-interest for Genzyme. IPR2016-00460 challenged the '415 patent, was filed by Genzyme Corporation on January

15, 2016, and identified Sanofi (the ultimate parent company of Genzyme) as the real party-in-interest for Genzyme.

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

Petitioner provides the following designation of counsel and service information:

| **Lead Counsel** | **Backup Counsel** |
|---|---|
| Deanne M. Mazzochi (Reg. No. 50,158)<br>dmazzochi@rmmslegal.com<br>Postal and Hand Delivery Address<br>Rakoczy Molino Mazzochi Siwik LLP<br>6 West Hubbard Street, Suite 500<br>Chicago, Illinois 60654<br>Tel: (312) 222-6305<br>Fax: (312) 222-6325<br><br>***Petitioner consents to email service at: Mylan_IPR_Service@rmmslegal.com.*** | Paul J. Molino (Reg. No. 45,350)<br>paul@rmmslegal.com<br>William A. Rakoczy<br>(*pro hac vice* to be filed)<br>wrakoczy@rmmslegal.com<br>Eric R. Hunt<br>(*pro hac vice* to be filed)<br>ehunt@rmmslegal.com<br>Postal and Hand Delivery Address<br>Rakoczy Molino Mazzochi Siwik LLP<br>6 West Hubbard Street, Suite 500<br>Chicago, Illinois 60654<br>Tel: (312) 222-5127<br>Fax: (312) 222-6321 |

Please direct all correspondence to lead counsel and back-up counsel at the contact information above. Petitioner will request authorization to file a motion for William A. Rakoczy and Eric R. Hunt to appear *pro hac vice*. Mr. Rakoczy and Mr. Hunt are experienced attorneys and both have an established familiarity with the subject matter at issue in this proceeding. Petitioner intends to file a motion seeking the admission of William A. Rakoczy and Eric R. Hunt to appear *pro hac vice* when authorized to do so.

## VII. CONCLUSION

Petitioner submits that issues have been presented that demonstrate a reasonable likelihood that claims 1-4, 11, 12, 14, 18-20, and 33 of the '415 patent are unpatentable in view of the prior art. Petitioner therefore requests that the Board institute *inter partes* review for each of those claims.

Please charge any fees or credit overpayment to Deposit Account 503626.

Respectfully submitted,

Dated: March 3, 2016

/Deanne M. Mazzochi/

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## CERTIFICATE OF SERVICE

The undersigned hereby certifies that true and correct copies of the foregoing 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. and Exhibits 1001-1060 were served on March 3, 2016, via FedEx Priority Overnight on the Patent Owners at the correspondence address of record for the '415 patent as evidenced in Public PAIR on March 3, 2016, namely:

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and

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Respectfully submitted,

Dated: March 3, 2016

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