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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

Case IPR2015-01624
Patent 6,331,415

PATENT OWNERS' PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107

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I. INTRODUCTION

In their Petition, Sanofi-Aventis U.S. LLC and Regeneron Pharmaceuticals, Inc. ("Petitioners") ask the Board to disregard the prior determinations of the Patent and Trademark Office (the "Office") that the claims of U.S. Patent No. 6,331,415 (the "Cabilly '415 patent") define a patentable invention. The grounds advanced by Petitioners, however, present arguments that were already thoroughly considered, and ultimately rejected, by the Office in prior proceedings, and ignore the substantial evidence considered by the Office in reaching that prior determination.

Petitioners contend the primary prior art references it is advancing—Bujard (Ex. 1002) and Cohen & Boyer (Ex. 1005)—describe or would have made obvious the claimed invention, which requires production of an immunoglobulin by independent expression of DNA sequences encoding the heavy and light chains in a single transformed host cell. But this prior art does not show actual production of an antibody, or doing so via a single transformed host cell as required by the claims. If anything, the prior art advanced in the Petition is ***less*** probative on the issues already considered and rejected by the Office.

Specifically, in earlier reexamination proceedings, the Office considered the question whether the mere appearance of the plural term "genes" along with the

inclusion of the word "antibody" in a laundry list of types of proteins that could be produced by the recombinant DNA methods described in the Axel patent (Ex. 1018) would have been read by the skilled person in April of 1983 as teaching or suggesting production of heavy and light chains of an immunoglobulin in a single transformed host cell. The Office considered that question in the context of whether claims to producing a single antibody chain read in combination with Axel's references to "genes" and "antibodies" would have led the skilled person to conclude production of both heavy and light antibody chains in a single transformed host cell would have been obvious in April of 1983. The Office concluded, in the face of substantial evidence to the contrary, it would not.

Petitioners ask the Office to ignore that past determination and find that the same types of simplistic textual references to "genes" and "antibodies" teach production of heavy and light chains of an antibody in a single transformed host cell as the claims require. Indeed, Petitioners expressly ask the Board to find that the Office was incorrect in ultimately determining that the parallel use of these terms in the Axel patent was insufficient, despite the substantial evidence considered by the Office.

Doing so would be substantively and legally improper. During the reexamination of the Cabilly '415 patent, the Office thoroughly considered and ultimately rejected the precise theories of unpatentability now being advanced in

the Petition. The Office found probative the substantial evidence presented by Patent Owners during the proceeding, evidence that Petitioners largely ignore in their Petition. The Board should dismiss the Petition because it does not advance a new theory of unpatentability that is not cumulative of those considered by the Office during the reexamination, and because it does not present evidence showing the Office's earlier determinations were incorrect.

The specific grounds advanced by the Petitioners cannot justify institution of trial. ***First***, Petitioners' anticipation grounds based on Bujard (Ex. 1003) are insufficient. Bujard fails to disclose many of the elements of the Cabilly '415 Patent claims, including the requirement for (i) independent expression of the light and heavy immunoglobulin chains in a single transformed host cell and (ii) the production of an intact immunoglobulin. In an attempt to navigate those fatal defects, the Petition asserts that general references to "genes" and "antibodies" within Bujard would have been read by the skilled person as inherently describing these claim elements. But that assertion fails because Petitioners cannot establish the skilled person would have read the general references in Bujard to "genes" and "antibodies" as ***necessarily*** describing the introduction of recombinant heavy and light chain DNA sequences into a single host cell, co-expressing the heavy and light chain DNA sequences as separate molecules, and producing a functional antibody. Indeed, such a manner of reading Bujard conflicts with the substantial

evidence in the record showing the skilled person would have read such terms as suggesting production of only one polypeptide per host cell in April of 1983.

***Second*,** the Petition contends but falls far short of establishing that the cited prior art would have made the claimed invention obvious to a person of ordinary skill in the art in April of 1983. Again, Petitioners' obviousness grounds fail to rebut the substantial evidence showing that, in April of 1983, if a skilled person were motivated to produce a recombinant antibody at all, such person would follow the one-protein-of-interest-per-host cell method used for insulin. Such method is described in, among other things, the Riggs & Itakura reference specifically relied upon by Petitioners in their grounds for the contrary proposition.

Remarkably, Petitioners and their declarant make no effort to dispute the ***technical*** underpinnings of the expert opinions considered during the reexamination and advance no new historical evidence showing that the experts' depiction of the mindset of the skilled person in April of 1983 was inaccurate. Instead, Petitioners and their declarant advance the same ***linguistic*** arguments already considered and rejected by the Office during the reexamination.

For example, during the reexamination proceedings, Patent Owners submitted declarations from six different scientific experts working in the field of the invention prior to April of 1983. Those declarations relied on numerous scientific publications as well as the substantial personal experience of the experts

before April of 1983. The expert declarations accurately depicted the perspective of how a skilled person would have approached the task of producing a complex multimeric[1] protein such as an antibody in April of 1983. Among other things, the experts described the emerging nature of the genetic engineering techniques being used to produce proteins at that time and identified the lack of demonstrated successes in producing large, complex proteins. The experts explained this perspective would have given those working in the field little confidence that a multimeric protein as complex as an antibody could be produced recombinantly by co-expressing both heavy and light chains as separate molecules in a single host cell.

The experts also explained why the prior art would not have steered a skilled person toward the recombinant production of antibodies through co-expression of the heavy and light chains in a single host cell, let alone given them confidence that such an endeavor would be successful. For example, several of the experts noted that the only example of successful production of a eukaryotic multimeric protein before the Cabilly '415 patent—the production of insulin, a far less complex protein than an antibody—employed a strategy of ***separately*** producing

[1] A multimeric protein consists of multiple polypeptides associated through non-covalent interactions or disulfide bonds. Ex. 2003, McKnight Decl. II at FN 12.

each chain of the protein in a host cell, isolating each chain from its independent culture, and then combining the separately produced insulin chains in a test tube.

Collectively, this evidence established that the skilled person, in April of 1983, would not have found a method of producing an antibody via the co-transformation and co-expression steps of the Cabilly '415 patent claims to have been obvious over prior art that is substantively indistinguishable from the prior art advanced by Petitioners.

That conclusion is fully consistent with the contributions of the Cabilly '415 patent, which represents a groundbreaking advance in the biotechnology industry—the first successful production of an active antibody by co-expression of the light and heavy chains of the antibody in a single co-transformed host cell. The Petition presents no evidence that at the time of the invention in April of 1983, any lab had achieved such a breakthrough.

The Cabilly '415 patent also has been subjected to more than thirteen years of Office-related proceedings, including: (i) its original examination; (ii) an interference proceeding and related section 146 litigation; and (iii) a merged *ex parte* reexamination proceeding. It has likewise emerged unscathed from six different federal court litigations. The claimed inventions of the Cabilly '415 patent have been widely adopted and extensively licensed by the biotechnology industry. Between 1991 and November 2013, Patent Owners have granted a total

of 70 licenses under the Cabilly '415 patent, including at least 12 that were entered into during pendency of the *ex parte* reexamination proceedings or afterward. *See,* Ex. 2009, Walton Rep. at p. 22.

Against this record, and for these reasons explained herein, Patent Owners respectfully request that the Board not institute trial on the basis of the Petition. Alternatively, in view of the substantial similarity of the grounds presented in the Petition to the issues addressed previously by the Office during reexamination, Patent Owners request that the Board decline to institute trial under 35 U.S.C. § 325(d).

II. THE CABILLY '415 PATENT CLAIMS

The Petition challenges claims 1-4, 9, 11, 12, 14-20 and 33 of the Cabilly '415 patent. Independent claims 1 and 33 define processes, and are reproduced below for convenience of the panel:

> 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.
>
> 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.

Independent claim 15 recites a single vector that contains the DNA sequences for both the heavy and light chain at different insertion sites, which is used to transform the single host cell, and independent claim 18 recites a host cell transformed with at least two separate vectors (one that includes heavy chain DNA and one that includes light chain DNA). *See,* Ex. 1001 at 29:22-27, 31-36.

During reexamination of the Cabilly '415 patent, Dr. Steven L. McKnight, Distinguished Chair in Basic Biomedical Research and The Sam G. Winstead and F. Andrew Bell Distinguished Chair in Biochemistry at the University of Texas

Southwestern Medical Center, described the requirements of the claims to the Office as follows:

> The '415 patent requires the production of an immunoglobulin molecule[2] . . . by expression of DNA sequences encoding both heavy and light immunoglobulin chain polypeptides in a single transformed host cell. This means that all of the following things must happen:
> (i) host cells must have been successfully transformed with DNA sequences encoding the heavy and light chain polypeptide sequences;
> (ii) the transformed host cell must independently express both sequences (*e.g.*, each DNA sequence must be accurately transcribed into an mRNA, and each mRNA must be translated into an appropriate amino acid sequence corresponding to each chain); and
> (iii) the polypeptides must be assembled into an immunoglobulin tetramer . . . either inside or outside of the cell.

Ex. 2003, McKnight Decl. II at ¶4. Petitioners do not dispute that these are requirements of the challenged process claims.

III. CLAIM CONSTRUCTION

In an *inter partes* review, the terms of the claims are to be given their broadest reasonable interpretation in light of the specification as commonly

[2] The Cabilly '415 patent claims recite "immunoglobulins." Petitioners argue that the term "immunoglobulin" is interchangeable with "antibody." Paper 1 at 4 n.1. For purposes of this Response, Patent Owners also use the terms interchangeably.

understood by those of ordinary skill in the art.[3] *See,* 37 C.F.R. § 42.100(b). Petitioners take the position that they "do not believe any special meanings apply to the claim terms in the '415 Patent." Paper 1 at 16. For purposes of this Preliminary Response, Patent Owners do not dispute Petitioners' position.

IV. BACKGROUND OF THE TECHNOLOGY

The technology background of the Cabilly '415 patent has been discussed at length both before the Office and in District Court litigations involving the Cabilly '415 patent. From those earlier proceedings, the following pertinent facts have been established, which the Petition does not dispute:

[3] For the limited purpose of this Preliminary Response, Patent Owners deem it unnecessary to contest the level of ordinary skill in the art. The level of ordinary skill in the art identified by Petitioners, Paper 1 at 15, is consistent with that identified during reexamination and litigation. *See, e.g.*, Ex. 2001, Fiddes Rep. at ¶37 ("Ph.D. in molecular biology or related discipline, such as biochemistry, microbiology or cell biology plus two to three years post-doctoral training and experience (whether in academia or industry) in the application of recombinant DNA technology to protein production").

A. Antibodies Are Large, Complex Multimeric Proteins

As shown in Figure 1 of the Cabilly '415 patent (Ex. 1001), an antibody is a multimeric protein composed of four polypeptide chains. Naturally occurring antibodies consist of two identical "heavy" chains (or "H" chains) and two identical "light" chains (or "L" chains) that form what is schematically depicted as a Y-shaped molecule. Ex 1001 at 3:17-27; Ex. 2005, Harris Decl. II at ¶17.

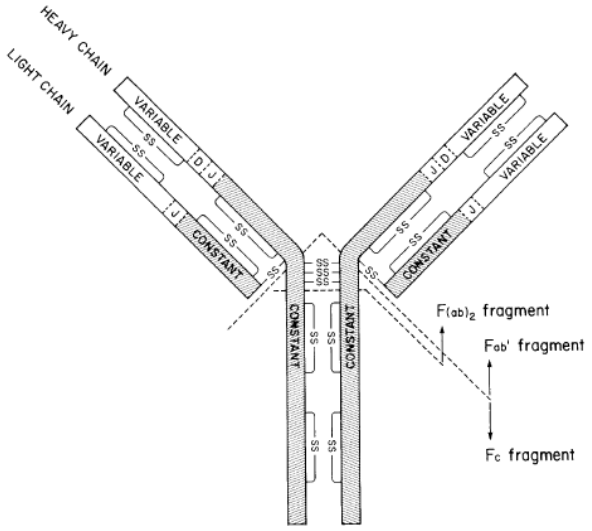

Fig. 1.

A disulfide bond joins each L chain to a respective H chain, forming the "arms" of the Y, and three disulfide bonds join the two H chains at the top of the "stalk" of the Y. *Id*. The heavy and light chains are so-called because they differ in molecular weight. Ex. 2001, Fiddes Rep. at ¶42.

Antibodies are large, complex molecules. For example, each heavy chain of an antibody of the immunoglobulin G ("IgG") isotype contains about 447 amino acids and has a molecular weight of about 50,000 Daltons. Ex. 2001, Fiddes Rep. at ¶42. Each light chain of an IgG isotype antibody contains about 214 amino acids and has a molecular weight of about 25,000 Daltons. *Id*. The molecular

weight of an IgG antibody made up of two heavy and two light chains is thus about 150,000 Daltons. *Id*.

Before April of 1983, scientists could create antibodies to an antigen by immunizing an animal (*e.g.*, a rat, mouse, or rabbit) with the antigen. *See generally,* Ex. 1001 at 1:42-2:19. This technique generated a mixture of antibodies with each antibody in the mixture binding to a unique epitope on the antigen. *Id.* These antibodies are called polyclonal antibodies because they are produced by multiple different cell lines in the animal in response to the foreign antigen. *Id*. The therapeutic usefulness of polyclonal antibodies is limited to some degree, however, because, by definition, these antibodies have varying specificities (*i.e.*, they bind to a variety of locations on an antigen). Ex. 1001 at 1:61-63.

Today, it is understood that many therapeutic applications require antibodies specific to the same part of a single antigen, *i.e.*, monoclonal antibodies. Ex. 1001 at 1:63-2:11. As the name suggests, monoclonal antibodies are produced by a single cell line, have the same amino acid sequence, and have the same specificity to a given antigen, *i.e.*, they all bind to the same part of the antigen, called an epitope. *Id.* The production of monoclonal antibodies was significantly advanced by the development of hybridoma techniques in 1975 by Georges Kohler and Cesar Milstein. A "hybridoma" results from the fusion of a cancer cell with an antibody-producing B-cell, which has the advantage of that the fused cell is

"immortalized" by the inclusion of the cancer cell. Ex. 2013, Kohler and Milstein. As a result, the hybridoma can be grown in cell culture and the antibody naturally produced by the fused B-cell can be produced. *Id*.

By April of 1983, the hybridoma technique was being used, but was limited. Specifically, the antibodies that were produced were what the animal being immunized would generate in response to immunization with the antigen. Ex. 1001 at 2:62-66. It was not possible to know, *a priori*, the sequence of the antibody or what its particular binding properties would be. *Id*. A significant need, thus, existed in 1983 for an alternative way to produce antibodies. *Id*. at 2:40-3:2.

B. As of April of 1983, Protein Production Using Recombinant DNA Technology Was Still in Its Infancy

One of skill in the art would have faced various uncertainties if he or she endeavored to try to recombinantly express any protein in April of 1983. This is because, as Dr. McKnight explained, as of April of 1983, "many of the biological mechanisms that controlled expression of foreign DNA and assembly of proteins were not well understood." Ex. 2003, McKnight Decl. II at ¶6. By April of 1983, only a few proteins with known therapeutic value had been recombinantly produced, and each success was considered a major scientific breakthrough. *See, e.g.*, Ex. 2005, Harris Decl. II at ¶12-13. Indeed, Dr. Timothy John Roy Harris, Chief Executive Officer of Novasite Pharmaceuticals, shared his then-

contemporaneous perspective on producing proteins using recombinant DNA techniques in April of 1983:

> By early April of 1983, I was aware that a number of groups had successfully expressed polypeptides using recombinant techniques. These experiments generally involved expression of genes encoding relatively small polypeptides with simple tertiary structures (e.g., monomeric or dimeric proteins). The state of the art in this time frame is reflected in a review paper I authored [Ex. 1027].

Ex. 2004, Harris Decl. at ¶16; *see also,* Ex. 2003, McKnight Decl. II at ¶7.

The Petition cites Dr. Harris's review article, Paper 1 at 18, but fails to address the fact that each and every one of the examples listed in the paper as having been produced through recombinant DNA techniques involved a protein that was significantly less complex than an antibody. As Dr. Harris explained, "all but one of the[] examples [in Ex. 1027] concerned production of relatively simple monomeric proteins. The exception was insulin . . . ." Ex. 2005, Harris Decl. II at ¶14; *see also,* Ex. 2001, Fiddes Rep. at ¶¶43-46.

Insulin is a relatively simple multimeric protein. It is made up of two polypeptide chains linked by two inter-chain disulfide bonds, with one of the two chains containing one intrachain disulfide bond. Ex. 2003, McKnight Decl. II at ¶10. The insulin A chain has 21 amino acids and the insulin B chain has 30 amino acids, Ex. 2003, McKnight Decl. II at ¶10, and, as a result, the assembled insulin

protein has a significantly lower molecular weight than an antibody. Ex. 2001, Fiddes Rep. at ¶52. By comparison, antibody light chains have between 210 and 220 residues and heavy chains have between 455 and 550 residues, an assembled antibody weighs approximately 150 kD, and an antibody is a complex tetramer that links four discrete polypeptides together via multiple disulfide bonds and non-covalent interactions. Ex. 2003, McKnight Decl. II at ¶10; Ex. 2001, Fiddes Rep. at ¶¶42, 49.

Like Dr. McKnight, Dr. Harris explained during the reexamination that the complexity of a tetrameric antibody compared to the few monomeric recombinant proteins, or the lone dimeric recombinant protein that had been produced as of April of 1983, would have impacted the mindset of a person of ordinary skill in the art in April of 1983, particularly with respect to how the person would have approached producing each protein using recombinant DNA techniques:

> "Based on [the] known structural characteristics of the tetrameric immunoglobulin molecule, I believe a person of ordinary skill in the art, in early April of 1983, would have expected that the production of an immunoglobulin tetramer using recombinant DNA techniques would have been a significantly more challenging undertaking than the types of projects described in my review article . . . ."

Ex. 2005, Harris Decl. II at ¶18.; *see also, id.* at ¶16 (in April of 1983 "I . . . was not aware of any published reports . . . of production of a multimeric protein of the size (~150 kD) or structural complexity of an immunoglobulin tetramer").

C. In April of 1983, Insulin, the Only Multimeric Protein Produced Using Recombinant DNA Technology, Was Produced by Expressing Each Subunit in a Separate Host Cell

As of April of 1983, the only successful report of a multimeric eukaryotic protein produced using recombinant DNA techniques was insulin. *See,* Ex. 2001, Fiddes Rep. at ¶48. Neither of the approaches taken for doing so involved production of more than one polypeptide in a single host cell. As Dr. Harris explained, insulin had been "produced by individually expressing each of the two chains of the insulin protein in different E. coli cell lines, or by expressing 'preproinsulin' (a single polypeptide) which was enzymatically processed *in vitro* to form mature insulin." *See,* Ex. 2005, Harris Decl. II at ¶14. This fact was established during the reexamination proceedings, and is not disputed by the Petitioner. *See,* Ex. 2003, McKnight Decl. II at ¶10-11; Ex. 2005, Harris Decl. II at ¶14.

During the reexamination, numerous experts who were active in the field of the Cabilly '415 patent in April of 1983 also confirmed that, as of that date, each was not aware of ***any*** example of production of a multimeric protein by co-expression of the constituent polypeptides of the protein in a single host cell:

- Dr. Harris testified he "was not aware of any published reports as of April of 1983 documenting production of a multimeric protein by independently expressing in a single cell recombinant DNA sequences corresponding to the constituent polypeptides of the multimeric protein." Ex. 2005, Harris Decl. II at ¶16.
- Dr. McKnight testified that he "was not aware of a single paper published by April of1983 that even suggested the concept of producing more than one eukaryotic polypeptide at a time in a single recombinantly transformed host cell." Ex. 2003, McKnight Decl. II at ¶5.
- Dr. Douglas R. Rice, a researcher at the Whitehead Institute, and author of one of the prior art references considered in the reexamination, testified that he "was not aware of any published reports by early April of 1983 describing the introduction and expression of both immunoglobulin heavy and light chain genes into a single host cell. As of that date, [he] also was not aware of any groups attempting to introduce and express both immunoglobulin heavy and light chain genes into a single host cell." Ex. 2006, Rice Decl. at ¶15.

This testimony is entirely consistent with the fact that ***"every example, without exception*** [in Dr. Harris's March 1983 review article] reports production of only

one polypeptide at a time in a transformed host cell." Ex. 2003, McKnight Decl. II at ¶9 (emphasis added); *see also,* Ex. 2005, Harris Decl. II at ¶15.

Petitioners have not disputed this evidence, nor have they provided a single example of co-expression of two or more polypeptides as separate molecules in a single transformed host cell before April of 1983.

The record evidence thus demonstrates that the established mindset in April of 1983 about production of a complex multimeric protein using recombinant DNA techniques was to break the problem into smaller, more manageable tasks—most notably, to first produce each component chain of the multimeric protein in a separate host cell, and to then assemble the individually produced polypeptides into the multimeric protein. That mindset is contrary to the path taken by the inventors of the Cabilly '415 patent, and was why the Office determined the claims of the Cabilly '415 patent were not obvious over the prior art.

D. The "Mindset" of a Person of Ordinary Skill in the Art at the Time of the Invention

Petitioners contend that Patent Owners "contrive[d]" a "so-called 'prevailing mindset' before April of 1983 that only one eukaryotic protein of interest should be produced in a transformed host cell." Paper 1 at 13. But, as the Petition itself acknowledges, *id.*, during the reexamination proceedings, Patent Owners submitted documentary evidence and testimony from several highly respected experts in the field of the '415 patent, including authors of prior art cited during the

reexamination proceedings, to demonstrate the perspective held by persons skilled in the art in April of 1983. Tellingly, ***Petitioners nowhere rebut any of this evidence***.

1. Substantial Evidence Demonstrates That an Ordinarily Skilled Person Would Approach Production of Multimeric Proteins by Producing One Protein of Interest Per Host Cell in April of 1983

During reexamination, Patent Owners submitted substantial evidence showing that a person of ordinary skill in the art in April of 1983 would have approached the task of producing a multimeric protein such as an antibody by following the then-prevailing approach of producing each polypeptide of the multimeric protein in a separate host cell. This evidence includes the following:

- Goeddel, D.V. et al., *Expression in Escherichia coli of chemically synthesized genes for human insulin*, Proc. Nat'l Acad. Sci. (USA) 76:106-110 (1979) ("Goeddel 1979") (Ex. 2011), describes a process of producing insulin via separate host cells. As the authors explained in that paper: "We deliberately chose to construct two separate bacterial strains, one for each of the two peptide chains of insulin: the 21-amino-acid A chain and the 30-amino-acid B chain." Ex. 2011 at 106; *see,* Ex. 2003, McKnight Decl. II at ¶11.
- The testimony of Dr. McKnight addressing references describing production of various types of proteins, where he states "these references would have

told a person or ordinary skill in the art in April of 1983 to not attempt to produce an immunoglobulin molecule by expressing two different DNA sequences encoding the heavy and light chains in one transformed host cell. Instead, I believe the references suggested taking the opposite approach, namely, to produce each chain in a separate cell culture and then (if that succeeds) attempt to assemble the immunoglobulin using these individually produced chains." Ex. 2003, McKnight II Decl. at ¶¶8-16 (emphasis original).

- The testimony of Dr. Rice, in connection with experiments he performed to transfect a B cell to produce an immunoglobulin light chain later published in his 1982 paper cited in the reexamination, that it "never occurred to" him "to attempt to express exogenous heavy and light chain genes in the [subject single] cell line," along with his opinion that his paper would not have made obvious the Cabilly '415 patent invention. Ex. 2006, Rice Decl. at ¶13.
- As described in section IV.B, above, Patent Owners also provided the Office with Dr. Harris's March 1983 review article, and corresponding testimony that every example therein employed a one-protein-per-host-cell approach.

The testimony submitted during the reexamination provided additional reasons why a person of ordinary skill would have been motivated to follow a one-

protein-per-host cell approach if they endeavored to attempt to produce a recombinant antibody in April of 1983. These included:

- In view of the complexity of producing an antibody, "[t]rying to produce the immunoglobulin [in separate host cells] would reduce some of the uncertainty by breaking the process down into more manageable steps." Ex. 2003, McKnight Decl. II at ¶8.
- Testimony that immunoglobulin systems are complex and that successful production of immunoglobulins in April of 1983 would be subject to numerous interrelated factors and would give rise to questions about the ability of cells to properly express the introduced sequences, or carry out post-transcriptional events (*e.g.*, polypeptide folding, assembly, or secretion). *See,* Ex. 2005, Harris Decl. II at ¶¶27-28; Ex. 2006, Rice Decl. at ¶13.

Patent Owners provided similar evidence during litigation in which the validity of the Cabilly '415 patent was challenged. For example, Dr. John Fiddes explained that before April of 1983, Eli Lilly & Co. stated that their "current method" of commercially manufacturing recombinant insulin was "to make the A and B chains ***in separate E. coli fermentations*** . . . ." indeed, "all the biosynthetic human insulin presently [*i.e.*, in 1983] being produced by Eli Lilly is derived from this chain combination procedure and that all clinical studies have been conducted

with such insulin." Ex. 2001, Fiddes Rep. at ¶¶53-54 (emphasis added); Ex. 2012, Frank 1983 at S14-S20.

Dr. Fiddes opined that the one-protein-per-host-cell approach to recombinant insulin production described in Goeddel 1979, and the adoption of it by a large pharmaceutical company like Eli Lilly, would have had a profound impact on the person of ordinary skill in the art. Ex. 2001, Fiddes Rep. at ¶55. Such a person would follow these leaders, particularly given the uncertainties surrounding recombinant protein production generally and the fact that there had been no other reports of production of a multimeric protein using recombinant DNA techniques at that time. *Id.* Thus, even if a person of ordinary skill in the art set out to recombinantly produce a functional antibody in April of 1983, he or she would have attempted to express the heavy and light chains of the antibody in separate host cells, consistent with the state of the art at the time. *Id.*

2. Petitioners Have Failed To Demonstrate a Countervailing "Mindset" of Multiple Proteins in One Host Cell as of April of 1983

Contrary to the substantial evidence already of record with respect to the Cabilly '415 patent, Petitioners assert that "[t]he prevailing mindset by April of 1983 was that one or more proteins of interest could be made in a single host cell." Paper 1 at 21. But that assertion is not supported by any contemporaneous evidence of successful efforts to produce multimeric proteins in this manner.

Instead, it rests on the Petitioners' effort to extrapolate the teachings of the claimed invention from non-specific disclosures in selected prior art references in ways that are implausible and contrary to the experiences of experts working the field of the invention in April of 1983. Specifically, Petitioners simply list four pages of citations to references—presumably selected because each uses the plural word "genes." Paper 1 at 21-24. But these references simply employ the same informal use of the word "genes" found in the prior art used in the proposed grounds and in the prior art previously considered by the Office during reexamination of the Cabilly '415 patent. As discussed below with respect to Petitioners' grounds, this proposed interpretation of the term "genes" as it appears in the prior art is scientifically unsupportable and incorrect.

Petitioners' citation to these references is also misleading, since none relates to recombinant production of more than one protein of interest in a single cell and most do not demonstrate expression of ***any*** recombinant protein of interest, let alone the constituent polypeptides of a multimeric protein as complex as an antibody:

- U.S. Patent No. 4,487,835 (Ex. 1033) does not mention antibodies or immunoglobulins, and does not discuss or teach co-expression of any eukaryotic protein (*see, e.g.*, Ex. 1033 at 8:35-55 (describing experimental

examples involving construction and isolation of plasmids including, at most, a single selectable marker));

- U.S. Patent No. 4,371,614 (Ex. 1034) does not mention antibodies or immunoglobulins, and describes construction of a bacterial cell used to produce L-tryptophan, a single amino acid. *See,* Ex. 1034 at abstract. The reference also cites to a Gilbert & Villa-Komaroff article for general recombinant DNA techniques. *See, id.* at 1:39-43. This article, in turn refers to work done by Riggs and Itakura to create insulin from A and B chains expressed in separate host cells. *See,* Ex. 2008 Gilbert & Villa-Komaroff, *Useful Proteins from Recombinant Bacteria*, Scientific American, 242: 74-94 (1980) at 88. Thus, Ex. 1034 actually illustrates the then-prevailing one-protein-of-interest-per-host-cell approach;
- U.S. Patent No. 4,762,785 (Ex. 1035) does not mention antibodies or immunoglobulins, does not illustrate any actual protein expression, and is directed toward construction of a hybrid plasmid that can be used to transfect plants. Ex. 1035 at abstract;
- U.S. Patent No. 4,476,227 (Ex. 1036) does not mention antibodies or immunoglobulins, does not demonstrate expression of any proteins, and is instead focused on constructing hybrid cloning constructs called cosmids. Ex. 1036 at abstract;

- U.S. Patent No. 4,362,867 (Ex. 1037) relates to cDNA synthesis and does not demonstrate production of any protein(s) of interest. Ex. 1037 at abstract;
- U.S. Patent No. 4,396,601 (Ex. 1038) does not mention antibodies or immunoglobulins, and shows no example of the introduction of more than one gene of interest into a host cell. Instead, it describes experiments showing transformation of a mammalian host cell, extracted from an animal, with DNA for a "selective marker" and introduction of the transformed host cell back into an animal. Ex. 1038 at 10:36-11:37.

In sum, Petitioners' assertions amount to smoke with no fire: none of these references employs the word "genes" in a relevant context, namely, as referring to multiple DNA sequences encoding two proteins of interest (*i.e.*, the heavy and light chain polypeptides) being used to co-transform and to co-express antibody heavy and light chains as separate molecules in a single host cell. And none provides any insights that would have changed expectations or beliefs of the ordinarily skilled person regarding successful production of a complex multimeric protein such as an antibody.

E. The Cabilly '415 Patent Inventors Advanced the Art by Demonstrating That Recombinant Heavy And Light Chains Could Be Co-Expressed in a Single Host Cell to Produce Functional Antibodies

The approach claimed in the Cabilly '415 patent was a dramatic departure from conventional thinking in the field of genetic engineering in April of 1983. As discussed above, up to that point, only a few recombinant eukaryotic proteins had been successfully expressed, and for each of these proteins, only one polypeptide of interest was produced in a given host cell. *See,* Section IV.B-IV.D, *supra*. Petitioners have cited no contrary example.

The Cabilly '415 patent inventors' work demonstrated proof of the concept that recombinant heavy and light chain DNA could be introduced in a single host cell and co-expressed as separate molecules to produce a functional antibody. *See, e.g.* Ex. 1001 at abstract, Claim 1. The inventors' approach sharply diverged from the conventional thinking in the field, namely, the one-protein-of-interest-per-host cell strategy that had been prevalent in the field, particularly for eukaryotic proteins, prior to April of 1983. The Cabilly '415 claimed invention instead required that, in addition to DNA sequences necessary to select for successfully transformed host cells (selectable marker DNA), two additional foreign DNA sequences (heavy and light chain DNA) must be independently expressed by the cell and produced as separate molecules. Ex. 1001 at Claim 1. The Cabilly '415 patent represented a paradigm shift that paved the way for commercial

recombinant antibody production. The widespread impact of this paradigm shift is evidenced by the widespread licensing of the Cabilly patent. *See, e.g.*, Ex. 2009, Walton Rep. at pp. 4-9.

V. EACH OF PETITIONERS' PROPOSED GROUNDS IS DEFICIENT AND REPETITIVE OF ARGUMENTS ALREADY REJECTED DURING REEXAMINATION

Petitioners' four grounds each employ the same strategy: they advance ***linguistic*** theories about what may be conveyed by a reference without rebutting the substantial and uncontroverted ***scientific*** reality about what that reference actually would have conveyed to the skilled person in April of 1983 about independent co-transformation and co-expression of the light and heavy chains of an antibody in a single host cell. Petitioners resort to citing references in the general field of the invention, finding words and phrases that relate generally to the claimed subject matter, and then extrapolating from those terms to argue that there is disclosure of the specific claim elements. As described below, this analysis is infected with hindsight and is wholly insufficient to warrant institution of *inter partes* review.

It is also demonstrably incorrect—the ***very same rationale*** about the use of the plural term "genes" and the inclusion of "antibodies" in aspirational lists of proteins that would be desirable to produce in the prior art cited in the Petition ***was thoroughly considered and ultimately rejected by the Office during***

reexamination. The Petition adds nothing to what was already considered by the Office and the prior art cited by Petitioners is cumulative to that considered during reexamination. The grounds advanced in the Petition therefore must fail for the same reasons. Because Petitioners have failed to demonstrate a reasonable likelihood of prevailing on any of their proposed grounds, the Board should decline to institute an *inter partes* review.

A. Petitioners Have Not Shown a Reasonable Likelihood That Bujard Anticipates Claims 1, 3-4, 9, 11-12, 15-17, 19 or 33

Petitioners have failed to carry their burden to show there is a reasonable likelihood that Bujard anticipates any claim of the Cabilly '415 patent. Anticipation cannot be proven by identifying "mere catalogs of separate parts, in disregard of the part-to-part relationships set forth in the claims and that give the claims their meaning." *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) (internal quotation marks and alteration omitted). "[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). Petitioners have done exactly what the Federal Circuit forbids—they assert anticipation by identifying some, but not all, of the claim limitations, and improperly combine

disparate references within Bujard to attempt to mimic how the claim elements are used in the challenged claims.

Moreover, in an attempt to fill in the gaps of Bujard, Petitioners rely on linguistic arguments that the terms "genes" and "immunoglobulin" are sufficient to disclose many elements of the claims. But these words are not used in a meaningfully different way than the very same words were used in the prior art reference—Axel—that was considered by the Office during reexamination. As the Office found with respect to Axel, the mere use of the words "genes" and "immunoglobulin" in a reference does not convey to the skilled person an actual description of how to produce a functional immunoglobulin or fragment by independent expression of its constituent heavy and light chains in a single transformed host cell. Ex. 1025 at 7. Petitioners have offered nothing beyond this already rejected rationale, and have thus not presented a reasonable basis for establishing that any of the Cabilly '415 patent claims is anticipated.

1. Bujard (Ex. 1002)

The Bujard patent, on which Dr. Cohen (of Cohen & Boyer) is a named co-inventor, is an extension of the basic recombinant DNA methodology disclosed in the earlier Cohen & Boyer reference. Ex. 2005, Foote Dep. Tr. at 141-42. Bujard is directed to optimizing transcription through the identification and use of strong "promoters" to drive transcription of DNA sequences introduced into a host cell by

recombinant DNA techniques. Ex. 1002, Bujard at 2:3-20. Specifically, the techniques described in Bujard relied on the use of a promoter that did not interfere with expression of the marker used to select transformants. *Id*. Bujard teaches that strong promoters required balancing from strong terminators. *Id.* at 2:41-43. Thus, Bujard's claimed invention provides methods and compositions for "preparing and cloning strong promoter and terminator regulatory signals and utilization of the strong regulatory sequences in the transcription and expression of genes of interest." *Id.* at 2:28-32.

2. Bujard Does Not Anticipate Independent Claims 1, 15, 17[4], and 33

Each of the independent method claims (claims 1 and 33) requires (1) the transformation of a single host cell with DNA sequences encoding the immunoglobulin heavy and light chains; (2) the independent expression by the transformed single host cell of those sequences to yield heavy and light immunoglobulin chains as separate molecules; and (3) production of an immunoglobulin molecule or immunologically functional immunoglobulin fragment. Claim 15 requires a vector for use in the claimed methods and, similarly, claim 17 requires a host cell transformed with the claimed vector. The disclosure in Bujard does not anticipate any of these claims.

[4] Although Petitioners refer to "independent" claim 17, it depends from claim 15.

a) Petitioners' Arguments Regarding the Prior Art's Disclosure of "Genes" and "Antibodies" Have Already Been Rejected

In advancing their case for anticipation, Petitioners present theories on how a person of ordinary skill might have read selected passages of Bujard in April of 1983, and based on that proposed interpretation of these passages, assert that Bujard describes a method of producing an immunoglobulin or fragment in the manner specified by the contested claims of the Cabilly '415 patent. But in advancing that argument, the Petition presents the same flawed reading of words and concepts in the prior art that was advanced but ultimately abandoned by the Office during reexamination of the Cabilly '415 patent.

During the reexamination, the Examiners issued four separate rejections in which they initially took the position that the prior art Axel reference, in combination with other references, rendered the Cabilly '415 patent claims obvious.[5] *See,* Exs. 1011 (Sept. 13, 2005); 1016 (Aug. 16, 2006); 1008 (Fab. 17,

[5] Specifically, Examiners considered obviousness type double patenting grounds based on a combination including U.S. Patent No. 4,816,567 ("Cabilly I") and Axel. *See,* Ex. 1008 at 22. Cabilly I is directed to the production of a single chimeric heavy or light chain in a host cell and does not require co-expression of the heavy and light chains as separate molecules in a single host cell. *See, id.* at 19.

2007); 1017 (Feb. 25, 2008). Specifically, the Office pointed to two passages in Axel to support its assertion that Axel taught independent co-expression of the light and heavy chains of an antibody in a single transformed host cell: (1) a passage where Axel referred to generation of an "antibody" in an aspirational list of proteins that potentially could be produced; and (2) a passage within Axel that referred to transformation cells with "genes" (plural). *See,* Ex. 1016 at 23, 34; Ex. 1008 at 51; Ex. 1017 at 28-29.

In response to those rejections, Patent Owners presented testimony from numerous, highly qualified individuals having actual experience working in the field of the invention in April of 1983. Those individuals explained in detail why the proposed reading of "genes" and "antibodies" being advanced in the rejections was flawed and scientifically implausible. Those reasons included (i) the absence of guidance and explanations within Axel that would logically have been included if it were referring to production of two or more constituent polypeptides of a multimeric protein, and (ii) the fact that plural references to "genes" would have been read as referring to multiple copies of the same gene or were informal references, rather than specific teachings of insertion and expression of multiple DNA sequences encoding different desired polypeptides that were to be isolated from the transformed host cells. As these experts explained:

- The reference to "antibodies" in Axel "neither suggests nor describes how one would transform a single eukaryotic cell to contain and express genes encoding two distinct polypeptides that are to be ultimately recovered from the transformed cell, much less a heavy and light chain of an immunoglobulin." Ex. 1009 at 36-37; Ex. 2004, Harris Decl. at ¶¶26-27.
- The inclusion of antibodies in a laundry list of molecules merely indicated that the invention might be applied to a wide range of proteinaceous material and did not disclose or suggest production of the heavy and light chains of the antibody in a single transformed cell. Ex. 1022 at 43; Ex. 2004, Harris Decl. at ¶26; *see also,* Ex. 1010 at 52; Ex. 2019, Ex. 2019, Ex. 2007 Botchan Decl. at ¶55 ("[i]n my opinion, a person skilled in this field would read this passing reference to 'antibodies' as simply indicating that antibody polypeptides (i.e., heavy or light chains) can be produced by the Axel procedure."); Ex. 1024 at 45-46 (citing Ex. 2002, McKnight Decl. at ¶68) (inclusion of antibodies on list "does not provide any specific guidance about <u>how to make</u> any of the[] particular proteins, especially 'antibodies,' " any more than the inclusion of enzyme on the same list describes how to co-express the ***ten*** subunits of RNA polymerase in one cell).
- References to the plural term "genes" in Axel are "connected to the idea of producing a transformed host cell having multiple copies of the same DNA

sequence encoding the same single desired polypeptide." Ex. 1022 at 44; *see also,* Ex. 1009 at 36; Ex. 2005, Harris Decl. II at ¶45.

- Axel did not show or suggest the production of a functional antibody, and "simply writing the word 'antibody' in the Axel patent specification would not be enough to advance the field . . . ." Ex. 1024 at 52-53.

The evidence provided by Patent Owners demonstrated that the Examiners' reading of "genes" and "immunoglobulins" within the Axel patent as teaching production of the heavy and light chains of an antibody in a single transformed host cell was scientifically implausible and contrary to how the skilled person would have actually interpreted these passages in April of 1983. In view of that evidence and after an agreed-upon clarifying amendment to several claims that are not challenged in the Petition, Ex. 2014 at 3, the Office confirmed the patentability of the '415 claims. Ex. 1025. In the statement of reasons for patentability and/or confirmation, the Office explained that Axel in combination with other references "do[es] not suggest or contain an enabling disclosure of a method to produce an immunologically functional immunoglobulin molecule by independently expressing immunoglobulin heavy chain and light chain in a single transformed host cell." Ex. 1025 at 7. The Office credited the declarations of Drs. Harris, McKnight, Rice, and Botchan (among others) and, in spite of its earlier reliance on

the disclosures of "antibody" and "genes," found that "Axel et al. did not teach co-expression of two foreign DNA sequences." *Id.* at 4.

Remarkably, Petitioners now seek to revive the same distorted reading of the terms "genes" and "immunoglobulins" that was abandoned by the Office during reexamination. The Petition is not subtle about doing so: it points to the use of the identical terms "genes" and "immunoglobulins" appearing in Bujard in the exact same manner as the Examiners initially relied on these terms within Axel, arguing the plural reference to "genes" and the inclusion of "immunoglobulins" within an aspirational list of possible proteins to produce support its arguments about how the skilled person would have interpreted the teachings of Bujard. In fact, the Petition ***expressly equates*** its rationale for reading these terms in Bujard with the abandoned rationale of the Office in reading the same terms in Axel—it presents its arguments under a heading entitled: "Bujard Teaches Introducing and Expressing a ***'Plurality of Genes'*** in Bacterial or Mammalian Host Cells and Identifies ***'Immunoglobulins'*** as a Protein of Interest." Paper 1 at 25 (emphasis added).

These linguistic analyses of the words "genes" and "immunoglobulin" were refuted by the evidence presented to the Office during the reexamination, and should likewise be found insufficient to establish a reasonable likelihood that the challenged claims of the Cabilly '415 patent are unpatentable in this proceeding.

That the Petitioners' arguments employ the same abandoned rationale overcome during the reexamination is readily seen by comparing portions of the Petition with the statements of the Examiner during the reexamination:

Examiners' Argument	**Petitioners' Arguments**
"[T]he Axel reference suggests expressing two immunoglobulin chains in a single cell, since Axel discloses and claims . . . DNA . . . ***encoding an antibody that necessarily possesses both light and heavy immunoglobulin chains***. In this respect, the Axel reference clearly encompasses one or more genes which encode one or more proteins: e.g., ' . . . DNA ***which includes a gene or genes*** coding for desired proteinaceous materials. . . .'" Ex. 1016, Aug. 16, 2006 Office Action at 340-341 (emphasis added); *see also,* Ex. 1008, Feb. 16, 2007 Office Action, at 651. "Axel's invention as described and claimed is as follows . . . 'DNA which includes a gene or genes coding for desired proteinaceous materials' . . .	Bujard "teaches a process for producing proteins of interest—among which the patent expressly identifies immunoglobulins—in a transformed host cell using a plasmid vector . . . Producing such proteins as taught by Bujard occurs in a single host cell . . . that is transformed with a single plasmid ***containing 'more than one gene, that is a plurality of genes. Bujard's identification of immunoglobulins*** . . . 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."*** Paper 1 at 37-38 (emphasis added). "The DNA sequence of interest, which 'usually' consists of 'structural genes,'

'cotransformation with the desired genes' . . . 'insertion of multiple copies of desired genes is accomplished by transformation' . . . Accordingly, [Axel] suggest co-transforming ***more than one desired gene*** for making proteinaceous materials which include multimeric proteins, such as interferon." Ex. 1017 Feb. 25, 2008 Office Action at 1078 (emphasis added).	is inserted between the strong promoter and terminator . . . The DNA sequence of interest may contain '***more than one gene, that is a plurality of genes, including multimers*** and operons." Paper 1 at 26 (emphasis added).

Indeed, aside from submitting a declaration that simply repeats the linguistic analysis of these terms in the Petition, Petitioners do nothing to advance the inquiry beyond what the Office has already considered. Instead, Petitioners expressly state their desire to revisit the determinations made by the Office during reexamination—they ***rely on Axel*** to describe what Bujard allegedly teaches, asserting that Bujard teaches "exactly what Axel taught" that is, "the independent expression of separate proteins in a single host cell transformed with a vector containing two different genes." Paper 1 at 40.

Consequently, just as with Axel, the Bujard reference to the plural term "genes" would not have been read by the skilled person as suggesting the production of constituent polypeptides of a multimeric protein in a single transformed host cell. Instead, it is more plausible that the plural term "genes"

would have been read by the skilled person in April of 1983 as referring to multiple copies of the same inserted gene, or would be seen as an informal reference to the DNA sequence of interest (*i.e.*, the sequence that encodes the desired polypeptide). Ex. 2001, Fiddes Rep. at ¶104; Ex. 2015, Christie 1980 at 2786-2790; Ex. 2016, Frommer 1982 at 547-563; Ex. 2017, Israelewski 1983 at 6985-6996. Petitioners' contrary argument fails for the same reason it failed during the reexamination: the disclosure of inserting multiple copies of the same gene into a host cell is not a disclosure of inserting DNA sequences encoding ***different*** desired polypeptides (*i.e.*, separate heavy and light chains) that are to be produced and isolated from a single transformed cell.

In addition, like Axel, Bujard neither discloses nor suggests the actual production of a functional antibody or antibody fragment. With respect to Axel, Patent Owners established and the Examiners agreed during reexamination that the inclusion of the word "antibody" in a laundry list of proteins of interest does not "suggest or contain an enabling disclosure." Ex. 1025 at 7. Bujard fares no better. It contains no description of all the limitations as claimed in the Cabilly '415 patent sufficient to allow one of skill in the art produce a functional antibody. Dr. Foote's hindsight assembly of the pieces of Bujard into the claims of the Cabilly (many of which are still missing) cannot remedy this defect. *See, Net MoneyIN*, 545 F.3d at 1371 (a reference "cannot be said to prove prior invention of

the thing claimed and, thus, cannot anticipate" if it does not recite "all of the limitations arranged or combined in the same way as recited in the claim").

b) The Petition Fails to Identify Each and Every Cabilly '415 Patent Claim Element in Bujard

The anticipation grounds presented in the Petition should also be denied because the Petition fails to identify where in Bujard each and every claim element is disclosed. This is evident from even cursory inspection of the passages of Bujard quoted in Petitioners' claim chart. Paper 1 at 41-42. Specifically, Petitioners cite general statements from Bujard that: (a) among a long list of other proteins, "immunoglobulins" are "of interest for production" (Ex. 1002 at 4:14-36); (b) describe a general approach to construct a vector (Ex. 1002 at 2:8-13); (c) describe a type of promoter that can be used "to provide for high and efficient transcription and/or expression of ***the sequence***" (singular) (Ex. 1002 at 3:46-48 (emphasis added)); (d) describe that transformation vectors may consist of a promoter and terminator "separated by more than one gene, that is, a plurality of genes" (Ex. 1002 at 3:46-48); and (e) describe that plasmids can be used to transform an appropriate host (Ex. 1002 at 3:61-62). Paper 1 at 41-42.

None of these cited passages actually describes the application of recombinant DNA techniques described in Bujard to produce an immunoglobulin molecule or immunologically functional immunoglobulin fragment. More directly, none of these passages describes a process whereby DNA sequences encoding the

heavy and light chains of an immunoglobulin are used to transform a single host cell, or that shows these sequences being independently expressed in that single host cell as separate molecules. Nor is there any disclosure in Bujard of procedures or approaches for assembling the immunoglobulin chains so produced into an intact antibody or an immunologically functional fragment. In short, Bujard nowhere describes the invention that is claimed by the Cabilly '415 patent claims.

Petitioners' claim chart makes clear the inadequacies of the actual disclosures of Bujard. As an initial matter, Petitioners' chart makes no attempt to show how the single set of cited passages meets the ***different*** requirements of claims 15, 17, and 33. Instead, Petitioners simply refers to the passages cited for claim 1 and generally allege those same citations somehow operate to anticipate claims 15, 17 and 33. As the Board has repeatedly warned, "[i]t is Petitioners' responsibility to explain specific evidence that support its arguments, not the Board's responsibility to search the record and piece together what may support Petitioner's arguments." *Hopkins Mfg. Corp. v. Cequent Performance Prods., Inc.*, IPR2015-00616, Paper 9 at 9 (Aug. 17, 2015) (internal quotation and citation omitted); *see also, e.g., Int'l Securities Exchange, LLC v. Chicago Board Options Exchange, Inc.*, IPR2014-00099, Paper 12 at 12 (declining institution where Petition did not provide element-by-element analysis for each claim).

The cited passages from Bujard make clear that the techniques being described by Petitioners are general ones; they do not show a particular application of the techniques to produce immunoglobulins in the manner required by the claims of the Cabilly '415 patent. Moreover, Petitioners have not matched the individual claim elements to particular disclosures within Bujard, let alone shown that these Bujard disclosures describe methods and elements arranged in the same way as required by the claims.

For example, Claim 1 includes three parts, and the disclosures listed in Petitioners' charts omit aspects of each:

- The claim 1 preamble recites 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***." Ex. 1001 at 28:36-40 (emphasis added).
    - Petitioners' claim charts do not cite (1) production of heavy and light chains; (2) production of an immunoglobulin molecule or functional fragment; (3) production from a single host cell.
- Element (i) of claim 1 requires "***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***." Ex. 1001 at

28:41-45 (emphasis added).

- Petitioners' claim charts do not cite (1) transformation with a DNA sequence encoding the variable domain of the immunoglobulin heavy chain; (2) transformation of the same host cell with a DNA sequence encoding the variable domain of the immunoglobulin light chain.

- Element (ii) of claim 1 requires "***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***." Ex. 1001 at 28:46-49 (emphasis added).
    - Petitioners' claim charts do not cite (1) expression of heavy and light chains; (2) independent expression of heavy and light chains as separate molecules; (3) expression of heavy and light chains in a single transformed host cell.

Petitioners' claim charts for Claims 15, 17, and 33 have the same defects. For example, Claim 15 requires 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" and that each of the sequences is "located in said vector at different insertion sites." Ex. 1001 at 29:22-17. Petitioners' claim charts do not cite any passages from Bujard describing a vector with sequences encoding heavy ***or*** light

chains, or different insertion sites. Petitioner's proposed grounds of anticipation of claims 15, 17 and 33 are thus plainly insufficient to justify institution of trial.

c) The Petition Does Not Establish That The Claim Elements Missing From Bujard Are Necessarily Present

Bujard does not disclose vectors, host cells, or methods for co-expressing heavy and light chain DNA in a single host cell, the production of the heavy and light chains as separate molecules within the cell, or the formation of an antibody using these chains. The absence of any explicit disclosure of these claim elements within Bujard lead Petitioners to instead argue these claim elements are somehow inherent in the Bujard disclosure. Paper 1 at 38. To advance that theory, Petitioners rely on the opinion of Dr. Foote. But Dr. Foote himself admits these limitations are not expressly taught in Bujard—he contends these elements could be derived by the ordinarily skilled person through that person's application of "simple logic and common sense." *Id.*; Ex. 1006, Foote Decl. at ¶91. Dr. Foote's admission is fatal to Petitioner's assertion of anticipation—his reasoning concedes the limitations of the claims are not taught by Bujard, but are, ***in his view***, obvious extensions of what is taught by Bujard. That conclusion is scientifically incorrect, contrary to the substantial evidence, and legally incapable of supporting anticipation. On this latter point, the Federal Circuit has made clear that, while an anticipation analysis "presupposes the knowledge of one skilled in the art of the

claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there. An expert's conclusory testimony, unsupported by the documentary evidence, cannot supplant the requirement of anticipatory disclosure in the prior art reference itself." *Motorola, Inc. v. Interdigital Tech. Corp*., 121 F.3d 1461, 1473 (Fed. Cir. 1997). Consequently, Petitioner's proposed ground of anticipation by Bujard is plainly insufficient to establish a reasonable likelihood that the challenged claims of the Cabilly '415 patent are anticipated by Bujard.

Dr. Foote's current testimony is also at odds with his previous testimony in litigation involving the Cabilly '415 patent. For example, Dr. Foote admitted during cross-examination that Bujard "doesn't say free heavy chains. I can't find it anywhere." Ex. 2005, Foote Dep. Tr. at 157-58. Because Dr. Foote admitted that Bujard does not describe processes that produce heavy chains, Bujard cannot disclose every element required by the claims, most notably the requirement that the expressed DNA sequences encode "at least the variable domain of the immunoglobulin heavy chain."

Petitioners alternatively contend the disclosures of various elements of the Cabilly '415 patent claims are "inherent" to Bujard because a disclosure of a host cell transformed with "more than one gene, that is, a plurality of genes, including multimers and operons" necessarily discloses "two foreign DNA sequences."

Paper 1 at 38. But "inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Indus., Inc. v. Top-U.S.A. Corp*., 295 F.3d 1292, 1295 (Fed. Cir. 2002). Petitioners have clearly failed to meet that standard, as they have failed to demonstrate that this disclosure could not be referring to production of multiple copies of the same gene on a single restriction fragment excisable from some natural source of DNA. In fact, as shown in Section V.A.2.a, *supra*, the reference to the plural term "genes" in the Bujard reference would have been understood by the skilled person to be referring to multiple repeating units of the same gene.

Petitioners also argue that because Bujard generally references immunoglobulins and discloses that proteins can be "prepared as a single unit or as individual subunits and then joined together in appropriate ways" after co-expression, it must ***necessarily*** teach co-expression of light and heavy immunoglobulin chains in the same host cell as separate molecules. Paper 1 at 40. This assertion simply assumes the desired result.

Petitioners have not and cannot exclude that the skilled person, being fully aware of the experience with the production of insulin, would have read this passage in Bujard in April of 1983 as referring to production of the immunoglobulin chains ***in separate host cells*** followed by assembly of the immunoglobulin from these separately produced heavy and light chains. That

reading of Bujard is the far more plausible one, as it would employ the same approach that had been successfully used to produce the only multimeric protein that had been produced at the time of the invention. *See* Section IV.C, *supra*. Indeed, Dr. Foote elsewhere relies on this experience with producing insulin as being highly pertinent to the person of skill in the art with regard to applying the teachings of Bujard. Ex. 1006, Foote Decl. at ¶101. In sum, Petitioners have failed to establish that Bujard ***necessarily*** discloses the co-transformation and co-expression of an immunoglobulin heavy chain and light chain from the same host cell, or that it anticipates claims 1, 15, 17 or 33 of the '415 patent.

3. Bujard Does Not Anticipate Dependent Claims 3, 4, 9, 11, 12, 16, and 19

Because Bujard does not anticipate independent claims 1, 15, and 33 of the Cabilly '415 patent, it also fails to anticipate the dependent claims. Indeed, the Petition cites no further disclosure to support its contention that Bujard anticipates the dependent claims, and instead simply repeats the same three lines taken out of context to support its contentions for all of claims 1, 3-4, 9, 11-12, 15-17, 19 and 33. Paper 1 at 42-44. Petitioners thus have not shown a reasonable likelihood of establishing that claims 3, 4, 9, 11, 12, 16 and 19 are anticipated by Bujard.

a) Claim 9

Claim 9 specifies the production of immunologically functional immunoglobulins or fragments that are assembled in the host cell and secreted out

of it as a functional immunoglobulin, *i.e.*, *in vivo* assembly. Petitioners' only argument concerning this claim is that it is anticipated by the reference in Bujard to a "single unit" of protein. Paper 1 at 40, 43. According to Petitioners, a "single unit" would be understood by one of skill in the art to be a reference to a functional antibody produced via *in vivo* assembly of co-expressed immunoglobulin light and heavy chains in a single host cell. *Id.* But the more natural reading of that phrase, which does not require one to insert multiple words and concepts that appear nowhere in the Bujard reference, is that "single unit" refers to a ***monomeric*** protein and that individual "subunits" refers to the constituent polypeptides that make up a multimeric protein. In both situations, a single polypeptide is to be expressed in a single host cell. Ex. 1002, Bujard at 4:19-21, 30-36; 5:11-27; *see,* Ex. 2001, Fiddes Rep. at ¶111. Nothing in the Petition or Dr. Foote's declaration bridges the gap from monomer to multimeric protein, and Bujard does not suggest that "single unit" could be applied to co-expression of separate heavy and light chains assembled *in vivo* in a single host cell.

B. Claims 1, 3-4, 11-12, 14, 19, and 33 Are Not Obvious Over Bujard in View of Riggs & Itakura

1. Riggs & Itakura (Ex. 1003)

Riggs & Itakura recounts the Genentech/City of Hope approach in the 1970s to making insulin using recombinant DNA techniques. This technology was also the subject of Goeddel 1979, discussed above in Section IV.D.1. In this approach,

the individual chains of insulin are produced in ***separate*** E. coli host cells, with each host cell being transformed with a ***different*** plasmid encoding either (1) the A polypeptide chain of insulin or (2) the B polypeptide chain of insulin. Ex. 1003 Riggs & Itakura at 531, Fig. 1. As Riggs & Itakura teach, the A and B chains were successfully expressed in separate host cells, and the two chains were then isolated from their respective cell cultures and were finally combined *in vitro* (*i.e.*, in a test tube) to form the insulin dimer. *Id.*at 531.

2. Petitioners Have Failed to Demonstrate a Reasonable Likelihood of Success

Petitioners have failed to demonstrate a reasonable likelihood that claims 1, 3-4, 11-12, 14, 19, and 33 would have been obvious over Bujard in view of Riggs & Itakura in April of 1983. For the reasons explained in section V.A, *supra*, Bujard does not disclose all of the limitations of the claims. Petitioners rely on Riggs & Itakura only to clarify Bujard's statement that "individual subunits" can be joined "in appropriate ways." Paper 1 at 45. This does not cure the many deficiencies of Bujard. Ex. 2001, Fiddes Rep. at ¶¶117-119.

Further, Petitioners have failed to provide rational underpinnings for why the ordinarily skilled person would combine Bujard with Riggs & Itakura to arrive at the claimed invention. *See, KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Petitioners argue that there was a motivation to combine the references because they are in "the same general field" and Bujard refers to joining protein

subunits together in "appropriate ways." Paper 1 at 45. But nothing in Riggs & Itakura suggests that the *in vitro* techniques described therein to combine proteins expressed in separate host cells would also be suitable for combining *in vitro* different proteins expressed in the same host cell.

Instead, the gap between the claims of the Cabilly '415 patent and the teachings of Bujard is widened and reinforced by Riggs & Itakura. Indeed, Riggs & Itakura teaches the skilled person to approach production of a multimeric protein by transforming ***different*** host cells with DNA sequences encoding each of the constituent polypeptides of the multimeric protein, isolating those individually produced polypeptides, and then assembling the individually produced and isolated polypeptides into the multimeric protein. Read accurately, the combined teachings of Bujard and Riggs & Itakura actually lead the skilled person ***away*** from the claimed invention of the Cabilly '415 patent. Ex. 1003, Riggs & Itakura at Fig. 1. Ex. 2001, Fiddes Rep. at ¶117.

Petitioners offer no explanation why one of skill in the art would rely upon Riggs & Itakura for some teachings (*e.g.*, how to assemble a multimeric protein), but ignore the overarching strategy it advances for producing multimeric proteins. This is particularly true given that the only method described in Riggs & Itakura for producing insulin expressly employs the strategy of producing the A and B chains in separate host cells and then reassembling the insulin multimer using these

individually produced chains. Ex. 1003, Riggs & Itakura at 531, Fig. 1; *see also,* Section V.B.1, *supra*. Accordingly, Petitioners' Ground II should not be instituted. *See, Fortinet, Inc. v. Sophos Inc.*, IPR2015-00617, Paper 9 at 16-18 (Aug. 13, 2015) (declining to institute obviousness grounds where Petitioner did not provide rational underpinning for combination and merely argued that references were in "same field," related to the "same technology" and solved the "same problem," and where reference taught away from the claimed invention).

C. Claims 1, 2, 18, 20 and 33 Are Not Obvious Over Bujard in View of Southern

1. Southern (Ex. 1004)

Southern discloses insertion of a bacterial gene, which confers resistance to neomycin-kanamycin antibiotics, into SV40 hybrid plasmid vectors and introducing those vectors into cultured mammalian cells. Ex. 1004 Southern at abstract. Once inserted, cells that have the resistant selectable marker conferred from the vector can be isolated by introducing neomycin-kanamycin antibiotics that kill all cells that did not express the marker gene. *Id.* Southern discloses that this new vector can be introduced to a host cell, alongside a vector with a different selectable marker. *Id*. Southern demonstrates that these two plasmids are compatible and can both be taken up by the host cell. *Id.* at 336. But Southern does not reference antibody production at all, nor does it demonstrate expression of any protein(s) of interest in conjunction with the selectable markers.

2. Petitioners Have Failed to Demonstrate a Reasonable Likelihood of Success

Petitioners fail to demonstrate a reasonable likelihood that claims 1, 2, 18, 20 and 33 would have been obvious to the ordinarily skilled person based on Bujard in view of Southern in April of 1983. As explained in Section V.A, *supra*, Bujard does not disclose a process for producing light and heavy immunoglobulin chains in a single transformed host cell, and thus does not meet all of the limitations of claims 1, 2, 18, 20, and 33. Southern does not cure the deficiencies of Bujard. Notably, Petitioners rely on Southern simply to contend that if Bujard teaches co-expression using one vector containing DNA sequences for both the heavy and light chains of an antibody, it would have been obvious to modify the Bujard technique by using two vectors instead, one containing the heavy chain DNA and one containing the light chain DNA. Paper 1 at 47-48. This contention, like Petitioner's assertions regarding the combination of Bujard with Riggs & Itakura, rests on an incorrect and unproven foundation. Specifically, Bujard does not teach production of a single vector containing DNA sequences encoding both the heavy and the light chains of an antibody, expression in a single host cell of heavy and light chain polypeptides as separate molecules, or production of a functional antibody. Southern, which does not mention antibodies at all, adds nothing to remedy these deficiencies of Bujard.

Further, Petitioners have not shown rational underpinnings for why a person

of ordinary skill would have combined the teachings of Bujard and Southern. Petitioners' arguments again rest on the premise that Bujard teaches "successful[] co-express[ion] in a single host cell" of "heavy and light chain genes . . . when present on one vector." Paper 1 at 49. As discussed above, Bujard teaches no such thing. *See,* Section V.A, *supra*. Second, Southern discloses the introduction of two ***selectable markers*** into a host cell, ***not*** the introduction of two DNA sequences that are meant to be co-expressed from a single host cell. Ex. 1004 Southern at abstract. Thus, even if Bujard taught use of a single vector to express DNA sequences encoding two different polypeptides of interest in a single host cell, Petitioners have offered no reason why a person of ordinary skill would have modified that approach to use Southern's technique of using multiple vectors with different selectable markers to produce multiple desired proteins. Petitioners certainly have not offered a reason why a person of ordinary skill would use this combined approach to produce both heavy and light chains in a single host cell.

D. Claims 1, 3-4, 11-12, 14, and 33 Are Not Obvious in View of Cohen & Boyer in Combination With Riggs & Itakura

Petitioners fail to establish a reasonable likelihood that claims 1, 3-4, 11-12, 14, and 33 would have been obvious to the skilled person in April of 1983 based on Cohen & Boyer in view of Riggs & Itakura. This ground is also redundant to the grounds based on Bujard and Riggs & Itakura. *See,* Section V.B, *supra*.

1. Cohen & Boyer (Ex. 1005)

U.S. Patent 4,237,224 to Cohen & Boyer is cited on the face of the Cabilly '415 patent and was identified for the Examiner during prosecution in an IDS submitted on October 3, 2001. Cohen & Boyer discloses a methodology for introducing foreign DNA into microbial host cells where it replicates and imparts new "genotypical capability" to the host. Ex. 1005, Cohen & Boyer at 1:53-55. Cohen & Boyer's approach was to modify a DNA vector, such as a bacterial plasmid, so that it would contain DNA not normally present in the vector. *Id.* at abstract, 1:56-62. Making such a "recombinant" construct provided a means for introducing foreign DNA into a host cell. *Id.* at abstract, 1:56-68.

While Cohen & Boyer is correctly recognized as describing an important advance in the then-emerging field of genetic engineering, it plainly does not teach or suggest the claimed invention of the Cabilly '415 patent. Notably, Cohen & Boyer was considered by the Office during original examination of the Cabilly '415 patent. In addition, during reexamination, Patent Owners provided a copy of an Expert Report by E. Fintan Walton, which extensively discussed the teachings of Cohen & Boyer. *See*, Ex. 2009, Walton Rep. at pp. 17-19. Despite this, as Petitioners note, the Cabilly '415 patent claims were "never the subject of a rejection by the PTO during prosecution or reexamination." Paper 1 at 29. This is hardly surprising, as Cohen & Boyer, while relevant as background technology, is

not focused on and does not show the recombinant production of any multimeric protein, much less a protein as complex as an antibody. Thus, the Office was intimately aware of the teachings of Cohen & Boyer, and treated it as nothing more than background art to the invention claimed in the Cabilly '415 patent.

2. Petitioners' Arguments Regarding the Prior Art's Disclosure of "Genes" and "Antibodies" Have Already Been Rejected

As discussed in Section V.A.1.a, *supra*, the Office found during the reexamination of the Cabilly '415 patent that prior art references that use the plural form of the word "genes" and the inclusion of "antibodies" in aspirational lists of potential proteins of interest do not teach production of antibodies by co-expressing DNA sequences encoding the light and heavy chains of the antibody in a single transformed host cell. Despite this evidence, and as with Bujard, Petitioners advance the same rationale for inaccurately reading these terms where they appear in Cohen & Boyer. *See,* Paper 1 at 28. As with Bujard, Petitioners' proposed reading of Cohen & Boyer must be rejected, given that Petitioners offer no new ***scientific*** evidence showing the Office erred during reexamination.

3. Petitioners Have Failed to Demonstrate a Reasonable Likelihood of Success

The Petition does not identify what teachings in Cohen & Boyer and/or Riggs & Itakura would have suggested every element of the claimed invention of the Cabilly '415 patent to the person of skill in the art. Instead, Petitioners cite

isolated portions of each reference, ignore the teaching away of Riggs & Itakura to use a one-protein-per-host-cell approach, and, using hindsight, contend these passages together would have rendered obvious the claimed invention.

Petitioners cite passages from Cohen & Boyer including: the inclusion of "antibodies" in an aspirational list of proteins that could be produced (Ex. 1005 at 9:12-30, 16:54-65); the transformation of a cell with a plasmid containing "one or more genes," "at least one intact gene," or "at least one foreign gene" (Ex. 1005 at 1:56-59, 4:29-38, 5:59-65); and the transformation of a host cell (Ex. 1005 at 16:42-47, 1:60-67). Paper 1 at 50-53. Notably absent is any description within Cohen & Boyer of a process for producing multiple proteins of interest (*e.g.,* heavy and light chains of an antibody) in a ***single*** host cell.[6] Indeed, Petitioners' claim chart does not cite disclosures from Cohen & Boyer corresponding to each of the claim elements: transformation of the same host cell with DNA sequences encoding variable domains of heavy and light chains, production of an immunoglobulin molecule or functional fragment, or production from a single host cell. *Id.* The claim chart thus falls well short of enumerating an invalidating disclosure. *Compare* Section V.A.2.b, *supra*.

[6] Petitioners' claim chart again cites the same disclosures for each of the independent claims and omits element-by-element comparisons. Paper 1 at 52-53.

Petitioners' use of Riggs & Itakura does not remedy these defects. The passages from Riggs & Itakura they cite are limited to passages showing (1) *in vitro* assembly of insulin; and (2) derivation of DNA sequences for light and heavy immunoglobulin chains from monoclonal antibody-producing hybridomas. Paper 1 at 55-56. As was the case with its proposed grounds based on Bujard and Riggs & Itakura, neither of these disclosures of Riggs & Itakura fills the substantial gaps in Cohen & Boyer relative to the Cabilly '415 patent claims. As was the case with its proposed grounds based on Bujard and Riggs & Itakura, the disclosures of Riggs & Itakura identified in the Petition do not fill the substantial gaps in Cohen & Boyer relative to the Cabilly '415 patent claims. Apparently recognizing that Cohen & Boyer does not expressly describe the production of multiple desired proteins in a single transformed host cell, Petitioners contend the skilled person would "understand" the terms "one or more genes" and the reference to "antibodies" to "necessarily" teach co-expression of multiple desired proteins in a single host cell. Paper 1 at 50-52. This argument can be readily dismissed—the phrases "one or more genes," "at least one intact gene" or "at least one foreign gene" as they are used in Cohen & Boyer simply refer to the possibility that a sequence of interest could ***span more than one gene***. Ex. 1005 at 12:40-14:39. Cohen & Boyer includes ***no description*** of methods that can be used to incorporate eukaryotic genes from ***different*** chromosomal locations (such as the genes

encoding the heavy and light chains of an antibody) into a single host cell. Ex. 2001, Fiddes Rep. at ¶¶67, 72.

In fact, as with Petitioners' arguments with respect to Bujard, Petitioners' arguments ignore that Riggs & Itakura actually teaches the skilled person to produce a multimeric protein by expressing DNA sequences encoding each of the constituent chains of the multimeric protein ***in separate host cells***, isolate each chain, and then combine these isolated chains outside of the cells. *See,* Section V.B, *supra*. Nothing in either Cohen & Boyer or Riggs & Itakura would change the perspective of the skilled person that he or she should follow that approach, and Petitioners identify no evidence to suggest the contrary. Read accurately, the combined teachings of Cohen & Boyer and Riggs & Itakura, thus, would have taught away from the approach reflected in the Cabilly '415 patent claims.

Also missing from the Petition is any explanation of how the teachings of Cohen & Boyer and Riggs & Itakura provide guidance that would have led the skilled person to reasonably expect to be able to produce an antibody via independent expression of light and heavy chain DNA sequences in a single host cell using these prior art methods. Particularly in the face of unrebutted countervailing evidence, *see,* Section IV.D, *supra*, Petitioners' conclusory assertion that a person of skill would have "reasonably predicted" that the combination

would result in the claimed invention, Paper 1 at 56, falls well short of meeting their burden. *See, Fortinet, Inc.*, IPR2015-00617, Paper 9 at 17-18.

VI. THE PETITION SHOULD BE DENIED UNDER 35 U.S.C. § 325(D)

"In determining whether to institute or order a proceeding under this chapter . . . the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). In this proceeding, the Board should deny institution because the Petition presents the same arguments that were raised and fully addressed in prior Office proceedings involving the Cabilly '415 patent. In particular, the Cabilly '415 patent went through an extensive reexamination during which the Office not only considered substantial evidence regarding the state of the art, none of which has been rebutted by Petitioners (*see,* Section IV, *supra*), but considered the same rationale for reading the prior art that undergirds the proposed grounds; namely, that references in the prior art to "genes" (plural) and inclusion of "antibodies" within aspirational lists of proteins that can be made should be read as suggesting expression of heavy and light chains of an antibody in a single transformed host cell. *See,* Section V.A.1.a, *supra*. Because the Office has already rejected these arguments based on strikingly similar prior art, the Board should decline to institute this proceeding pursuant to Section 325(d). *See, e.g.*, *Nora Lighting Inc. v. Juno Mfg., LLC*, IPR2015-00601, Paper 13 at 11 (Aug.

12, 2015) (declining to institute proceeding where grounds were substantially similar to arguments in *ex parte* reexamination); *see also, Integrated Global Concepts, Inc. v. Advanced Messaging Techs., Inc.*, IPR2014-01027, Paper 16 at 7-8 (same, rejecting argument that Patent Owner offered "misleading statements" where Petitioner did "not present any persuasive evidence to supplement the record that was in front of the Office during reexamination").

VII. THE GROUNDS PRESENTED IN THE PETITION ARE REDUNDANT

Petitioners make no attempt to explain how the four separate grounds it proposes are meaningfully different. First, Petitioners rely on Bujard to support both anticipation (Ground I) and obviousness (Grounds II and III). To the extent that Petitioners argue that Bujard in fact presents all elements of the claims under Section 102, it should not be permitted to also present grounds premised on the absence from Bujard of one or more elements. Indeed, the assertions advanced by Petitioners for obviousness are not meaningfully different than those it offers for anticipation, and Petitioners do not meaningfully explain why the grounds are not redundant. Second, the putative teachings in Cohen & Boyer relied upon to support Ground IV are all present within Bujard, namely, reference to plural genes, and the listing of an antibody as one potential protein of interest. Petitioners identify no distinction in the teachings of Cohen & Boyer relative to Bujard. Absent some articulation of a meaningful distinction between them, including

strengths and weaknesses thereof, Petitioners' redundant grounds should not be instituted. *See, e.g.*, *Oracle Corp. v. Clouding IP, LLC*, IPR2013-00088, Paper 13 at 2-3 (June 13, 2003).

VIII. CONCLUSION

For the foregoing reasons, the Petition fails to present new, non-cumulative arguments that were not previously considered by the Office, and fails entirely to rebut the substantial record supporting patentability. Accordingly, the Board should deny institution because the Petition is insufficient to establish that the references anticipate or render obvious the Cabilly '415 patent claims and/or exercise its discretion and deny the Petition under § 325(d).

Respectfully submitted,

Date: November 9, 2015

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CERTIFICATE OF SERVICE

I hereby certify that, on November 9, 2015, I caused a true and correct copy of the foregoing materials:

- Patent Owner Preliminary Response 37 C.F.R § 42.107
- Exhibits 2001-2018
- List of Exhibits for Patent Owner Preliminary Response 37 C.F.R § 42.107

to be served via electronic mail on the following attorneys of record:

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Patent Owners Exhibit Number	**Exhibit Name**
2001	Expert Report of John Fiddes, Ph.D., *Bristol-Myers Squibb Company v. Genentech, Inc.*, No. 2:13-cv-05400-MRP-JEM (C.D. Cal.) (Nov. 10, 2014) ("Fiddes Rep.")
2002	Declaration of Steven Lanier McKnight Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (May 18, 2007) ("McKnight Decl.")
2003	Second Declaration of Steven Lanier McKnight Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (June 3, 2008) ("McKnight Decl. II")
2004	Declaration of Dr. Timothy Roy Harris Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (Nov. 23, 2005) ("Harris Decl.")
2005	Second Declaration of Dr. Timothy Roy Harris Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (Oct. 26, 2006) ("Harris II Decl.")
2006	Declaration of Dr. Douglas A. Rice Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (Oct. 26, 2006) ("Rice Decl.")
2007	Declaration of Michael Botchan Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (May 20, 2007) ("Botchan Decl.")
2008	Gilbert, W. & Villa-Komaroff, L., *Useful Proteins from Recombinant Bacteria*, Scientific American, 242:74-94 (1980)
2009	Expert Report of Dr. E. Fintan Walton, *MedImmune, Inc. v. Genentech, Inc.*, No. 03-cv-2567 (C.D. Cal.) (Feb. 29, 2008) ("Walton Rep.")
2010	Transcript of Deposition of Dr. Jefferson Foote , *Bristol-Myers Squibb Company v. Genentech, Inc.*, No. 2:13-cv-05400-MRP-JEM (Jan. 9, 2015) ("Foote Dep.")
2011	Goeddel, D.V., *et al.*, *Expression in Escherichia coli of chemically synthesized genes for human insulin*, Proc. Nat'l Acad. Sci. (USA) 76:106-110 (1979) ("Goeddel 1979")
2012	Frank, B.H., *et al.*, *Two Routes for Producing Human Insulin Utilizing Recombinant DNA Technology*, Munch. Med. Wschr., 125, Suppl. 1:S14-S20 (1983) ("Frank 1983")

2013	Kohler, G. and Milstein, C., *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, Nature 256:495-497 (Aug. 7, 1975) ("Kohler and Milstein")
2014	90/007,542 Office Action Response filed 2/13/2009
2015	Christie, N.T., *et al.*, *Selective amplification of variants of complex repeating unit in DNA of a crustacean*, Proc. Nat'l Acad. Sci., 77(5):2786-2790 (1980) ("Christie 1980")
2016	Frommer, *et al.*, *Simple repeated sequences in human satellite DNA*, Nuc. Acids Res. 10(2):547-563 (1982) ("Fromer 1982")
2017	Israelewski, N., *Structure and function of an AT-rich, interspersed repetitive sequence from Chironomus thummi: solenoidal DNA, 142 bp palindrome-frame and homologes with the sequence for site-specific recombination of bacterial transposons*, Nuc. Acids Res. 11(20):6985-6996 (1983) ("Israelewski 1983")
2018	Declaration of Robert J. Gunther Jr. in Support of Motion for Admission Pro Hac Vice