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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS, INC.,
Petitioner,

v.

GENENTECH, INC. AND CITY OF HOPE,
Patent Owners.

Case IPR2016-00710
Patent 6,331,415

PATENT OWNERS' RESPONSE

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I. INTRODUCTION

When U.S. Patent No. 6,331,415 ("the '415 patent") was filed in April 1983, scientists were struggling to produce even a single antibody light chain using recombinant technology, and no one had reported the successful expression of an antibody heavy chain. Nobel laureates and other leading scientists had speculated about the possibility of recombinantly producing an antibody (which has two light chains and two heavy chains), but even they were uncertain whether and when that goal might be achieved.

Faced with those uncertainties, the '415 inventors not only demonstrated that it was possible to produce a functional antibody recombinantly, but they did so in an innovative way: by inserting the different genes encoding for the heavy and light chains into a single host cell. Their invention is reflected in the challenged claims, which recite a process for producing a functional antibody by expressing the heavy and light chains "in a single host cell" (claims 1, 33) or "[a] transformed host cell comprising at least two vectors" with each vector separately containing the DNA encoding for either the heavy or light chain (claim 18).

The '415 patent was a dramatic advance. As of April 1983, no one had reported making ***any*** eukaryotic protein containing multiple different polypeptide chains by inserting more than one gene into a single host cell. The '415 inventors not only made a functional antibody, but did so by adopting a single host cell

approach that had never been demonstrated to work even with much simpler proteins.

Decades later, Mylan seeks to rewrite this history leading up to the '415 patent by attributing its invention to others. But the primary reference underlying both grounds, U.S. Patent No. 4,495,280 ("Bujard") (Ex. 1002), does not disclose co-expressing the genes encoding for antibody heavy and light chains in a single host cell, as required by the challenged claims. Indeed, the Board itself previously held that Bujard does not anticipate the challenged claims because it "does not teach" that key limitation "either expressly or inherently." (IPR2015-01624, Paper 15 at 15.)

Based on the record at the institution stage—including Dr. Jefferson Foote's then-untested declaration assertions—the Board concluded that Bujard "suggests" the '415 invention.[1] The full record, including Dr. Foote's own deposition testimony, now leads to the opposite conclusion.

Bujard addressed how to construct expression vectors containing strong bacterial promoters—a very different problem from the one addressed in the '415

[1] Dr. Foote's declaration was submitted in a prior proceeding (IPR2015-01624), which Mylan sought to join. Mylan also relies on Dr. Foote's declaration in this proceeding. (Paper 2 at 3; Paper 13 at 6.)

patent. The only place Bujard even mentions antibodies is in a lengthy, generic list of "proteins of interest," and the record now shows that Bujard's prosecuting attorney simply recycled that list from several dozen prior, unrelated patent applications.

The record now contains the testimony of Dr. John Fiddes (Ex. 2019)—a molecular biologist with 40 years of experience—who, among other things, explains that Bujard's reference to a "multimer" does not refer to a multimeric protein, as Dr. Foote suggested, and instead refers to multiple repeating copies of the same gene.

The record also now contains the testimony of Dr. Reiner Gentz (Ex. 2021), who worked in Dr. Bujard's lab in the early 1980s and co-authored the scientific paper corresponding to the Bujard patent. Dr. Gentz testified that he was not aware of anyone in Dr. Bujard's lab who used or mentioned co-expressing multiple different eukaryotic genes in a single host cell, much less using that approach to make an antibody.

Moreover, even Dr. Foote's post-institution testimony supports the patentability of the challenged claims. For example, Dr. Foote admitted at his deposition that there were numerous challenges with producing antibodies recombinantly as of April 1983, such that even leading antibody scientists doubted whether it would ever be possible to produce recombinant antibodies. And Dr.

Foote further admitted that neither Bujard nor any of the other cited references purports to solve those challenges.

Mylan also relies upon Dr. Kathryn Calame's declaration. But Dr. Calame merely adopted Dr. Foote's declaration in its entirety without any further elaboration of her own, and her deposition testimony confirms that her opinion is not based on an objective assessment of the state of the art. Indeed, despite extensive work as an expert attempting to invalidate the '415 patent in a prior litigation, Dr. Calame had not even read Bujard until ***after*** reviewing the '415 patent and Dr. Foote's declaration. And at the time of her deposition, Dr. Calame still had not read or considered the significant evidence rebutting Dr. Foote's declaration opinions, including Dr. Foote's deposition testimony, Dr. Fiddes's declaration in IPR2015-01624, or even the Board's institution decision in IPR2015-01624 that had rejected several of Dr. Foote's opinions, which Dr. Calame nevertheless adopted.

Bujard's failure to show that recombinant techniques could be deployed to make a functional antibody or that both antibody chains could be expressed in a single host cell is dispositive of both instituted grounds. The combinations of references in each ground do not cure Bujard's shortcomings.

For Ground 1, Mylan relies upon Bujard combined with Riggs & Itakura (Ex. 1003). But as the Board previously found, "Riggs & Itakura takes a different

approach than the 'single host cell' approach required by the claims." (IPR2015-01624, Paper 15 at 19.) Riggs & Itakura teaches a ***separate*** host cell for each polypeptide chain—contrary to the single host cell approach of the challenged claims. Moreover, nothing in Riggs & Itakura would have given a person of ordinary skill any expectation of success in producing an antibody in a single host cell, particularly given the state of the art and uncertainties at the time.

For Ground 2, Mylan relies upon Bujard combined with Southern (Ex. 1004) to challenge certain claims that cover using two vectors in a single host cell. But Southern does not disclose any experiment expressing two genes corresponding with the different chains of a multi-unit protein in a single host cell, let alone suggest that such a technique could be used with antibodies (which Southern never mentions). And in any case, the techniques described in Bujard and Southern are incompatible: Bujard relates to bacterial cells, whereas Southern describes a mammalian expression vector. A person of ordinary skill thus would have had no reason to combine them.

Finally, although not addressed in the institution decision or even considered by Drs. Foote or Calame, the record also now includes strong objective evidence of non-obviousness. The industry has embraced the validity of the '415 patent, taking dozens of licenses, amounting to well over a billion dollars in royalties. And the commercial success of the many "blockbuster" products made by Genentech and

others using the '415 invention cannot be disputed—Genentech alone has generated over $100 billion in sales of products made with the '415 invention. Finally, at a time when leading scientists were skeptical that the many challenges to producing an antibody recombinantly could be overcome, the '415 inventors not only succeeded, but did so in an unexpected way—by co-expressing antibody heavy and light chains in a single host cell. This objective evidence weighs heavily against a hindsight-based finding of obviousness.

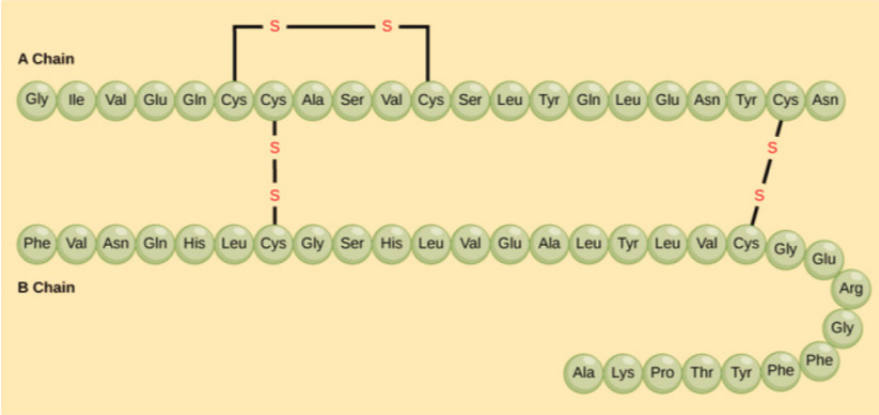
Accordingly, Patent Owners respectfully request that the Board affirm the patentability of the challenged claims.

II. TECHNOLOGY BACKGROUND

A. Proteins Vary In Size And Complexity.

There are many different proteins, which vary in size and complexity. Monomeric proteins consist of a single polypeptide chain, while multimeric proteins consist of multiple polypeptide chains. (Ex. 2019, Fiddes Decl. ¶¶ 24-34.)

A simple example of a multimeric eukaryotic protein is insulin, which has an A chain (21 amino acids) and a B chain (30 amino acids) linked by two disulfide bonds (and a third intrachain bond):



(*Id.* ¶¶ 35-37; Ex. 2020, Foote Dep. 83, 116-18; Ex. 1003 at 532.)[2]

Antibodies (also called immunoglobulins) are larger and far more complex than insulin. Antibodies play a critical role in the body's immune system by binding to foreign substances called "antigens" (*e.g.*, bacteria, viruses), facilitating removal of the antigen from the body. Each antibody consists of at least four chains—typically, two identical heavy chains and two identical light chains assembled into a "Y"-shape, held together by over a dozen disulfide bonds:

[2] "Eukaryotic" organisms have cells with a nuclear membrane and distinct chromosomes containing their genetic material, which distinguishes them from simpler "prokaryotic" organisms (*e.g.*, bacteria). (Ex. 2018 at 11-12, 15-20, Table 1-1.)

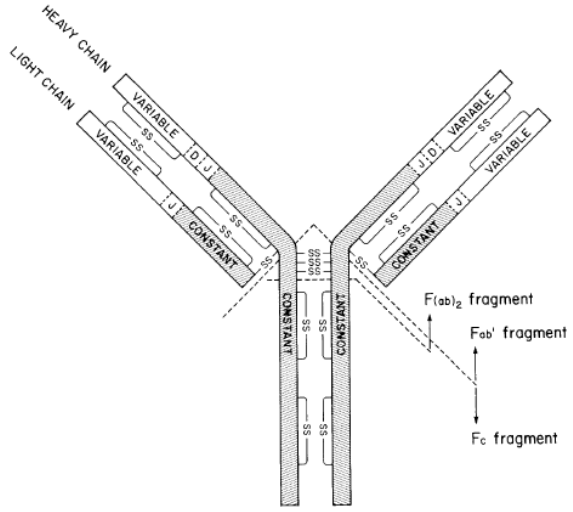
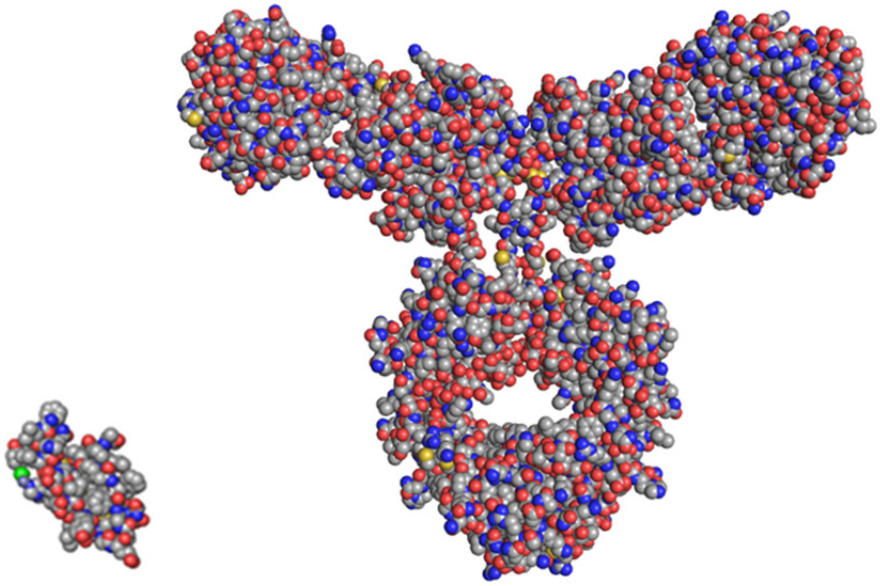


Fig. 1.

(Ex. 1001, 3:17-26, Fig. 1; Ex. 2019, Fiddes Decl. ¶¶ 38-42; Ex. 2020, Foote Dep. 86.) The molecular models below illustrate the larger size and complexity of an antibody (right) as compared to insulin (left):



(Ex. 2019, Fiddes Decl. ¶¶ 43-45.) An antibody of the immunoglobulin G ("IgG") isotype contains more than 1,300 amino acids and has a molecular weight of about

150,000 Daltons, while insulin contains only 51 amino acids and weighs just 5,800 Daltons. (*Id.* ¶¶ 39-44; Ex. 2020, Foote Dep. 105-06.)

B. Prior Art Antibody Production Techniques

For decades before the '415 patent, antibodies could be produced by immunizing an animal (*e.g.*, a mouse) with an antigen, generating a polyclonal mixture of antibodies with different binding characteristics. By April 1983, polyclonal antibodies were widely used. (Ex. 1001, 1:45-63; Ex. 2019, Fiddes Decl. ¶¶ 46-47.)

But many diagnostic and therapeutic applications will not work with polyclonal antibodies, and instead require compositions that contain only one type of antibody with uniform binding characteristics, called "monoclonal" antibodies. (Ex. 1001, 1:45-2:11; Ex. 2019, Fiddes Decl. ¶¶ 46-50.) Before the '415 invention, such monoclonal antibodies were produced using "hybridomas" (developed in 1975 by Dr. César Milstein),[3] which fuse an antibody-producing B cell with a cancer cell. (Ex. 2019, Fiddes Decl. ¶¶ 48-50.) By April 1983, hybridomas were being used extensively to produce monoclonal antibodies, and these uses were "expanding very rapidly." (Ex. 1039, Milstein at 407; Ex. 2019, Fiddes Decl. ¶ 50;

[3] Dr. Milstein won the Nobel Prize for this work.

Ex. 2020, Foote Dep. 37, 48-49 (hybridomas were a "[v]ery big" deal in the early 1980s due to "significant achievements"); Ex. 1001, 1:64-2:11.)

C. By April 1983, Recombinant Techniques Were Not Well Understood And Had Only Been Used To Make Simple Proteins.

Recombinant techniques allow scientists to introduce a new gene into a host cell that does not naturally contain that gene, and then to produce a desired protein from the inserted gene. (Ex. 2019, Fiddes Decl. ¶¶ 51-56.)

In April 1983, many of the biological mechanisms controlling the expression of foreign DNA and assembly of the resulting proteins were poorly understood. For example, Dr. Timothy Harris published an article in April 1983 explaining: "[I]t is clear that not all the rules governing the expression of cloned genes have been elaborated and those rules that do exist are still largely empirical." (Ex. 1027, Harris at 129; Ex. 2020, Foote Dep. 135; Ex. 2010, Calame Dep. 233-34; Ex. 2019, Fiddes Decl. ¶ 57.)

Only a few relatively small and simple proteins had been recombinantly-produced by April 1983—as reflected in Harris's Table 2, which provided "an up to date summary of the higher eukaryotic proteins that have been expressed in *E. coli*." (Ex. 1027, Harris at 163-69, Table 2; Ex. 2068, Harris Decl. ¶ 16 (describing listed proteins as "relatively small polypeptides with simple tertiary structures"); Ex. 2020, Foote Dep. 76-79; Ex. 2019, Fiddes Decl. ¶ 57.)

Harris identified several perceived problems as of April 1983 with producing eukaryotic proteins recombinantly in prokaryotic hosts, such as (1) the presence of introns (non-coding sequences) in eukaryotic genes; (2) the different regulatory signals found in eukaryotic DNA; (3) the different codon usage in eukaryotic genes; and (4) factors "not well defined" affecting protein folding, solubility, and post-translational modifications. (Ex. 1027, Harris at 131-33, 156, 173.) Those perceived challenges explain why the only reported recombinantly-produced eukaryotic proteins at that time were relatively simple. (Ex. 2019, Fiddes Decl. ¶¶ 58-80.) At his deposition, Dr. Foote agreed with Harris's summary of the many challenges that existed with recombinant DNA techniques as of April 1983. (Ex. 2020, Foote Dep. 136-46.)

The prospect of using recombinant DNA to produce a multimeric protein was especially challenging. By April 1983, only one multimeric eukaryotic protein (insulin) produced from two different genes had been made recombinantly. That work with insulin involved either producing preproinsulin (a single polypeptide), or separately expressing the A and B chains in two different host cells and joining the subunits afterward. (Ex. 2019, Fiddes Decl. ¶¶ 81-91; Ex. 2020, Foote Dep. 103, 109-11; Ex. 2007, Harris Decl. II ¶ 14; Ex. 2010, Calame Dep. 120-21.)

Just like insulin, every other eukaryotic protein reported in the literature before April 1983 was made using one host cell per polypeptide chain. (Ex. 2019,

Fiddes Decl. ¶¶ 127-28.) Indeed, even Drs. Foote and Calame admitted at their respective depositions that the record is devoid of evidence that anyone had co-expressed the different subunits of ***any*** multimeric eukaryotic protein in the same host cell before the '415 inventors. (Ex. 2020, Foote Dep. 114-15; *id.* at 111-12 (all of Harris's examples "involved production of one polypeptide in one transformed host cell"); Ex. 2010, Calame Dep. 204, 230 (confirming no proteins identified in Dr. Foote's declaration or Harris were produced by co-expressing different polypeptide chains in a single host cell).) Testimony from multiple persons of extraordinary skill in other proceedings involving the '415 patent confirms that conclusion; all were unaware of anyone who had independently expressed the multiple different subunits of a eukaryotic protein in a single host cell before April 1983. (Ex. 2007, Harris Decl. II ¶¶ 15-16; Ex. 2041, McKnight Decl. II ¶ 5; Ex. 2080, Rice Decl. ¶ 15.)

At her deposition, Dr. Calame noted that Harris's list included proteins that contain multiple chains of the same polypeptide encoded by a single gene, such as influenza HA. (Ex. 2010, Calame Dep. 222-28.) But that only underscores the absence of any multimeric eukaryotic protein containing polypeptide chains encoded by ***different*** genes—such as an antibody. (Ex. 2019, Fiddes Decl. ¶ 80.) Proteins like influenza HA were made using the same one-polypeptide-per-host-cell approach as every other eukaryotic protein before April 1983. (*Id.*)

It is not surprising that no one as of April 1983 had reported producing more than one polypeptide of a eukaryotic multimeric protein in a single host cell. Co-expressing multiple different polypeptides in a single host cell is far more complicated than the prior art approach that used multiple host cells. For example, before April 1983, it would have been (i) more difficult to engineer expression constructs for use in a single host cell; (ii) uncertain that separate genes of interest would even co-express; and (iii) unclear whether the desired polypeptides would be produced in the correct ratios, or whether that was even necessary. (Ex. 2019, Fiddes Decl. ¶¶ 129-37; Ex. 2021, Gentz Decl. ¶¶ 27-30.)

D. As Of April 1983, Leading Scientists Were Uncertain Whether It Was Possible To Make Antibodies Recombinantly.

By the early 1980s, a handful of scientists had begun to theorize that it might be possible in the future to produce antibodies recombinantly. But the uncertainties with producing antibodies recombinantly were even greater than with other proteins—for example, some scientists believed antibodies required special "helper" proteins to coordinate the expression and proper assembly of heavy and light chains. (Ex. 2019, Fiddes Decl. ¶¶ 95, 136.) As such, even by April 1983, highly-respected scientists still had serious doubts whether antibodies could ever be produced recombinantly, and nobody had suggested that antibodies could be produced by co-expressing the heavy and light chains in a single host cell.

For example, in March 1981, an article reported then-recent comments from Dr. Milstein—inventor of the hybridoma technique, future Nobel laureate, and prominent antibody scientist. In his closing remarks, Dr. Milstein speculated about the future—noting he could "***imagine*** the next stage is to move away from the animals," and that it was "***perhaps*** not too premature ***to start thinking*** along these lines."[4] (Ex. 1039, Milstein at 409.) He did not offer any solution; rather, he just said that "***[s]omehow*** the DNA fragments will have to go into cells capable of transcribing and translating the information with adequate efficiency." (*Id.* at 409-10; Ex. 2020, Foote Dep. 47-61 (agreeing Milstein's comments are "directed towards possible things that might be done in the future"); Ex. 2019, Fiddes Decl. ¶¶ 102-03.)

In fact, Dr. Milstein conceded that his wishful idea might not work: "[W]e 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." (Ex. 1039, Milstein at 410.) He explained that the basic science presented "very serious problems," was "not so well established," and was "clouded by uncertainties and multiple possibilities." (*Id.*; Ex. 2020, Foote Dep. 55-61; Ex. 2019, Fiddes Decl. ¶¶ 102-07.)

[4] All emphases added unless otherwise indicated.

The years leading up to the '415 patent confirmed the many problems forecast by Dr. Milstein. During that period, leading antibody scientists encountered numerous uncertainties and unexplained results while attempting to recombinantly express just a ***single*** antibody chain:

- In 1982, Falkner & Zachau could not explain why they had failed to express antibody light chain, speculating that "something may be missing from our systems" or "some as yet undefined factors provided in tissue-specific differentiation events may have a role." (Ex. 2022 at 288.)
- In December 1982, Dr. David Baltimore, a Nobel laureate, observed that "relatively little is known about the molecular mechanisms that control [antibody] gene expression." (Ex. 1020 at 7862.)
- In February 1983, Oi et al. could not explain why two cell lines failed to produce any detectable light chain from recombinant DNA. (Ex. 1031 at 827-28.)
- In March 1983, Ochi et al. reported introducing the gene encoding for antibody light chain into cells already producing heavy chains, and could not explain why nearly all cell lines had no detectable antibody production or the observed "variability in gene expression." (Ex. 1021 at 341-42.)

(Ex. 2019, Fiddes Decl. ¶¶ 108-20.) Consistent with this evidence, Dr. Calame's literature search failed to identify anyone who successfully expressed a complete antibody heavy chain from recombinant DNA prior to April 1983. (Ex. 2010, Calame Dep. 74.)

This uncertainty and unpredictability continued through April 1983. Indeed, even Sir Gregory Winter—a world-leading antibody scientist—confirmed that he was "uncertain in the spring of 1983 about how to express recombinant antibodies," and that he still believed at the time that any solution "would be a major undertaking without any certainty of success." (Ex. 2023, Winter Rep. ¶ 61; Ex. 2019, Fiddes Decl. ¶¶ 122-26.) Dr. Foote testified that he has no basis to disagree with that description of the uncertainty in the art (Ex. 2020, Foote Dep. 178-80), or with Dr. Winter's similar statements that:

- "[T]he field of heterologous protein expression (the expression of a protein in cells that do not normally express the protein) was ***an emerging and unpredictable*** field in April 1983." (Ex. 2023, Winter Rep. ¶ 31; Ex. 2020, Foote Dep. 173; Ex. 2019, Fiddes Decl. ¶¶ 123, 126.)
- "[T]he reasons for success or failure in the expression or secretion of the light chain in different cell types [in Falkner, Oi, Ochi, and Rice] ***were not clear***," and as of April 1983 "there were ***no publications*** describing

the expression of recombinant antibody heavy chains in mammalian cells." (Ex. 2023, Winter Rep. ¶¶ 56-57; Ex. 2020, Foote Dep. 174-77.)

- "[He] was sufficiently ***uncertain*** in the spring of 1983 about how to express recombinant antibodies, and in sufficient yield, that [he] ***postponed*** [his] proposed project to engineer the functional sites of antibodies." (Ex. 2023, Winter Rep. ¶ 61; Ex. 2020, Foote Dep. 178-80; Ex. 2019, Fiddes Decl. ¶¶ 124, 126.)
- "Prior to [April 1983] it likewise [would] have been unpredictable that one could co-express both the heavy and light chains of an antibody in a single host cell and recover functional antibody." (Ex. 2024, Winter Dep. 117-18; Ex. 2020, Foote Dep. 190; Ex. 2019, Fiddes Decl. ¶¶ 125-26.)

Dr. Winter's summary of these many remaining uncertainties as of April 1983 is confirmed by the lack of evidence that anyone prior to the '415 inventors had independently expressed the subunits of ***any*** multimeric eukaryotic protein in a single host cell, or had recombinantly produced an antibody—whether using one host cell or two.

III. THE '415 PATENT

A. The Invention

The state of the art changed dramatically in April 1983 with the invention of the '415 patent, which reflected the work of several leading scientists. Dr. Arthur Riggs, a molecular biologist at the non-profit research hospital City of Hope, had previously collaborated with scientists at Genentech to achieve early advances in recombinant DNA technology, such as the production of somatostatin in 1977 (Ex. 2025) and human insulin in 1978 (Ex. 2011). In 1980, Dr. Riggs went to Genentech on sabbatical "to explore the possibility of producing antibodies in bacteria." (Ex. 2026, Riggs Decl. ¶ 3.) After his sabbatical, Dr. Riggs proposed a further collaboration with Genentech to pursue making antibodies recombinantly. (*Id.*)

At the time, Genentech was a small startup with talented scientists, including molecular biologist Dr. Herbert Heyneker and protein chemist Dr. Ronald Wetzel. Together with Dr. Shmuel Cabilly, a post-doctoral fellow in Dr. Riggs's lab, they worked over several years to develop recombinant techniques for producing antibodies. (*Id.* ¶¶ 4-6; Ex. 2027, Wetzel Decl. ¶¶ 4-11; Ex. 2028, Perry Decl. ¶¶ 2-14; Ex. 2029, Holmes Decl. ¶¶ 3-20; Ex. 2030, Rey Decl. ¶¶ 2-7; Ex. 2031, Mumford Decl. ¶¶ 2-13; Ex. 2032, Cabilly Decl. ¶¶ 3-9.) By early 1983, they had successfully co-expressed the heavy and light chains of a monoclonal antibody in a

single host cell, which they had folded and assembled into a functional antibody. (Ex. 2032, Cabilly Decl. ¶¶ 4-8.) Their success was the first proof of concept for their novel single host cell invention, and was the first time anyone had created an antibody entirely using recombinant DNA techniques—whether in one host cell or otherwise. (Ex. 2020, Foote Dep. 190-92 ("yes, that was the first transcription and translation of light and heavy chain"); Ex. 2024, Winter Dep. 68 (same); Ex. 2019, Fiddes Decl. ¶¶ 138-42.)

The challenged claims reflect that novel single host cell approach. Claims 1, 3-4, 11-12, 14, 19, and 33 (Ground 1) recite "[a] process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment … in a single host cell" by incorporating the DNA sequences for both the heavy and light chains "so that said immunoglobulin heavy and light chains are produced as separate molecules." Claims 1-2, 14, 18, 20, and 33 (Ground 2) cover a process wherein the DNA encoding for heavy and light chains "are present in different vectors" (claim 2) or "[a] transformed host cell comprising at least two vectors" with at least one vector separately containing the DNA encoding for heavy and light chains (claim 18).

B. Industry Recognition

The industry has recognized the '415 patent as a foundational invention that launched a whole new field of therapeutic antibodies. More than seventy of the

world's leading biotechnology companies have recognized the significance of the '415 patent by taking a license. (Ex. 2033, Davis Decl. ¶¶ 34-45.) Those licenses have generated royalties totaling well over a billion dollars, reflecting the value of the claimed invention as a manufacturing platform. (*Id.*) And the products made using the '415 invention have been highly successful—resulting in over $100 billion in revenues—due, in part, to the benefits of the '415 invention as an efficient and stable manufacturing platform. (*Id.* ¶¶ 51-65.)

That broad industry recognition and commercial success are even more remarkable because they were was so unexpected. As explained above, even extraordinarily skilled persons were skeptical in April 1983 that it was possible to recombinantly produce antibodies, let alone to do so in a single host cell. The '415 inventors' success in the face of those skeptics further underscores the groundbreaking nature of their work.

IV. PROCEDURAL HISTORY

The Patent Office has rigorously tested the merits of the '415 patent, not only through its original examination but also through two reexaminations. The '415 patent has also been tested multiple times in litigation. It has withstood every test. No party challenging the '415 patent has identified a single instance in which anyone before April 1983 successfully produced a functional antibody from

recombinant DNA in any manner—much less through co-expressing the heavy and light chains in a single host cell.

More recent efforts to attack the '415 patent through *inter partes* review have been similarly unsuccessful. In IPR2016-00383, the Board refused to institute a challenge that certain claims of the '415 patent are anticipated by U.S. Patent No. 4,396,601 ("Salser") or obvious in view of Salser in combination with Southern or Ochi. (IPR2016-00383, Paper 16.)[5]

And in IPR2015-01624, the Board refused to institute an anticipation challenge based upon Bujard, holding that "Bujard does not teach" co-expressing antibody heavy and light chains in a single host cell "either expressly or inherently." (IPR2015-01624, Paper 15 at 15.) The Board also refused to institute an obviousness challenge combining U.S. Patent No. 4,237,224 ("Cohen & Boyer") (Ex. 1005) and Riggs & Itakura. (IPR2015-01624, Paper 15 at 23-24.) The Board instituted two obviousness grounds based on Bujard combined with Riggs & Itakura (Ground 1) and Bujard combined with Southern (Ground 2). (*Id.*

[5] The Board has yet to rule on institution in IPR2016-01373, in which Merck has challenged certain '415 claims on obviousness grounds. For the reasons stated in Patent Owners' Preliminary Response (IPR2016-01373, Paper 13), the Board should deny institution of that petition.

at 17-22.) IPR2015-01624 was terminated by settlement shortly after Patent Owners deposed Dr. Foote and filed their response. (IPR2015-01624, Paper 43.)

While IPR2015-01624 was pending, Mylan filed this petition seeking institution on the same two grounds and requesting joinder with that proceeding. Mylan relied upon Dr. Foote's declaration as the primary support for its petition. (Paper 2 at 3.) It also submitted Dr. Calame's declaration "[s]olely to preserve its right to rely on expert testimony in the event that joinder is not granted or in the case that [IPR2015-01624] is settled." (*Id.*) Dr. Calame adopted Dr. Foote's declaration opinions, wholesale without elaboration. (Ex. 1059, Calame Decl. ¶ 16 ("I fully agree with, and hereby adopt, the opinions set forth in the Foote Declaration.").)

In fact, Dr. Calame even adopted the opinions that the Board had rejected in its institution decision. (Ex. 2010, Calame Dep. 85, 91.) At her deposition, Dr. Calame testified that she did not review the institution decisions in this proceeding or IPR2015-01624, or consider them relevant to her analysis. (*Id.* at 91-93.) Dr. Calame also had not reviewed the materials submitted in IPR2015-01624 that undermine her adopted opinions from Dr. Foote's declaration, including (i) Dr. Foote's deposition testimony; (ii) Dr. Fiddes's declaration or deposition testimony; (iii) or Dr. Gentz's declaration. (Ex. 2010, Calame Dep. 96-97, 200, 234-35.)

The Board instituted this proceeding on the same grounds previously instituted in IPR2015-01624 and denied Mylan's motion for joinder as moot. (Paper 13 at 3, 12-15.) The institution decision in this proceeding adopted the reasoning from the institution decision in IPR2015-01624. (*Id.* at 3, 14.)[6]

V. PERSON OF ORDINARY SKILL

For purposes of this proceeding, Patent Owners do not dispute Mylan's proposed level of ordinary skill.

VI. CLAIM CONSTRUCTION

For purposes of this proceeding, Patent Owners believe no claim terms require construction.

VII. ARGUMENT

A. Ground 1: Claims 1, 3-4, 11-12, 14, 19, And 33 Would Not Have Been Obvious Over Bujard In View Of Riggs & Itakura.

Each claim challenged under Ground 1 recites a process for producing a functional antibody, referred to in the claims as an "immunoglobulin molecule or

[6] After institution, Merck filed a separate petition asserting the same grounds and moved for joinder with this proceeding. (IPR2017-00047, Papers 2-3.) Patent Owners have responded to Merck's joinder motion (IPR2017-00047, Paper 9), and the Board has not yet decided that motion.

an immunologically functional immunoglobulin fragment."[7] Each claim requires producing this functional antibody by "independently expressing" the heavy and light chains "as separate molecules" in a "single host cell."

Combining Bujard with Riggs & Itakura does not render obvious the production of an antibody in a "single host cell." As explained below, Bujard does not suggest co-expressing the genes encoding the different polypeptide chains of any multimeric protein, let alone the heavy and light chains of an antibody. Riggs & Itakura does not provide the "single host cell" limitation either; in fact, the ***only*** technique described in Riggs & Itakura involved ***two*** host cells (*i.e.*, one for each polypeptide chain). Only in hindsight can Mylan contend that a skilled artisan would have achieved the '415 patent's single host cell approach by combining Bujard with Riggs & Itakura.

1. Bujard does not suggest co-expression in a single host cell to produce antibodies.

a) Summary of Bujard

Bujard (a patent filed in May 1981) addresses a very different problem than the '415 patent: the fact that strong promoters, such as those of bacteriophage T5, could not be stably cloned into plasmids. (Ex. 1002, 1:36-46; Ex. 2019, Fiddes

[7] As Mylan recognizes, the terms "immunoglobulin" and "antibody" are interchangeable for purposes of this proceeding. (Paper 2 at 4 n.1.)

Decl. ¶¶ 157-59.)[8] Bujard claims to have discovered that strong promoters can be stably cloned into a recombinant DNA construct if paired with a "balanced" strong terminator—*i.e.*, a DNA sequence that stops transcription. (Ex. 1002, 2:8-16, 6:53-58; Ex. 2035 at 66; Ex. 2020, Foote Dep. 297-98, 303-04; Ex. 2019, Fiddes Decl. ¶¶ 160-63.)

Bujard's assignee (Stanford University) allowed the patent to expire in 1989—only four years after it issued—by failing to pay maintenance fees. (Ex. 2034; Ex. 2020, Foote Dep. 222-24.)

b) Bujard does not disclose any process for producing antibodies.

The challenged claims require recombinantly producing an "immunoglobulin" (*i.e.*, an antibody). But the record now confirms that, as of April 1983, a skilled artisan attempting to produce antibodies recombinantly would not have even considered Bujard—which does not contain ***any*** disclosure specific to antibody production. (Ex. 2019, Fiddes Decl. ¶¶ 166-69.)

Indeed, Bujard was filed only two months after the publication of Dr. Milstein's comments warning of the "very serious problems" and "uncertainties"

[8] Promoters are short DNA sequences that do not encode proteins, but instead instruct when to start transcription. (Ex. 1002, 1:25-35, 3:11-38; Ex. 2019, Fiddes Decl. ¶ 54.)

surrounding any potential future efforts to produce antibodies recombinantly, and speculating that those problems and uncertainties might never be overcome. (Ex. 1039 at 410 (published 3/27/81); *see supra* p. 14.) As Dr. Foote admitted at his deposition, Bujard does not purport to overcome (or even address) these many prior art challenges. (Ex. 2020, Foote Dep. 73-74.)[9] Likewise, Dr. Calame admitted at her deposition that Bujard does not disclose any actual experiment involving antibodies and that she is unaware of anyone before 1983 who applied Bujard's teachings to antibody production. (Ex. 2010, Calame Dep. 146-49.)

Without the benefit of the complete record, the Board concluded at the institution stage that Bujard's "specific identification of immunoglobulins among 'proteins of interest' … demonstrated a reasonable likelihood that the skilled artisan would have found it obvious to insert the genes encoding for the heavy and light chains" into a single host cell when combined with Bujard's "general teachings." (IPR2015-01624, Paper 15 at 19; *see* Paper 13 at 10.) But the record now confirms a skilled artisan would not have interpreted Bujard in that manner.

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[9] On re-direct, Dr. Foote referred to "some developments in recombinant DNA technology" between Dr. Milstein's statements and April 1983. (Ex. 2020, Foote Dep. 435.) But Dr. Foote admitted that the art remained "unpredictable" and "uncertain" through April 1983, despite those "developments." (*Id.* at 172-90.)

Indeed, the ***only*** place where Bujard even mentions antibodies is in a laundry list of "proteins of interest"—a list that Dr. Foote admitted at his deposition is "enormous" (including "millions" of different proteins even if antibodies are not counted). (Ex. 2020, Foote Dep. 280-84; Ex. 2019, Fiddes Decl. ¶¶ 198-207.) The Board has repeatedly held "that the inclusion of [an item] in a laundry-list of untested potential targets" is legally insufficient to disclose each listed target. *Amgen, Inc. v. AbbVie Biotechnology Ltd.*, IPR2015-01514, Paper 9, at 18 (Jan. 14, 2015); *Apotex Inc. v. Merck Sharpe & Dohme Corp.*, IPR2015-00419, Paper 14, at 11 (June 25, 2015) (skilled artisan would not have selected specific compound disclosed in "laundry list of 600 other specific compounds").

Relying on Dr. Foote's then-untested declaration assertions, the Board assumed that Bujard's inventors intended to convey their intent to cover antibody production through the ordering of the protein list and by including "free light chains" in the list, but not "free heavy chains." (IPR2015-1624, Paper 15 at 18-19; Paper 13 at 10; Ex. 1006, Foote Decl. ¶¶ 69-71.) But Dr. Foote admitted at his deposition that there was nothing special or intentional about Bujard's list; Bujard's prosecuting attorney merely copied the ***same*** list of proteins in the ***same*** order from dozens of unrelated patent applications previously filed for others beginning in 1975. (Exs. 2004, 2036-40, 2042-59; Ex. 2020, Foote Dep. 232-56, 417-22 (admitting the attorney "most likely" just "recycl[ed] a word processing

file" from one patent to the next); Ex. 2019, Fiddes Decl. ¶¶ 215-26; Ex. 2010, Calame Dep. 161-65.)[10] Consistent with the list's origins, the scientific paper corresponding to Bujard contains no list of proteins and no mention of antibodies. (Ex. 2060.) Mylan can hardly attribute a novel method of producing antibodies to Bujard based upon a lengthy generic list of proteins lifted from unrelated patents.

Nor has the scientific community read Bujard's laundry list as relevant to antibody production. Nobody (outside of litigation) has cited Bujard or its related publication for any teachings about antibody production. Indeed, Dr. Foote had not even heard of Bujard until lawyers challenging the '415 patent gave him the reference. (Ex. 2020, Foote Dep. 209-10.) Neither had Dr. Calame—who did not find or rely on Bujard (or its related publication) for her invalidity opinions when serving as an expert in a prior litigation challenging the '415 patent. (Ex. 2010, Calame Dep. 49, 59-60, 96.)

Dr. Calame claims to have "realized the Bujard patent was important" only after reading Dr. Foote's declaration. (*Id.* at 58-59, 68-69.) But even then, she did not bother to consider the plentiful record evidence refuting the assertions in Dr.

[10] The fact that Bujard's list includes "free light chains" but not "free heavy chains" is not surprising, since free heavy chains (unlike free light chains) were not known to have any therapeutic use. (Ex. 2019, Fiddes Decl. ¶¶ 223-24.)

Foote's declaration, including Dr. Foote's own deposition testimony. (*Id.* at 96-97.) Dr. Calame could not identify anyone other than Dr. Foote who had cited Bujard as teaching recombinant antibody production (*id.* at 140-44), and Dr. Foote himself admitted that he cannot identify anyone who has used Bujard's vectors to produce an antibody (in a single host cell or otherwise) (Ex. 2020, Foote Dep. 298-99).

Mylan's reading of Bujard is also refuted by Dr. Gentz—who worked in Dr. Bujard's lab in the early 1980s and co-authored the paper corresponding to the Bujard patent (Ex. 2060). Dr. Gentz testified that he did not use Bujard's technique to co-express the subunits of a multimeric eukaryotic protein, and is not aware of anyone in Dr. Bujard's lab who did. (Ex. 2021, Gentz Decl. ¶¶ 23-26, 31-34, 37-38, 49.) Indeed, Bujard's plasmids would have required significant modifications to include an additional "promoter/terminator cassette" to be used for that purpose. (*Id.* ¶¶ 31-32, 34, 48.)

In sum, Bujard does not disclose any teaching concerning the recombinant production of antibodies, let alone suggest the '415 patent's single host cell approach. That alone compels a finding that Mylan has not carried its burden to demonstrate that the challenged claims in Ground 1 are unpatentable.

c) Bujard does not disclose co-expressing multiple genes of interest in a single host cell.

Even if Bujard's mere mention of antibodies in a lengthy list could be read to teach ***something*** about making recombinant antibodies, Bujard still would not teach the '415 patent's innovation of making both antibody chains in a "single host cell." The challenged claims recite a "first DNA sequence" encoding "immunoglobulin heavy chain" and a "second DNA sequence" encoding "immunoglobulin light chain" and "independently expressing" these DNA sequences in a "single host cell." Mylan's effort to find those limitations in Bujard revolves around stringing together isolated phrases—such as "one or more structural genes," or "a plurality of genes, including multimers." But this is just wordplay. If the Bujard inventors had discovered or even suggested how to co-express different genes encoding for the distinct polypeptide chains of a multimeric protein, they would have said that directly. Mylan cannot cobble together such a groundbreaking invention by cherry-picking phrases from Bujard and stretching them beyond their actual meaning.

(i) Bujard's "multimers" do not refer to a multi-chain protein, such as an antibody.

In its institution decision, the Board interpreted Bujard's use of the term "multimers" "as referring to genes encoding for proteins with more than one subunit." (IPR2015-01624, Paper 15 at 19; *see* Paper 13 at 9-10.) But the record

now shows that is not how a skilled artisan in April 1983 would have interpreted the term as used in Bujard.

Bujard uses the term "multimer" to refer to repeating ***DNA*** sequences, not a protein with multiple polypeptide chains. The only place the word "multimers" appears in Bujard is in a paragraph describing "***the DNA sequence***" of Bujard's vector, and in a sentence explicitly identifing "multimers" as types of "genes" ("a plurality of ***genes***, ***including multimers***"). (Ex. 1002, 3:39-48.) In this context, "multimers" refers to a ***gene*** (*i.e.*, a piece of DNA), and not a protein. (Ex. 2019, Fiddes Decl. ¶¶ 170-74.) Indeed, consistent with Bujard's stated reliance on "conventional" methods (Ex. 1002, 7:40-41) and focus on stably cloning strong promoters into plasmids to facilitate efficient transcription (*e.g.*, *id.* at 2:3-20, 2:33-38), Bujard was simply referring to the known technique of including multiple copies of the same gene to increase yield of the desired protein. (Ex. 2019, Fiddes Decl. ¶¶ 178-79; Ex. 2021, Gentz Decl. ¶¶ 43-47; *see, e.g.*, Ex. 1018, 3:62-68.)

Other usage of the term "multimer" in the art confirms that interpretation. For example, the record now includes multiple references in which persons of skill used "multimer" to refer to repeating DNA sequences, and not to a multimeric protein—including a 1978 paper from Bujard co-inventors Stanley Cohen and Annie Chang, and a later patent from Bujard. (Exs. 2005, 2016-17, 2061-67; Ex. 2020, Foote Dep. 361-65 (admitting later Bujard patent (Ex. 2005) uses

"multimerized" to refer to a repeating DNA sequence); Ex. 2019, Fiddes Decl. ¶¶ 175-80; Ex. 2021, Gentz Decl. ¶¶ 42-47.)

At the institution stage, the only evidence that the Board had on this issue was Dr. Foote's assertion that "[i]n biochemistry, circa 1983 and now, the word multimer refers to a protein with more than one subunit." (Ex. 1006, Foote Decl. ¶ 67.) The record now confirms that Dr. Foote's declaration assertion was based on pure hindsight.

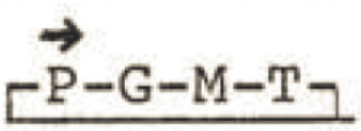
The only support that Dr. Foote cited for his "multimer" theory was the Medical Subject Headings index of the National Library of Medicine from ***2016***—which does not bear on how persons of skill might have understood that term more than three decades earlier. (Ex. 1006, Foote Decl. ¶ 67; Ex. 2020, Foote Dep. 356-57; Ex. 2019, Fiddes Decl. ¶¶ 181-82.) Dr. Foote did not consider the 1983 version of that index (Ex. 2020, Foote Dep. 357), which does not use the term "multimer." (Ex. 2069.) Dr. Calame's testimony "that 'multimer' is referring to multimeric proteins" (Ex. 2010, Calame Dep. 166) is even less credible. Dr. Calame did not even review the Medical Subject Headings index that Dr. Foote cited—or know that it post-dated the '415 invention by over three decades. (*Id.* at 167-68.) This faulty evidence cannot support Mylan's interpretation of Bujard's use of the term "multimers," particularly in the face of this contrary evidence.

(ii) "One or more structural genes" includes selectable markers, and is not a disclosure of the heavy and light chains of an antibody.

Again relying on Dr. Foote's declaration, the Board interpreted Bujard's statements that "one or more structural genes may be introduced between the promoter and terminator" (Ex. 1002, 7:61-63) and that "the promoter and terminator may be separated by more than one gene, that is, a plurality of genes" (*id.* at 3:46-48) as "suggest[ing]" the co-expression of the subunits of a multimeric protein in a single host cell. (IPR2015-01624, Paper 15 at 18-19; Paper 13 at 10.) But the record now shows that a skilled artisan in April 1983 would not have understood these general statements as teaching recombinant constructs containing genes encoding for the different chains of a multimeric eukaryotic protein, such as the heavy and light chains of an antibody.

As an initial matter, Bujard expressly defined "structural genes" as including ***markers***: "a structural gene ***which may be a marker***." (Ex. 1002, 2:42; Ex. 2020, Foote Dep. 342; Ex. 2010, Calame Dep. 192.) Accordingly, "structural genes" would have been understood to include a gene for the protein of interest and a marker. (Ex. 2019, Fiddes Decl. ¶ 188.) Nothing about Bujard's use of the term "structural genes" would have led a skilled artisan to conclude that Bujard was referring to multiple genes encoding for the different chains of a multimeric protein.

Indeed, Bujard undisputedly does not disclose ***any*** embodiment in which genes encoding two different eukaryotic polypeptides are located between the promoter and terminator. (Ex. 2020, Foote Dep. 302; Ex. 2010, Calame Dep. 204.) Aside from multimers of DNA for the same gene and bacterial operons,[11] the only time the Bujard inventors disclosed multiple "structural genes" between a promoter (P) and terminator (T) was the following example in the file history involving a single gene of interest (G) and a marker (M):



(Ex. 2035 at 64; Ex. 2020, Foote Dep. 334-43; Ex. 2019, Fiddes Decl. ¶¶ 185-89.)[12]

That is not an example of co-expressing genes encoding for different proteins of interest, such as the heavy and light chains of an antibody, in a single host cell. Rather, as Dr. Foote has explained, a marker simply "permit[s] scientists

[11] Operons are sequences of ***prokaryotic*** genes occurring in nature that have no relevance to producing recombinant eukaryotic proteins. (Ex. 2019, Fiddes Decl. ¶¶ 183-84.)

[12] Dr. Calame did not consider Bujard's file history. (Ex. 2010, Calame Dep. 192.)

to identify which host cells have been transformed" and "is not, strictly speaking, a protein 'of interest' or a 'desired' protein" because "it is not intended to be isolated or studied." (Ex. 1006, Foote Decl. ¶ 39 n.4; Ex. 2019, Fiddes Decl. ¶¶ 55, 159.) The absence of any disclosure or suggestion in Bujard to co-express different proteins of interest is confirmed by Dr. Gentz, who testified that he was not thinking in April 1983 about using Bujard's vectors to co-express different eukaryotic proteins in a single host cell and is not aware of anyone in Dr. Bujard's lab who was either. (Ex. 2021, Gentz Decl. ¶¶ 23-26, 31-34, 37-38, 49.)

Even under Mylan's theory that "one or more structural genes" could include multiple nonselectable (*i.e.*, non-marker) genes of interest, a skilled artisan in April 1983 would have understood that phrase to refer to multiple copies of the ***same*** gene or a bacterial operon, consistent with Bujard's reference to "multimers and operons." (Ex. 1002, 3:48; Ex. 2019, Fiddes Decl. ¶¶ 185-86; Ex. 2021, Gentz Decl. ¶¶ 42-49.) Using multiple copies of the same gene within a construct was a known technique to increase yield of a desired protein—for example, as described in U.S. Patent No. 4,399,216 ("Axel").[13] (Ex. 1018, 3:62-68 ("By inserting multiple copies of genes coding for desired materials into eucaryotic cells … it is

[13] Axel was the primary reference at issue in the reexaminations of the '415 patent. (Ex. 1025, NIRC at 4.)

possible to produce eucaryotic cells which yield desired materials in high concentrations.").) Other publications from the 1980s similarly describe using multiple copies of the same gene to boost expression levels. (Ex. 2070, Shen at 4627; Ex. 2071, Wilcken-Bergmann at 3219; Ex. 2021, Gentz Decl. ¶¶ 43-47.) Interpreting "one or more structural genes" in that manner is consistent with Bujard's stated purpose "to provide for high and efficient transcription and/or expression of the sequence." (Ex. 1002, 2:36-38.) It also is precisely how Dr. Gentz understands Bujard's use of the phrase. (Ex. 2021, Gentz Decl. ¶¶ 42-43.)

Accordingly, a person of ordinary skill would not have interpreted Bujard's use of the terms "structural genes" or "plurality of genes" as referring to the co-expression of multiple genes encoding for the subunits of a multimeric protein.

(iii) "A plurality of translational stop codons" efficiently terminates translation of a single gene.

In its institution decision, the Board interpreted Bujard's reference to "a plurality of translational stop codons" in "one or more reading frames of the vector" as allowing "multiple structural genes to be translated into separate polypeptides." (IPR2015-01624, Paper 15 at 19; *see* Paper 13 at 10.) However, the record now shows that is not how a skilled artisan would have understood Bujard as of April 1983.

Stop codons are needed even when expressing a single gene, and multiple stop codons can be used with a single gene. As Bujard explains, several stop codons in multiple reading frames "aid in the efficiency of termination." (Ex. 1002, 3:19-21; Ex. 2019, Fiddes Decl. ¶¶ 190-96.) Nothing about having multiple stop codons suggests co-expressing multiple genes.

Rather, Bujard's reference to multiple stop codons makes sense to offset the effects of its "strong" promoter. A skilled artisan would have understood that, much like pumping the brakes of a car when attempting to reduce speed going down a steep hill, Bujard found it helpful to have several stop codons staggered across multiple reading frames to improve the efficiency of terminating translation. (Ex. 2019, Fiddes Decl. ¶¶ 192-93.) Again, Dr. Gentz has confirmed that Bujard's discussion of multiple stop codons does not refer to including multiple different eukaryotic genes, and that a skilled artisan would not have interpreted Bujard in that manner. (Ex. 2021, Gentz Decl. ¶¶ 57-61.)

(iv) There was no "prevailing mindset" that multiple eukaryotic genes could be co-expressed in a single host cell.

Mylan contends that there was a "prevailing mindset" in April 1983 that "more than one mammalian gene could be introduced and expressed by a single host cell" based upon several other references cited in Dr. Foote's declaration.

(Paper 2 at 23-27; Ex. 1006, Foote Decl. ¶¶ 52-60.)[14] But those references do not support Mylan's position. Indeed, Drs. Foote and Calame both admitted at their depositions that none of those references describes any actual work co-expressing multiple eukaryotic genes of interest in a single host cell, and that no one else had reported doing so as of April 1983. (Ex. 2020, Foote Dep. 114-16, 205-08; Ex. 2010, Calame Dep. 204, 230; *see* Ex. 2019, Fiddes Decl. ¶¶ 96-100.) Mylan cannot establish that a "mindset" existed about something that admittedly had never previously happened.

To be sure, the references that Dr. Foote cited in his declaration include generic references to "one or more genes." (Ex. 1006, Foote Decl. ¶¶ 53-57.) But the Patent Office previously considered similar generic references to "genes" in Axel[15] during the '415 reexamination and in Salser during IPR2016-00383, and

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[14] At the institution stage, the Board concluded that "at least the Bujard reference suggests that the skilled artisan's mindset would include making multimeric proteins within a single host cell." (IPR2015-01624, Paper 15 at 20.) However, for the reasons discussed above, the record now confirms that a skilled artisan would not have interpreted Bujard that way as of April 1983.

[15] The Board stated that Bujard's teachings are "more specific and robust than the Axel reference." (IPR2015-01624, Paper 15 at 16.) But as discussed above,

rightly concluded that those general terms and phrases did not teach the '415 invention. (Ex. 1025, NIRC at 4; IPR2016-00383, Paper 16 at 18, 20-29.) There is no reason to reach a different result here. (Ex. 2019, Fiddes Decl. ¶¶ 233-38.)

d) Mylan's remaining arguments about Bujard lack merit.

Mylan points to two other portions of Bujard that the Board did not rely upon in its institution decision. Neither supports Mylan's obviousness theories.

(i) "One or more hosts for gene expression"

Mylan cites Bujard's statement that its strategy "can be used with one or more hosts for gene expression." (Paper 2 at 30 (quoting Ex. 1002, 8:1-3).) But that statement defeats Mylan's interpretation of Bujard. In fact, the Board in IPR2015-01624 cited this very passage to find that Bujard does not anticipate the challenged claims. As the Board explained, Bujard contains ***no*** "teaching that all the genes encoding for the different subunits (polypeptides) of the 'proteins of interest' identified in Bujard must *necessarily* be expressed within the same host cell," and "it is possible that a skilled artisan could have chosen to express the

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Bujard, like Axel, contains no suggestion to co-express multiple eukaryotic proteins of interest in a single host cell. Bujard merely echoes Axel's teaching that multiple copies of the same gene can be used to increase yields. (Ex. 1018, 3:62-68; Ex. 2019, Fiddes Decl. ¶¶ 233-38.)

genes for the heavy and light chains in separate host cells, as also suggested by Bujard." (IPR2015-01624, Paper 15 at 16, 20 (emphasis in original).) That same passage undermines Mylan's obviousness arguments.

Indeed, the full quotation in Bujard refers to "a vehicle which can be used with one or more hosts for gene expression" (Ex. 1002, 8:1-3), which a skilled artisan would have understood as a suggestion to use the disclosed plasmids as an expression construct in different ***types*** of bacterial host cells. That is consistent with Dr. Bujard's own published research and how Dr. Gentz understands the term. (Ex. 2021, Gentz Decl. ¶¶ 55-56.) And Dr. Foote at his deposition testified that he interpreted that "one or more hosts" language as simply referring to using different types of cell lines to express proteins—not a choice whether to use one host cell versus more than one. (Ex. 2020, Foote Dep. 366-67; Ex. 2021, Gentz Decl. ¶¶ 53-56; Ex. 2019, Fiddes Decl. ¶¶ 231-32.) In sum, there is no basis to interpret Bujard's reference to "one or more hosts" as referring to the choice between using a single or multiple host cells.

(ii) "Prepared as a single unit or as individual subunits"

Mylan argues that Bujard's statement that "[t]he proteins may be prepared as a single unit or as individual subunits and then joined together in appropriate ways" (Ex. 1002, 4:19-21) describes preparing "an *in vivo* assembled multimeric

protein, such as an immunoglobulin," from a single host cell. (Paper 2 at 31; Ex. 1006, Foote Decl. ¶ 73.) But the quoted passage says nothing about the number of host cells. It simply describes whether the protein is a "single unit" (*i.e.*, one polypeptide chain) or "individual subunits" that are "then joined together." If anything, "individual subunits" that are "then joined together" suggests preparation in ***separate host cells*** followed by *in vitro* assembly—exactly the approach used in the prior art to produce insulin recombinantly. (Ex. 1003 at 531-32.)

Indeed, if Bujard had actually disclosed preparing a multimeric protein "as a single unit" in a single host cell, it would have been an important discovery—one warranting more explanation than mere reference to "a single unit," and that would have caused others to cite Bujard for that disclosure. Yet the record contains no evidence that anyone outside of litigation has ever interpreted Bujard that way, as even Drs. Foote and Calame now admit. (Ex. 2020, Foote Dep. 220, 298-99; Ex. 2010, Calame Dep. 140-44.)

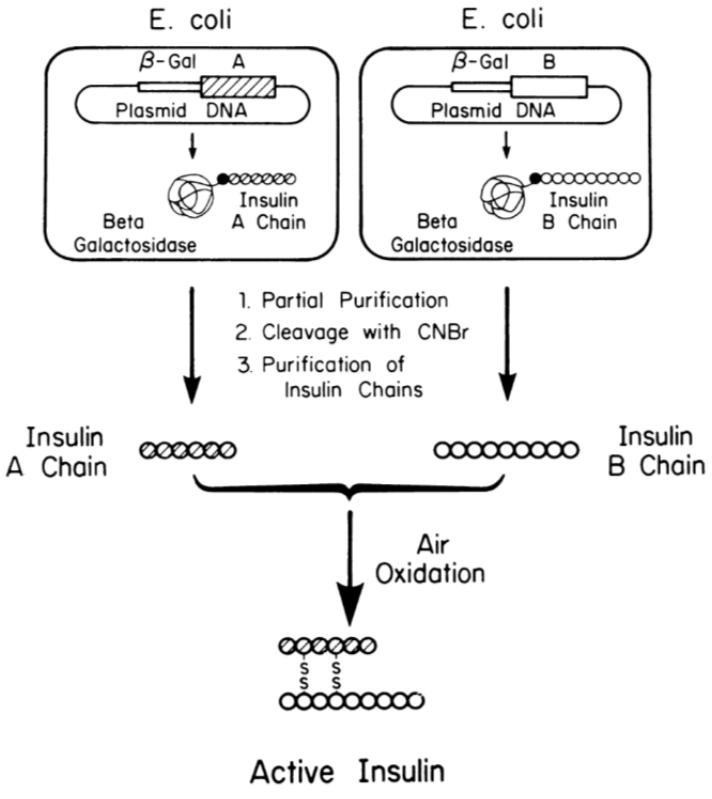
2. Riggs & Itakura does not disclose the co-expression in a single host cell limitation absent from Bujard.

Riggs & Itakura cannot fill the gaps in Mylan's obviousness theory left by Bujard. As a threshold matter, a skilled artisan wishing to produce antibodies in April 1983 would have had no reason to combine Bujard (which contains no teachings specific to antibody production) with Riggs & Itakura (which also

provides no guidance on making antibodies). And even if combined, Riggs & Itakura would not have led to any challenged claim because it specifies using a ***separate*** host cell for each polypeptide subunit of insulin.

a) Summary of Riggs & Itakura

Riggs & Itakura is a 1979 review article summarizing prior work using a two host cell process for producing insulin from bacterial cells, in which (1) genes for Chain A and Chain B were inserted into separate host cells, (2) the chains were separately expressed in their respective host cells, and (3) the resulting chains were joined together *in vitro*:



(Ex. 1003 at 532 (Fig. 1); Ex. 2019, Fiddes Decl. ¶¶ 239-42.)

Riggs & Itakura ends with what it calls "speculation on additional potential applications," including antibody production, without providing any details how that might be done. (Ex. 1003, at 531, 537-38.) Dr. Foote admitted this statement is mere speculation about the future. (Ex. 2020, Foote Dep. 377.)

b) A person of ordinary skill would have had no reason to combine Bujard with Riggs & Itakura.

A skilled artisan seeking to produce an antibody in April 1983 would have had no reason to combine Bujard with Riggs & Itakura. As discussed above (pp. 25-29), Bujard does not describe any process specific to antibody production. Neither does Riggs & Itakura. Riggs & Itakura describes an approach that cleaves polypeptides containing methionine (such as antibody heavy and light chains), which even Dr. Foote now admits is incompatible with antibody production. (Ex. 1003 at 531; Ex. 2020, Foote Dep. 373-77 ("[T]here are too many methionines in an antibody."); Ex. 2019, Fiddes Decl. ¶¶ 246-47.) And Dr. Calame conceded at her deposition that "there were lots of differences" between expressing insulin and antibodies. (Ex. 2010, Calame Dep. 121.) As such, even under Mylan's theory that a skilled artisan would have applied Bujard's strong promoter techniques to antibodies, such a person would have had no reason to look to Riggs & Itakura for guidance. (Ex. 2019, Fiddes Decl. ¶¶ 243-49.)

Nor has Mylan articulated any reasoned basis for combining Bujard with Riggs & Itakura. Mylan simply contends that Bujard instructs that proteins may be prepared "as individual subunits and then joined together in appropriate ways" (Ex. 1002, 4:20-21), and that Riggs & Itakura describes one of the "known methods" for assembling "a multi-subunit protein such as an immunoglobulin." (Paper 2 at 36.) Such conclusory explanations are legally insufficient to demonstrate an obvious combination. *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1366 (Fed. Cir. 2016) (reversing Board's determination of obviousness where the supposed reason to combine references rested on "conclusory statements and unspecific expert testimony").

Finally, Mylan has not presented any contemporaneous evidence indicating that a skilled artisan would have thought to combine Bujard and Riggs & Itakura as of April 1983. In fact, Dr. Calame analyzed Bujard in combination with Riggs & Itakura only after reading Dr. Foote's declaration (Ex. 2010, Calame Dep. 96-97)—underscoring her hindsight-driven perspective grounded in Dr. Foote's opinions offered decades after the '415 invention.

c) Bujard combined with Riggs & Itakura would have led to a two host cell approach, not the single host cell invention of the challenged claims.

Even if Bujard were combined with Riggs & Itakura, that combination would not have rendered obvious the "single host cell" limitation of the challenged

claims. Riggs & Itakura discloses only a two host cell approach for producing insulin—the opposite of what the '415 patent claims. Combining Bujard with Riggs & Itakura would have resulted in the same one-chain-per-host-cell approach that Riggs & Itakura used with insulin. The '415 invention is a dramatic—and non-obvious—departure from that approach. (Ex. 2019, Fiddes Decl. ¶ 250.)

The Board recognized this difference, acknowledging that "Riggs & Itakura takes a different approach than the 'single host cell' approach required by the claims." (IPR2015-01624, Paper 15 at 19.) But it disregarded that difference in concluding that "Bujard itself suggests the incorporation of a plurality of structural genes encoding for the subunits of a multimeric protein, such as immunoglobulin heavy and light chains, within a vector that would be placed in a single host cell." (*Id.* at 18-19.) As discussed above (pp. 24-41), however, the record now shows that Bujard contains no such suggestion.

The Board also interpreted Riggs & Itakura as "merely presenting an alternative option" that does not "teach away from the claimed invention" (*id.* at 20). Respectfully, that conclusion is incorrect for two reasons.

First, Riggs & Itakura exclusively teaches a two host cell approach. (Ex. 1003 at 531 ("The insulin chains … are made in separate bacterial strains ….").) Mylan's selective combination of the *in vitro* assembly teachings of Riggs & Itakura with Bujard (while disregarding Riggs & Itakura's two host cell teaching)

is an impermissible combination only possible with hindsight. *See Panduit Corp. v. Dennison Mfg. Co*., 810 F.2d 1561, 1568 (Fed. Cir. 1987) ("[A] prior [art reference] must be considered in its entirety, *i.e.*, as a *whole*, including portions that would lead away from the invention in suit." (emphasis in original)).

Second, Riggs & Itakura did not merely present an "alternative option." (IPR2015-01624, Paper 15 at 20.) As of April 1983, Riggs & Itakura's two separate host cell approach was the ***only option*** that had been used to independently express the different polypeptide chains of a multimeric eukaryotic protein—as confirmed by Drs. Foote's and Calame's admissions that they are not aware of anyone who had co-expressed the different subunits of any multimeric eukaryotic protein before the '415 inventors. (Ex. 2020, Foote Dep. 114-15; Ex. 2010, Calame Dep. 204, 230; Ex. 2019, Fiddes Decl. ¶¶ 251-73.) Under these circumstances where there was no other proven alternative to Riggs & Itakura's successful two host cell approach for insulin, Riggs & Itakura teaches away from the one host cell approach first disclosed by the '415 patent. *See Allergan, Inc. v. Sandoz Inc*., 796 F.3d 1293, 1305 (Fed. Cir. 2015) (a reference teaches away "when a person of ordinary skill, upon reading the reference … would be led in a direction divergent from the path that was taken by the applicant"); *Kinetic Concepts, Inc. v. Smith & Nephew, Inc*., 688 F.3d 1342, 1361-62 (Fed. Cir. 2012) (same); *Spectralytics, Inc. v. Cordis Corp*., 649 F.3d 1336, 1343 (Fed. Cir. 2011)

("teaching away" does not require a specific warning against the path taken by the invention, but rather may be established where the prior art addresses the same problem via an opposite approach).

3. The '415 invention was not obvious to try.

The Board alternatively suggested that the single host cell solution of the '415 patent "would have been among the 'known options within [the skilled artisan's] technical grasp' that the skilled artisan would have chosen to pursue" when making an antibody. (IPR2015-01624, Paper 15 at 20 (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)).) But to be obvious to try, a solution must be among "a ***finite*** number of ***identified***, ***predictable*** solutions." *KSR*, 550 U.S. at 421. The record now shows that Mylan's obviousness theory fails each of these requirements.

First, a skilled artisan would not have considered Bujard to present a "finite" number of options. Even Dr. Foote now admits that Bujard's list of "proteins of interest" is so large that he cannot determine its size—including "thousands" of histocompatibility proteins and "a million" variations of each listed protein. (Ex. 2020, Foote Dep. 278-83.) That takes this situation well outside the realm of the "small or easily traversed[] number of options that would convince an ordinary skilled artisan of obviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); *see Allergan, Inc. v. Apotex Inc.*, 754 F.3d

952, 972-73 (Fed. Cir. 2014) (rejecting obvious to try argument where the prior art disclosed "hundreds of thousands, or even millions" of options). Only in hindsight would a skilled artisan in April 1983 have selected antibodies from Bujard's large and undifferentiated protein list.

Second, recombinant DNA techniques would not have been a "predictable" path to success for antibody production. (*See supra* pp. 10-17.) That path was so unpredictable as of April 1983 that Dr. Winter—a person of extraordinary skill—postponed his research in the area, given his uncertainty whether antibodies could be produced recombinantly at all. (Ex. 2023, Winter Rep. ¶ 61; Ex. 2020, Foote Dep. 178-79; Ex. 2019, Fiddes Decl. ¶ 205.) By contrast, hybridoma techniques were "expanding very rapidly" at the time (Ex. 1039, Milstein at 407; Ex. 2020, Foote Dep. 48-49; Ex. 2019, Fiddes Decl. ¶ 203), so much so that even highly-skilled scientists like Dr. Carlo Croce aggressively pursued hybridoma research and "could not see the advantages of a recombinant approach the way Cabilly et al. had" (Ex. 2072, Croce Rep. ¶ 94; *see id.* ¶¶ 82-95). It would not have been obvious to try recombinant DNA techniques given their unknown and uncertain chance of success, especially when hybridomas provided an established alternative. *See Rolls-Royce, PLC v. United Techs. Corp.*, 603 F.3d 1325, 1339 (Fed. Cir. 2010) (obvious to try requires the invention to be an "anticipated success").

Third, even if a skilled artisan had decided to pursue recombinant DNA techniques to make an antibody, the single host cell approach of the '415 patent was not an "identified" option. It is undisputed that no one prior to the '415 inventors had reported making ***any*** eukaryotic multimeric protein by co-expressing its polypeptides as separate molecules in a single host cell. (Ex. 2020, Foote Dep. 114-15; Ex. 2019, Fiddes Decl. ¶¶ 128-37.) A skilled artisan could not have considered the single host cell approach of the '415 patent as an "identified" option for producing antibodies in April of 1983, given that no one had ever used such an approach to produce any protein at that time. *See Rolls-Royce*, 603 F.3d at 1339 (rejecting obvious to try theory where the "invention would not have presented itself as an option at all"). The ***only*** identified approach at the time for independently expressing the subunits of a multimeric eukaryotic protein from recombinant DNA was the ***separate*** host cell approach used by Riggs & Itakura for insulin.

Any of the foregoing factors on its own defeats a finding of obviousness to try, and together they overwhelmingly foreclose that conclusion.

4. A person of ordinary skill would not have had a reasonable expectation of success in extending Riggs & Itakura's techniques to antibodies.

Given the many uncertainties and overall unpredictability of the art, a skilled artisan in April 1983 would have had no reasonable expectation of success in

producing an antibody recombinantly in a single host cell, including based upon the combination of Bujard with Riggs & Itakura.

First, Riggs & Itakura discloses a recombinant technique for producing insulin. But there are significant differences between insulin and antibodies that would have caused a skilled artisan to have no reasonable expectation of success that insulin-based techniques could be extended to antibodies. (Ex. 2010, Calame Dep. 121 (acknowledging "lots of differences" between producing insulin and antibodies recombinantly); Ex. 2019, Fiddes Decl. ¶¶ 243-49.) For example, insulin consists of two small subunits—with a combined total of 51 amino acids—joined by two interchain disulfide bonds and one intrachain disulfide bond. (Ex. 1003 at 531-32; Ex. 2020, Foote Dep. 83, 292-93; Ex. 2019, Fiddes Decl. ¶¶ 35-37.) By contrast, antibodies consist of four large subunits—two heavy chains and two light chains, each containing hundreds of amino acids—joined together in a representative IgG1 class antibody by 12 interchain and 4 intrachain disulfide bonds. (Ex. 2019, Fiddes Decl. ¶¶ 38-45; Ex. 2020, Foote Dep. 86, 108, 371-72.) Given the greater number of subunits and structures that must form correctly, the proper folding and assembly for a functional antibody presents a far more challenging task than insulin. (Ex. 2019, Fiddes Decl. ¶ 43.)

Second, Riggs & Itakura contains almost no details on how to assemble a multimeric protein *in vitro*—further increasing the degree of uncertainty in

extending its teachings to antibodies. All that Riggs & Itakura says is that the two insulin chains were joined by "air oxidation." (Ex. 1003 at 531.) Neither Riggs & Itakura nor Bujard describes how to properly fold and assemble a large, complex protein, such as an antibody, from recombinantly produced polypeptide chains.

Third, as of April 1983, it was unknown what was required for antibodies to fold correctly. For example, some scientists believed that "helper" proteins found in B cells were necessary to facilitate the translation and assembly of functional antibodies, which would not be available using recombinant techniques. (Ex. 2073, Wabl at 6976-77; Ex. 2019, Fiddes Decl. ¶¶ 95, 136.) Riggs & Itakura and Bujard contain no suggestion that functional antibodies could be assembled without those helper proteins. (Ex. 2019, Fiddes Decl. ¶ 263.)

Fourth, Riggs & Itakura and Bujard also do not discuss the complication of "inclusion bodies"—"a tangled mass of polypeptide chain" that results when expressing eukaryotic proteins in a prokaryotic host—which Dr. Foote agreed was "an issue in terms of producing eukaryotic proteins in prokaryotic cells in April of 1983." (Ex. 2020, Foote Dep. 145-46; Ex. 1027, Harris at 173 (explaining, in an April 1983 publication, that "several normally soluble proteins are found to be insoluble when made in *E. coli*" and that this issue required "[f]urther work").) The possibility of inclusion bodies was another challenge that might have hindered

the folding and assembly of a functional antibody produced using recombinant techniques. (Ex. 2019, Fiddes Decl. ¶¶ 70-72, 267.)

Given these numerous uncertainties and difficulties, a person of ordinary skill would not have reasonably expected success in assembling vastly more complex proteins such as antibodies based on the barebones description in Riggs & Itakura. (Ex. 2019, Fiddes Decl. ¶¶ 274-79.)

B. Ground 2: Claims 1, 2, 18, 20, And 33 Would Not Have Been Obvious Over Bujard In View Of Southern.

In Ground 2, Mylan challenges a different set of claims that cover a process wherein the DNA encoding for heavy and light chains "are present in different vectors" (claim 2), or "[a] transformed host cell comprising at least two vectors" with each vector separately containing the DNA encoding for either the heavy or light chains (claim 18). Mylan's arguments for these claims fare no better.

1. Bujard does not suggest co-expression in a single host cell to produce antibodies.

Mylan's argument depends upon the same flawed interpretation of Bujard for the single host cell limitation of the challenged claims addressed in connection with Ground 1. Ground 2 therefore fails for the same reasons discussed above (pp. 24-41): Bujard does not suggest the co-expression of antibody heavy and light chains in a single host cell to produce a functional antibody.

2. Southern does not disclose or suggest the "single host cell" or the two vector limitations absent from Bujard.

Mylan points to Southern as supposedly disclosing the use of two vectors encoding for different proteins, and argues that these two vectors could have been used to produce the two antibody chains in a single host cell. (Paper 2 at 39-41; Ex. 1006, Foote Decl. ¶¶ 86-90, 103-05.) But Dr. Foote admitted at his deposition that Southern does not disclose any experiment involving even a single protein of interest—let alone two different proteins of interest in a single host cell. (Ex. 2020, Foote Dep. 383-84.) Nor would it have been obvious as of April 1983 to use two of Southern's vectors with a single host cell method of antibody production. And Southern does not provide any guidance on how that might be done. Accordingly, because Southern does not provide the "single host cell" and two vector limitations of the challenged claims absent from Bujard, Ground 2 should be rejected for this reason as well.[16]

[16] Neither Mylan nor the Board advanced an obvious to try theory for Ground 2. Nevertheless, any such theory would fail for the same reasons stated for Ground 1. The claimed invention was not among a finite number of identified, predictable solutions. (*See supra* pp. 47-50.)

a) Summary of Southern

Southern is a 1982 publication that does not mention antibodies. Instead, its focus is a new selectable marker ("*neo*") for use in a vector to transform cultured mammalian cells. (Ex. 1004 at 328.) Southern describes several experiments involving the *neo* marker, including one involving a single vector that included both the *neo* and *gpt* markers. In that experiment, "selection was applied for one or the other (or both) of the genes and transformants were scored for expression of the non-selected marker." (*Id.* at 336.) "For comparison" purposes, Southern performed a second experiment where a mixture of separate vectors containing *neo* or *gpt* were used to co-transform cells. (*Id*.; Ex. 2019, Fiddes Decl. ¶¶ 280-85.)

The last paragraph of Southern speculates that "[c]otransformation with nonselectable genes can be accomplished by inserting genes of interest into vector DNAs designed to express neo or gpt." (Ex. 1004 at 339.) But Southern's reference to "genes of interest" merely refers to the vector's ability to express various ***types*** of genes, depending upon which particular gene is desired—not multiple different genes at the same time. (Ex. 2019, Fiddes Decl. ¶¶ 302-04.) Southern did not include ***any*** nonselectable "genes of interest" in the vectors tested, let alone multiple nonselectable "genes of interest"—as Dr. Foote admitted. (Ex. 1006, Foote Decl. ¶ 90.) It would take Southern's words out of context to

interpret its reference to "genes of interest" as supposedly referring to multiple nonselectable genes that express different polypeptides in the same host cell.

Southern's final sentence states that "[t]he 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.) But Southern never identified what those supposed experiments were or any results from them, and Dr. Foote was not aware of any subsequent reporting of any such results. (Ex. 2020, Foote Dep. 385-86; Ex. 2019, Fiddes Decl. ¶ 305.)

b) A person of ordinary skill would not have combined Bujard with Southern.

Bujard and Southern address fundamentally different issues, and there would have been no reason in April 1983 for a skilled artisan to even consider their teachings together. Bujard discloses techniques to identify strong promoter and terminator combinations using T5 phage promoters in bacteria (*e.g.*, Ex. 1002, 2:39-47, cls. 1, 15),[17] while Southern discloses vectors containing selectable markers for use in mammalian cells using an entirely different promoter (SV40 early promoter). (Ex. 1004 at 327.)

Because Bujard and Southern are directed to different cell types (bacterial versus mammalian), and different promoters (T5 phage versus SV40 early

[17] Bujard mentions mammalian cells only in passing. (Ex. 1002, 6:34-37.)

promoter), a person of ordinary skill starting with Bujard in April 1983 would have had no reason to look to Southern. Bujard's expression constructs and Southern's expression systems are incompatible with one another. (Ex. 2019, Fiddes Decl. ¶¶ 286-91; Ex. 2020, Foote Dep. 387-88.) Further, because Bujard already identified numerous selectable markers for use with its invention, there would have been no need for the markers described in Southern. (Ex. 1002, 7:21-34.)

The record evidence concerning Bujard and Southern further confirms that a skilled artisan would not have considered them together in April 1983. Dr. Calame testified that she was not familiar with Southern until provided a copy by counsel for this proceeding. (Ex. 2010, Calame Dep. 52.) And her perspective was tainted by reading Dr. Foote's declaration before even considering the underlying references. (*Id.* at 96-97.) And although Dr. Foote noted in his declaration that Southern has been cited more than 3,500 times since its publication, he later admitted that he cannot identify any publication that also cites Bujard. (Ex. 2020, Foote Dep. 388-90.)

c) Southern does not disclose including multiple "genes of interest" in separate vectors.

Southern does not describe the expression of even a single nonselectable gene of interest, let alone multiple such genes—and certainly not antibody heavy and light chains in a single host cell. (Ex. 1004 at 336-37; Ex. 2019, Fiddes Decl.

¶ 301.) Southern therefore cannot cure Bujard's deficiencies because it too fails to describe independently expressing antibody heavy and light chains in a single host cell.

Mylan does not appear to disagree. It relies on Southern only for the limited purpose of arguing that claim limitations requiring separate vectors for expression of heavy and light chains would have been obvious. (Paper 2 at 39-41.) But even then, Southern showed "a significant reduction (10-fold or greater) in the number of stable transformants" when using two vectors versus one in its experiments using selectable markers. (Ex. 1004 at 337.) It would have been a non-obvious choice to pursue a two-vector approach that Southern indicated was less efficient than a single vector.

In its institution decision, the Board relied upon three statements in Southern, which it suggested might refer to expressing multiple nonselectable genes of interest in a single host cell. But the record now shows that a person of ordinary skill would not have interpreted Southern that way.

First, the Board cited Southern's statement that "vectors containing these markers provide a way to cotransduce other genes whose presence and/or expression can not be selected." (IPR2015-01624, Paper 15 at 12; Ex. 1004 at 338.) But that simply describes the function of selectable markers—*i.e.*, to provide

a way to express nonselectable genes.[18] It does not suggest expressing multiple nonselectable genes of interest in a single host cell—an interpretation that even Mylan has not advocated. (Paper 2 at 39-41.)

Second, the Board cited Southern's discussion of "inserting *genes of interest* into vector DNAs designed to express neo or gpt" as demonstrating "the general applicability of its disclosed co-transformation technique." (IPR2015-01624, Paper 15 at 12, 22 (emphasis in original); Ex. 1004 at 339; *see* Paper 13 at 11.) But as discussed above (pp. 54-55), Southern does not disclose any co-transformation technique involving multiple nonselectable genes of interest, let alone demonstrate its "general applicability." Southern only describes experiments inserting multiple selectable markers into the same host cell. (Ex. 1004 at 336; Ex. 2019, Fiddes Decl. ¶¶ 284-85.)

Even Dr. Foote acknowledged in his declaration (and thus Dr. Calame too) that Southern does not disclose co-transformation with two different nonselectable genes of interest. (Ex. 1006, Foote Decl. ¶ 90.) Dr. Foote attempted to dismiss the

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[18] The quoted passage does not even relate to work described in Southern; it refers to earlier research involving selectable markers. (Ex. 1004 at 337-38.) Discussion of Southern's work begins in the next sentence. (*Id.* at 338 ("In the present work ….").)

lack of multiple genes as a mere "experimental convenience." (*Id.*) But that mischaracterizes Southern, the primary focus of which was to describe a new selectable marker. (Ex. 1004 at 328 ("In this paper, we describe a second bacterial gene which, when incorporated into the same family of plasmid vectors, also provides a dominant selective marker for transformation of cultured mammalian cells.").) The fact that Southern did not cotransform multiple nonselectable markers in a single host cell was not a matter of "convenience," but rather a reflection of its focus on selectable markers. (Ex. 2019, Fiddes Decl. ¶¶ 292-301.)

Third, the Board quoted the last line of Southern: "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." (IPR2015-01624, Paper 15 at 12; Ex. 1004 at 339; *see* Paper 13 at 11-12.) But Southern did not report the results of any two-vector scheme used to express two different proteins of interest, and Dr. Foote is not aware that the Southern authors ever reported the successful use of such a two-vector scheme. (Ex. 2020, Foote Dep. 385-86; Ex. 2019, Fiddes Decl. ¶¶ 302-06.) At most, Southern described the need for future experimentation regarding some undisclosed use for the two-vector approach. But that vague description would not have led a skilled artisan to the '415 invention or provided a reasonable expectation of success in doing so. Indeed, Southern explains that its own tests using both markers involved a poorly

understood process. (Ex. 1004 at 339 ("It remains to be determined if removal of the upstream AUG triplets would affect the efficiency of translation of phosphotransferase, as was the case with gpt."); *id.* ("We have no information that clarifies the difference between the apparent molecular weight of the APH(3')II produced in *E. coli* containing the pBR-neo plasmid and the pSV-neo transformed Ltk$^-$ cells."); *id.* ("This question needs further study.").)

d) Other publications confirm that a skilled artisan would not have applied Southern to express heavy and light chains from separate vectors in the same host cell.

The Board cited Rice & Baltimore (Ex. 1020), Ochi (Ex. 1021), and Oi (Ex. 1031) as "evidence that Southern's pSV2gpt and pSV2neo vectors were adopted by independent research groups for single chain immunoglobulin expression prior to the filing date of the '415 patent." (IPR2015-01624, Paper 15 at 22.) But as the Board recognized, each reference (from highly distinguished researchers) discloses an attempt to produce a "***single*** chain immunoglobulin" from ***one*** vector. (*Id.*) If those researchers of exceptional skill did not apply Southern as Mylan suggests, there is no reason to believe that a person of ordinary skill would have. (Ex. 2019, Fiddes Decl. ¶¶ 307-09.)

3. A skilled artisan would have had no reasonable expectation of success combining Bujard with Southern.

A person of ordinary skill would not have had a reasonable expectation that functional antibodies could be produced using two of Southern's vectors in a single host cell. The same uncertainties discussed above (pp. 10-17) surrounding recombinant DNA techniques—and the production of antibodies in particular—forecloses any argument that a skilled artisan would have reasonably expected success.

Mylan asserts that "[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." (Paper 2 at 40.) But Mylan does not cite any teaching that a skilled artisan would have been "confident" that heavy and light chains could be made recombinantly with the same expression machinery. (Paper 2 at 40-41; Ex. 1006, Foote Decl. ¶ 104; Ex. 2019, Fiddes Decl. ¶¶ 315-17.) In fact, Mylan's own cited references confirm precisely the opposite. Rice & Baltimore (Ex. 1020), Ochi (Ex. 1021), and Oi (Ex. 1031) show that uncertainties remained about how the expression of immunoglobulin genes was regulated and whether such expression would occur,

even in host cells that were still producing native heavy chains. (*See supra* pp. 15-16; Ex. 2019, Fiddes Decl. ¶¶ 307-14.)

4. Southern cannot invalidate claims 1, 2, and 33.

Even under Mylan's flawed theory, combining Bujard with Southern would not have rendered claims 1, 2, or 33 obvious. Those process claims require producing an assembled antibody, as Mylan admits. (Paper 2 at 8.) But Bujard does not teach antibody assembly; that is why Mylan cites Riggs & Itakura in Ground 1 (which does not disclose that limitation either). And Mylan does not even argue that Southern discloses antibody assembly. Accordingly, Ground 2 cannot invalidate claims 1, 2, and 33 for this reason as well.

C. Objective Indicia Confirm The Patentability Of The Challenged Claims.

Evidence concerning the real world impact of a patented invention is a critical safeguard against hindsight reasoning—a safeguard particularly important here because the obviousness analysis depends upon the perspective of a skilled artisan from April 1983. *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) ("Secondary considerations can be the most probative evidence of non-obviousness in the record, and enables the ... court to avert the trap of hindsight." (internal quotation marks omitted)). Indeed, the Board has recognized that such evidence alone may rebut other evidence of obviousness. *InnoPharma*

Licensing, Inc. v. Senju Pharm. Co., IPR2015-00902, Paper 90 at 14-22, 25-27 (July 28, 2016) (affirming patentability based upon evidence of unexpected results, commercial success, and industry praise).

Despite the importance of this type of evidence, Dr. Calame testified that she had never heard of objective indicia of non-obviousness before her deposition and had not taken that evidence into account before concluding that the challenged claims would have been obvious. (Ex. 2010, Calame Dep. 236-38.) Dr. Foote did not address objective indicia in his analysis either. (Ex. 1006.) Their conclusion that the challenged claims would have been obvious, without considering the objective evidence, is legally erroneous. *See Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc) (explaining "it is error to reach a conclusion of obviousness" without first considering objective indicia of non-obviousness).

Here, several objective indicia confirm the non-obviousness of the challenged claims.

First, the '415 patent is one of the most widely licensed patents in the industry, with over 70 licenses to many of the world's leading biotechnology companies, generating total royalties well over a billion dollars. (Ex. 2033, Davis Decl. ¶ 34.) There is a direct nexus between those licensing revenues and the challenged claims: Genentech received over a billion dollars in royalty payments

from March 2006 until April 2011, when the '415 patent was the ***only*** issued patent covered by those licenses. (*Id.* ¶¶ 43, 50.) This licensing evidence confirms the widespread recognition of the patent as a groundbreaking invention. *See*, *e.g.*, *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013) (reversing Board's obviousness determination where patentee's "licensing activities provide probative and cogent evidence of non-obviousness of the claims at issue" (internal quotation marks omitted)).

The contrast between the '415 patent and Bujard in this regard is striking. Whereas the '415 patent is one of the most licensed, foundational patents in the biotechnology industry, Bujard was allowed to expire after only four years. (Ex. 2034.)

In addition, the '415 patent has been cited as prior art more than 700 times by over 200 different entities. (Ex. 2015.) These numerous citations are further objective evidence of the patent's place as a core invention in the field.

Second, some of Genentech's most successful products embody the '415 patent, including several "blockbuster" drugs, which together have generated over $100 billion in revenue. (Ex. 2033, Davis Decl. ¶¶ 51-60.) Products developed by other companies using the '415 invention have also been highly successful—again, resulting in well over $100 billion in revenue. (*Id.* ¶¶ 61-65.) There is a direct nexus between the commercial success of those products and the challenged

claims; each is produced using the claimed single host co-expression. (*Id.* ¶¶ 52-54.) That process enables the efficient and stable manufacture of those products, contributing to their commercial success. (*Id.*)

Third, in April 1983, several leading scientists were highly skeptical that an antibody could even be produced using recombinant DNA—let alone by co-expressing its heavy and light chains in a single host cell as claimed in the '415 patent. (*See supra* pp. 13-17.) The '415 inventors' success in the face of such skepticism underscores the non-obviousness of their invention. *See Kinetic Concepts*, 688 F.3d at 1367-68 (holding that skepticism, followed by widespread acceptance and praise, supported non-obviousness); *see also In re Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511, 518 (Fed. Cir. 2012) (rejecting obvious to try theory, in part, due to "general skepticism" toward the claimed invention).

These objective indicia of non-obviousness reaffirm the conclusions detailed above—that the challenged claims of the '415 patent are not obvious.

VIII. CONCLUSION

The Board should affirm the patentability of the challenged claims.

Respectfully submitted,

Date: December 22, 2016

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing, Patent Owners' Response, contains 13,980 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

Respectfully submitted,

Dated: December 22, 2016

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CERTIFICATE OF SERVICE

I hereby certify that, on December 22, 2016, I caused a true and correct copy of the following materials:

- Patent Owners' Response
- Exhibits 2003-2005, 2007, 2010-2137
- Patent Owners' Updated List of Exhibits
- Patent Owners' Motion to Seal

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Patent Owners' Exhibit List
IPR2016-00710

Exhibit Number	Exhibit Name
2001	Declaration of Robert J. Gunther, Jr. in Support of Motion for Admission *Pro Hac Vice* (Sept. 22, 2016)
2002	Declaration of Daralyn J. Durie in Support of Motion for Admission *Pro Hac Vice* (Sept. 22, 2016)
2003	Institution of *Inter Partes* Review, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624, Paper 15 (Feb. 5, 2016)
2004	U.S. Patent No. 3,996,345
2005	EP 1 532 260 B1
2006	Withdrawn
2007	Declaration of Dr. Timothy John Roy Harris Under 37 C.F.R. § 1.132 in Reexaminations 90/007,542 and 90/007,859 (Oct. 26, 2006) ("Harris II Decl.")
2008	Declaration of Joseph M. Lipner in Support of Motion for Admission *Pro Hac Vice* (Nov. 15, 2016)
2009	Declaration of David I. Gindler in Support of Motion for Admission *Pro Hac Vice* (Nov. 28, 2016)
2010	Transcript of Deposition of Dr. Kathryn Calame, *Mylan Pharm. Inc. v. Genentech, Inc.*, IPR2016-00710 (Nov. 18, 2016) ("Calame 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	Google Patents, U.S. Patent No. 6,331,415 and List of Patent Citations, https://www.google.com/patents/US6331415?dq=6331415&hl=en&sa=X&ved=0ahUKEwjPhr2C2dTMAhWBVSYKHfVRDtIQ6AEIHDAA (last visited Dec. 19, 2016)

Exhibit Number	**Exhibit Name**
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	Bruce Alberts, et. al, Molecular Biology of the Cell, Chapter 1 (1983)
2019	Expert Declaration of John Fiddes, Ph.D., *Mylan Pharm. Inc. v. Genentech, Inc.*, IPR2016-00710 ("Fiddes Decl.")
2020	Transcript of Deposition of Dr. Jefferson Foote, *Sanofi-Aventis U.S. LLC v. Genentech, Inc.*, IPR2015-01624 (Apr. 21, 2016) ("Foote Dep.")
2021	Expert Declaration of Reiner Gentz, Ph.D., *Mylan Pharm. Inc. v. Genentech, Inc.*, IPR2016-00710 ("Gentz Decl.")
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2028	Declaration of Jeanne Perry, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 27, 1991)

Exhibit Number	**Exhibit Name**
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2030	Declaration of Michael Rey, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
2031	Declaration of Michael Mumford, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
2032	Declaration of Shmuel Cabilly, *Cabilly v. Boss*, Interference No. 102,572 (Oct. 28, 1991)
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